2-(INDAZOL-5-YL)-6-(PIPERIDIN-4-YL)-1,7-NAPHTHYRIDINE DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS FOR SPLICING NUCLEIC ACIDS AND FOR THE TREATMENT OF PROLIFERATIVE DISEASES

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 63/047,898, filed July 2, 2020; U.S. Application No. 63/072,921, filed August 31, 2020; and U.S. Application No. 63/126,495, 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.

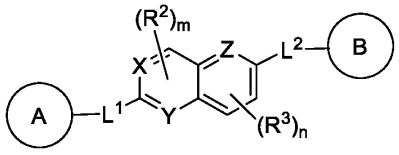
SUMMARY

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) or (II), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, or stereoisomers thereof. The present disclosure additionally provides methods of using the compounds of the disclosure (e.g., compounds of Formulas (I) and (II), 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 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.

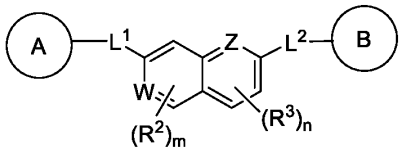
In another aspect, the compounds described herein may be used for the prevention and/or treatment of a disease, disorder, or condition, e.g., a disease, disorder or condition associated with splicing, e.g., alternative splicing. In some embodiments, the compounds described herein (e.g., compounds of Formulas (I), (II), 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), (II), 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), (II), 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 each of A, B, L^1, L^2, X, Y, Z, R^2, R^3, m, n, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure provides compounds of Formula (II):



(II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, W, Z, R^2, R^3, m, n, and subvariables thereof are defined as described herein.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (I) or (II), 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 a therapeutically effective amount of a compound of Formula (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II) 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 Formulas (I) or (II) 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 Formulas (I) or (II), e.g., in a healthy or diseased cell or tissue). In some embodiments, the presence of a compound of Formulas (I) or (II) 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II) 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

Formulas (I) or (II) 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 Formulas (I) or (II) 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 Formulas (I) or (II), 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 Formulas (I) or (II), 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 2018/226622, WO 2019/028440, WO 2019/060917, WO 2019/199972, WO 2019/005993, WO 2019/005980, WO 2020/005882, WO 2020/005877, WO 2020/005873 and WO 2020/004594, each of which is incorporated herein by reference in its entirety. 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 2018/226622, WO 2019/028440, WO 2019/060917, WO 2019/199972, WO 2019/005993, WO 2019/005980, WO 2020/005882, WO 2020/005877, WO 2020/005873, and WO 2020/004594, each of which is incorporated herein by reference in its entirety.

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

DETAILED DESCRIPTION

Selected Chemical Definitions

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

Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

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

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

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

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

As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 24 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds ("C_2-C_{24} alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C_2-C_{10} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_2-C_8 alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_2-C_6 alkenyl").

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

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

As used herein, the term "haloalkyl," refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one halogen selected from the group consisting of F, Cl, Br, and I. The halogen(s) F, Cl, Br, and I may be placed at any position of the haloalkyl group. Exemplary haloalkyl groups include, but are not limited to: $-CF_3$, $-CCl_3$, $-CH_2-CF_3$, $-CH_2-CCl_3$, $-CH_2-CBr_3$, $-CH_2-CI_3$, $-CH_2-CH_2-CH(CF_3)-CH_3$, $-CH_2-CH_2-CH(Br)-CH_3$, and $-CH_2-CH=CH-CH_2-CF_3$. Each instance of a haloalkyl group may be

independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted haloalkyl") or substituted (a "substituted haloalkyl") with one or more substituents *e.g.,* for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

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

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

"unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_6-C_{14} aryl. In certain embodiments, the aryl group is substituted C_6-C_{14} aryl.

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

Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–

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

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

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

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

Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenyl. Exemplary 4–membered heterocyclyl groups

containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin–2–one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, 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 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.

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 substituent having two oxygen atoms bound to a nitrogen atom, e.g., -NO_2.

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

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

thereof (*e.g.,* degenerate codon substitutions), alleles, orthologs, SNPs, and complementarity sequences as well as the sequence explicitly indicated.

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

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

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

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

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 ^{11}C, ^{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) or (II) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

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

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

Other Definitions

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

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

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

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

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

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

An "effective amount" of a compound of Formula (I) or (II) 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) or (II) 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) or (II) 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) or (II)) 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) or (II)). 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.

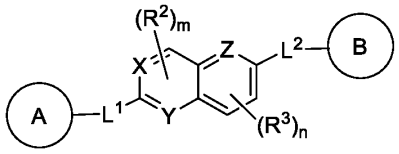
A "proliferative disease" refers to a disease that occurs due to abnormal extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally 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

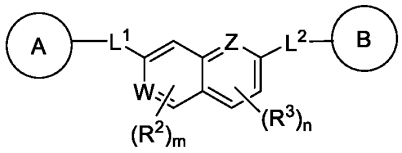
In one aspect, the present disclosure features a compound of Formula (I):



(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^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -$N(R^4)$-, -$N(R^4)C(O)$-, -$C(O)N(R^4)$-, -$N(R^4)C(O)N(R^4)$-, or C_1-C_6-alkylene-$N(R^4)C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 is

independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, $-OR^A$, or $-NR^BR^C$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $-C(O)R^D$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, cycloalkyl, heterocyclyl, or $-OR^A$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 0 or 1; n is 0, 1, or 2; and x is 0, 1, or 2. In an embodiment, when X is CH and Y and Z are each independently N, one of L^1 and L^2 is independently not $N(CH_3)$ or O. In an embodiment, when X is CH and Y and Z are each independently N, L^1 is not $N(CH_3)$ or O. In an embodiment, when X is CH and Y and Z are each independently N, L^2 is not $N(CH_3)$ or O. In an embodiment, when X is CH and Y and Z are each independently N, each of L^1 and L^2 is independently not $N(CH_3)$ or O.

In another aspect, the present invention features a compound of Formula (II):



(II), 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^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -$N(R^4)$-, -$N(R^4)C(O)$-, -$C(O)N(R^4)$-, -$N(R^4)C(O)N(R^4)$-, or C_1-C_6-alkylene-$N(R^4)C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; W and Z are each N or $C(R^6)$, wherein at least one of W and Z is 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–S(O)_xR^D$; each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, $–OR^A$, or $–NR^BR^C$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $–OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^8; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, 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, $-OR^A$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

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

In some embodiments, for each of Formula (I) and (II), A and B are independently a monocyclic ring, e.g., monocyclic cycloalkyl, monocyclic heterocyclyl, monocyclic aryl, or monocyclic heteroaryl. The monocyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a monocyclic ring comprising between 3 and 10 ring atoms (e.g., 3, 4, 5, 6, 7, 8, 9, or 10 ring atoms). In some embodiments, A is a 4-membered monocyclic ring. In some embodiments, B is a 4-membered monocyclic ring. In some embodiments, A is a 5-membered monocyclic ring. In some embodiments, B is a 5-membered monocyclic ring. In some embodiments, A is a 6-membered monocyclic ring. In some embodiments, B is a 6-membered monocyclic ring. In some embodiments, A is a 7-membered monocyclic ring. In some embodiments, B is a 7-membered monocyclic ring. In some embodiments, A is an 8-membered monocyclic ring. In some embodiments, B is an 8-membered monocyclic ring. In some embodiments, A or B are independently a monocyclic ring optionally substituted with one or more R^1.

In some embodiments, A and B are independently a bicyclic ring, e.g., bicyclic cycloalkyl, bicyclic heterocyclyl, bicyclic aryl, or bicyclic heteroaryl. The bicyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a bicyclic ring comprising a fused, bridged, or spiro ring system. In some embodiments, A or B are independently a bicyclic ring comprising between 4 and 18 ring atoms

(e.g., 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 ring atoms). In some embodiments, A is a 6-membered bicyclic ring. In some embodiments, B is a 6-membered bicyclic ring. In some embodiments, A is a 7-membered bicyclic ring. In some embodiments, B is a 7-membered bicyclic ring. In some embodiments, A is an 8-membered bicyclic ring. In some embodiments, B is an 8-membered bicyclic ring. In some embodiments, A is a 9-membered bicyclic ring. In some embodiments, B is a 9-membered bicyclic ring. In some embodiments, A is a 10-membered bicyclic ring. In some embodiments, B is a 10-membered bicyclic ring. In some embodiments, A is an 11-membered bicyclic ring. In some embodiments, B is an 11-membered bicyclic ring. In some embodiments, A is a 12-membered bicyclic ring. In some embodiments, B is a 12-membered bicyclic ring. In some embodiments, A or B are independently a bicyclic ring optionally substituted with one or more R^1.

In some embodiments, A and B are independently a tricyclic ring, e.g., tricyclic cycloalkyl, tricyclic heterocyclyl, tricyclic aryl, or tricyclic heteroaryl. The tricyclic ring may be saturated, partially unsaturated, or fully unsaturated (e.g., aromatic). In some embodiments, A or B are independently a tricyclic ring that comprises a fused, bridged, or spiro ring system, or a combination thereof. In some embodiments, A or B are independently a tricyclic ring comprising between 6 and 24 ring atoms (e.g., 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 ring atoms). In some embodiments, A is an 8-membered tricyclic ring. In some embodiments, B is an 8-membered tricyclic ring. In some embodiments, A is a 9-membered tricyclic ring. In some embodiments, B is a 9-membered tricyclic ring. In some embodiments, A is a 10-membered tricyclic ring. In some embodiments, B is a 10-membered tricyclic ring. In some embodiments, A or B are independently a tricyclic ring optionally substituted with one or more R^1.

In some embodiments, A and 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.

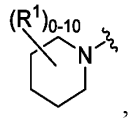
In some embodiments, A and B are independently a nitrogen-containing heterocyclyl, e.g., heterocyclyl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heterocyclyl may be at any position of the ring. In some embodiments, the nitrogen-containing heterocyclyl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

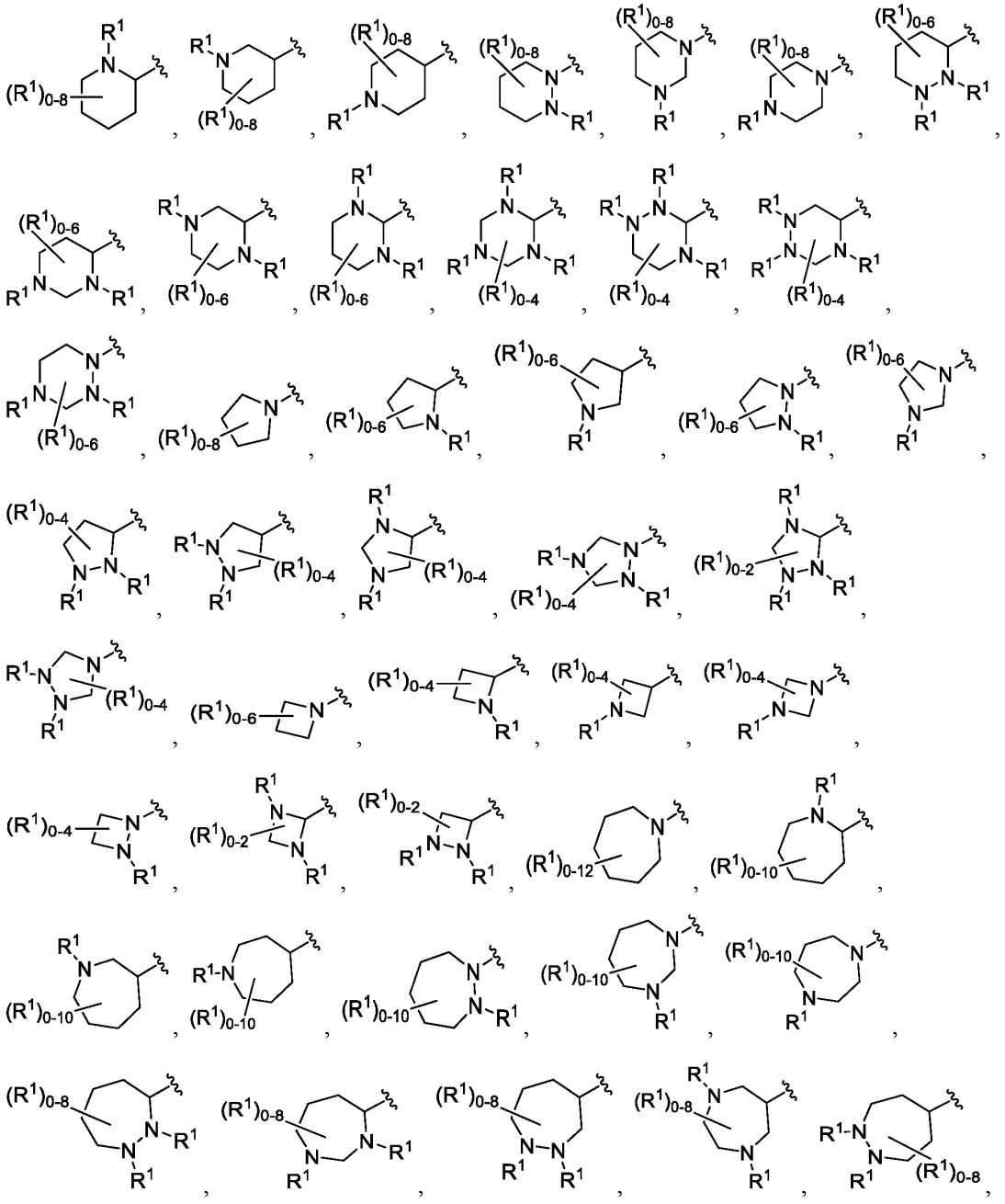
In some embodiments, A and B are independently a nitrogen-containing heteroaryl, e.g., heteroaryl comprising one or more nitrogen atom. The one or more nitrogen atom of the nitrogen-containing heteroaryl may be at any position of the ring. In some embodiments, the nitrogen-containing heteroaryl is monocyclic,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

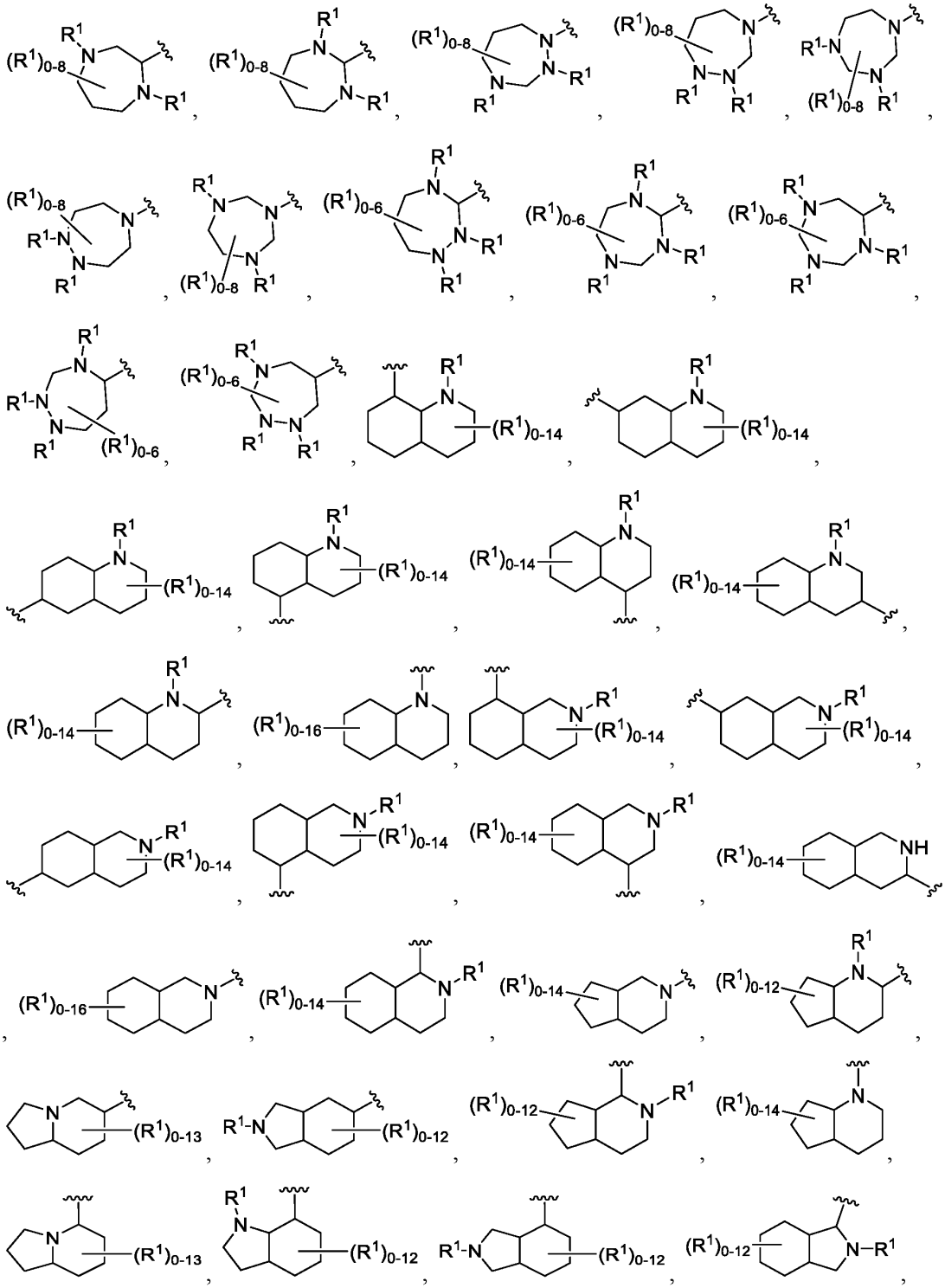
boron, silicon, or phosphorus. In some embodiments, the one or more nitrogen of the nitrogen-containing heteroaryl is substituted, e.g., with R^1.

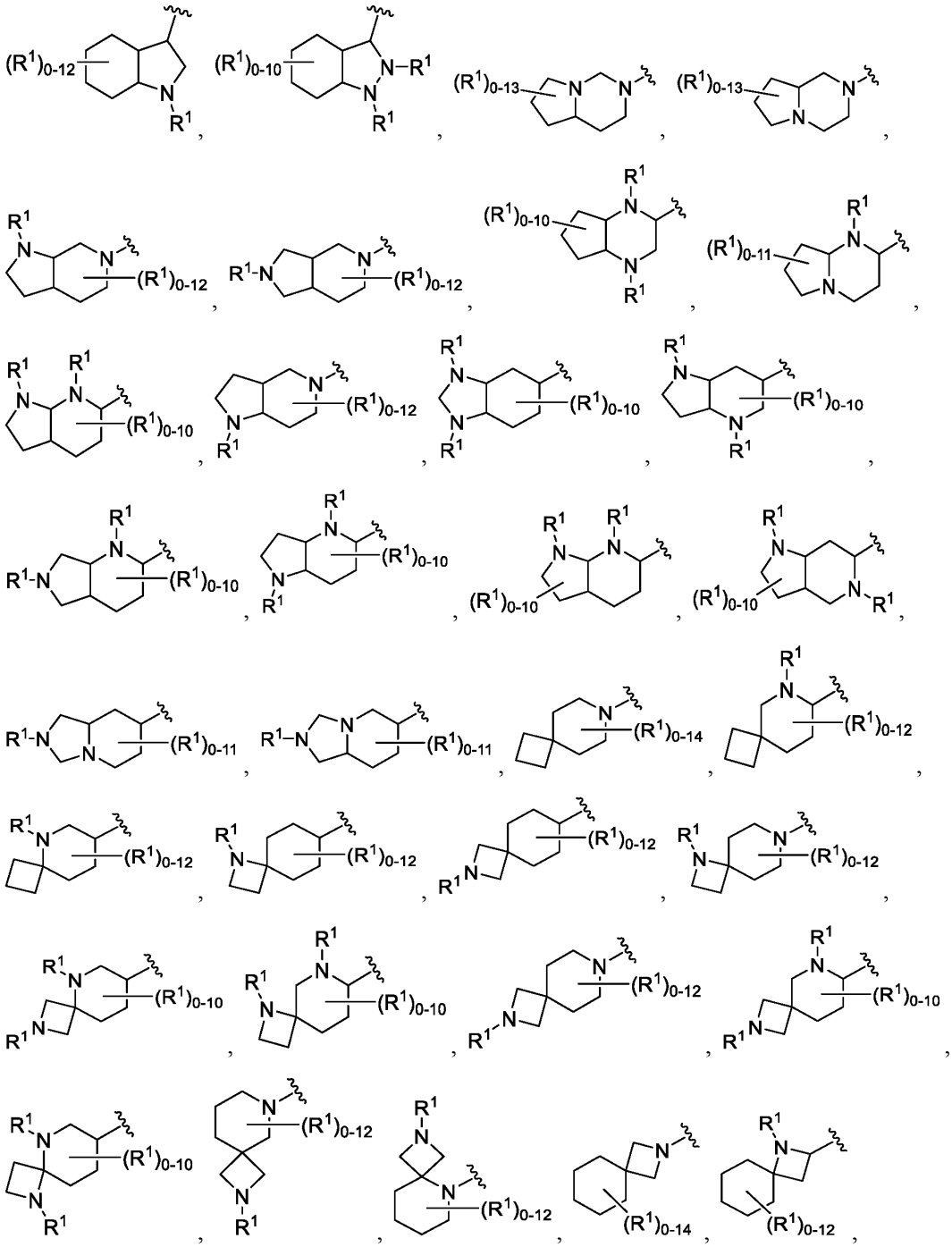
In some embodiments, A is a 6-membered nitrogen-containing heterocyclyl, e.g., a 6-membered heterocyclyl comprising one or more nitrogen. In some embodiments, A is a 6-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, A is a 6-membered heterocyclyl comprising 2 nitrogen atoms. In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

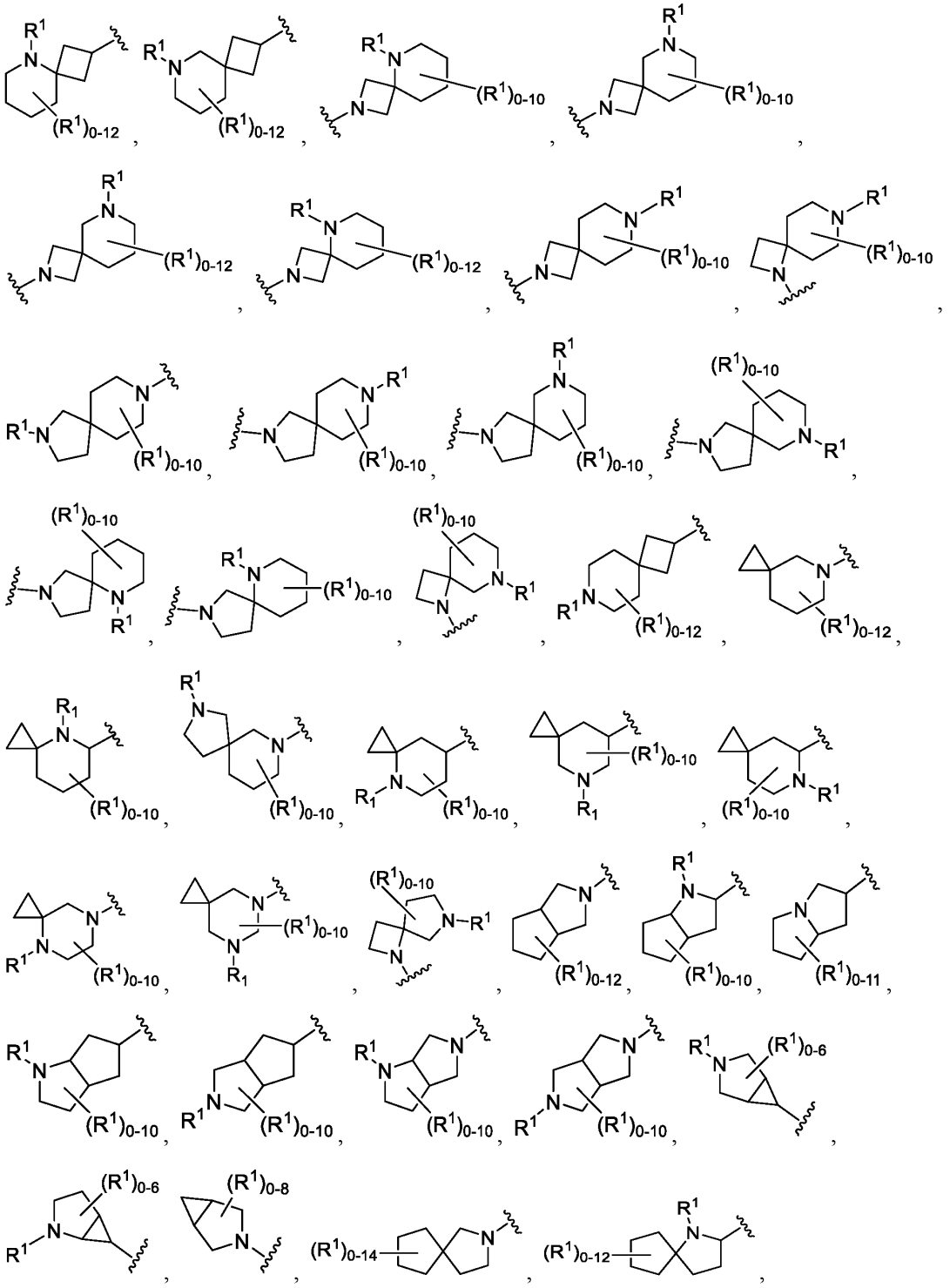
In some embodiments, B is a 5-membered nitrogen-containing heterocyclyl or heteroaryl, e.g., a 5-membered heterocyclyl or heteroaryl comprising one or more nitrogen. In some embodiments, B is a 5-membered heterocyclyl comprising 1 nitrogen atom. In some embodiments, B is a 5-membered heteroaryl comprising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

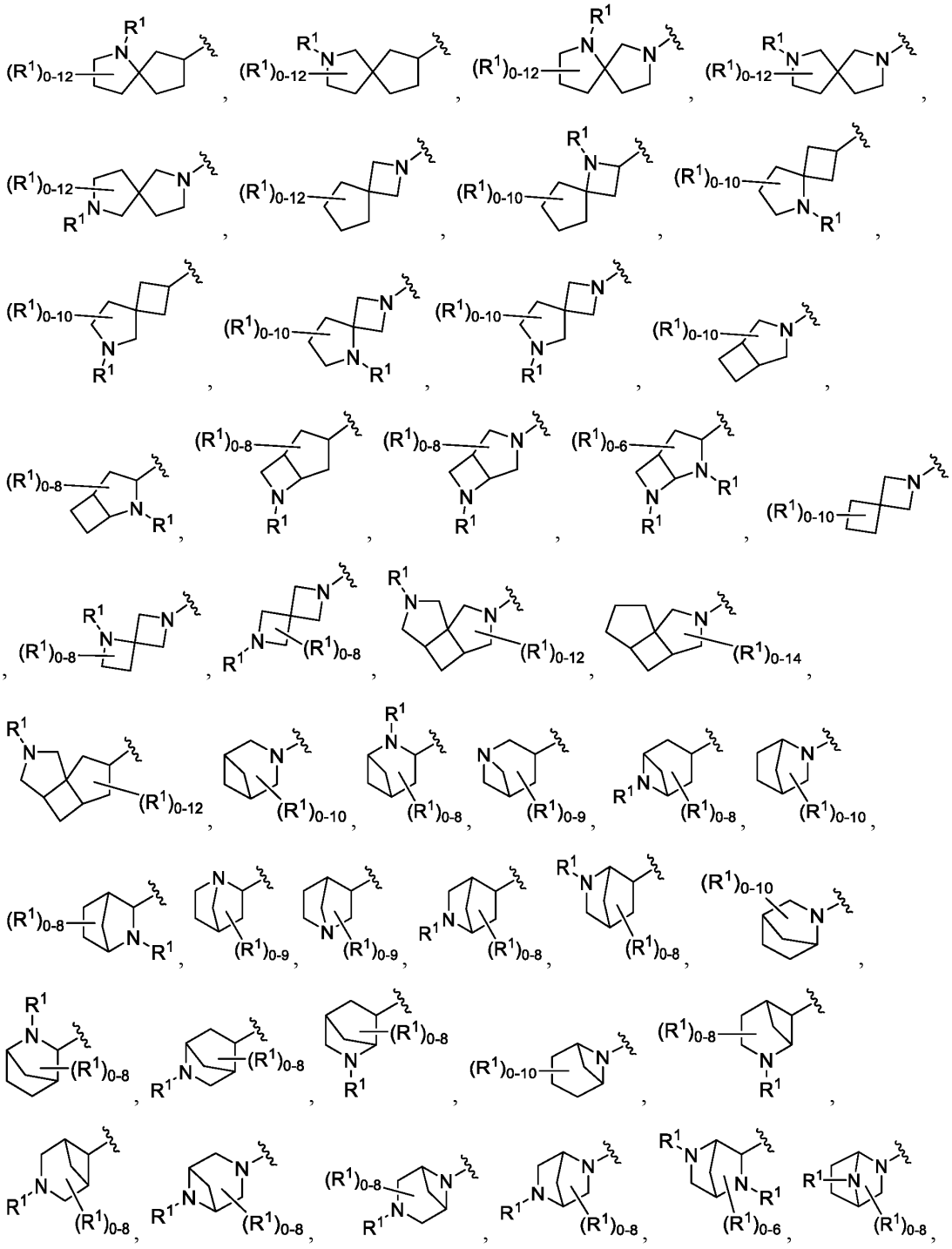
In some embodiments, each of A and B are independently selected from: ,

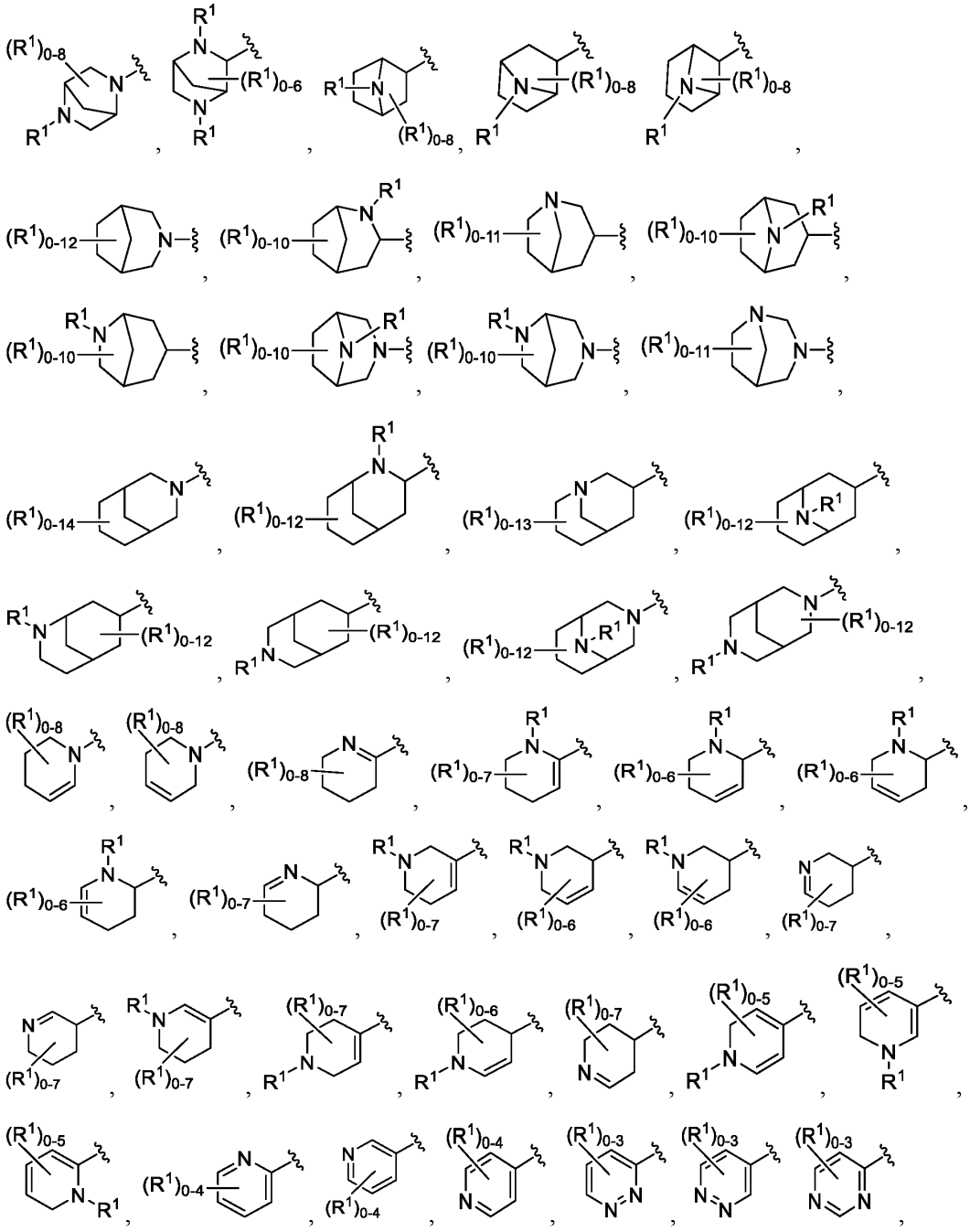


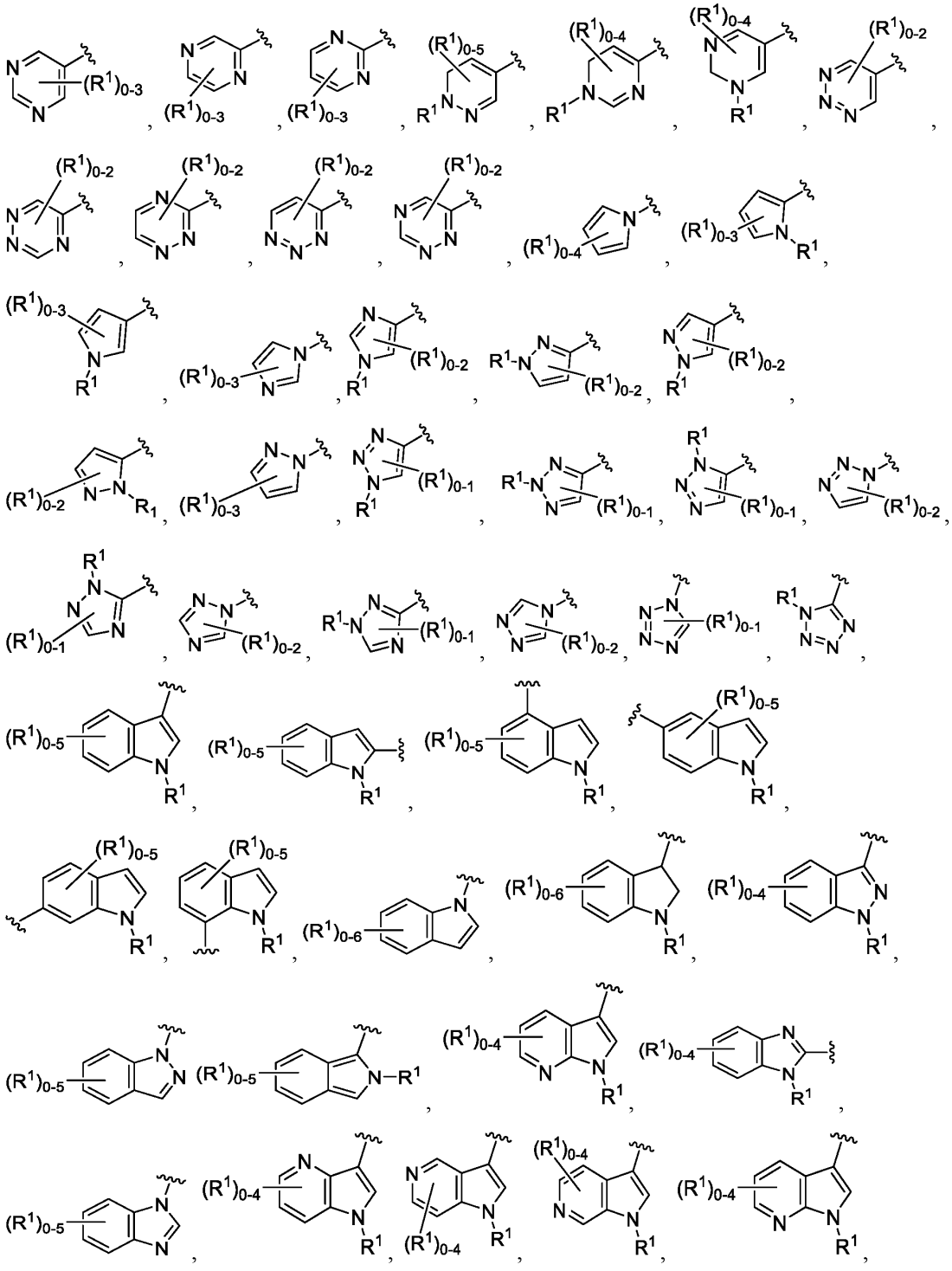


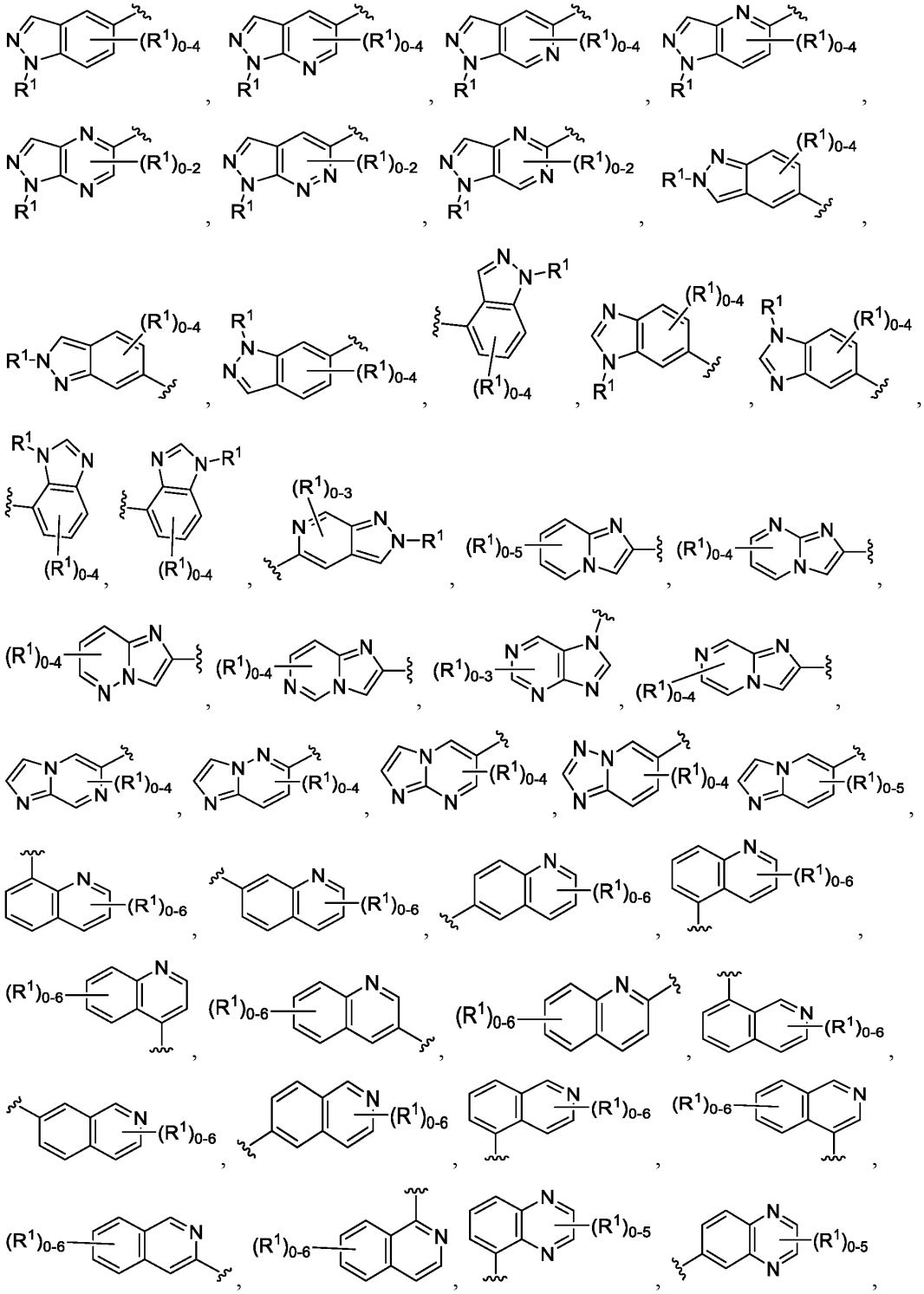


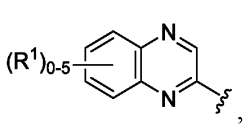
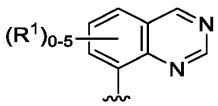
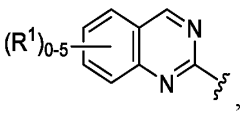
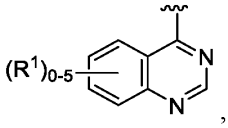
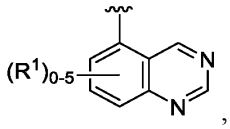
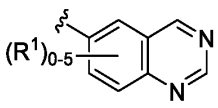
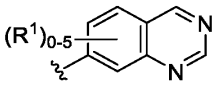
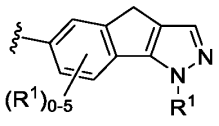


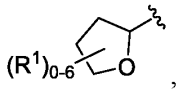


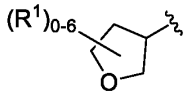
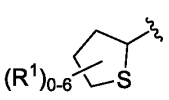
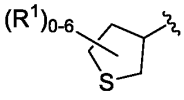
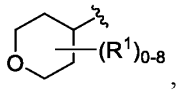
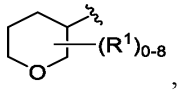
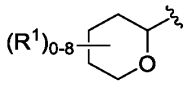
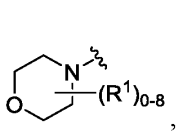
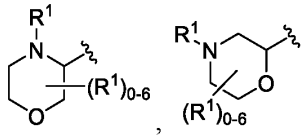
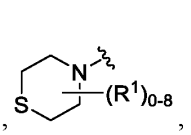
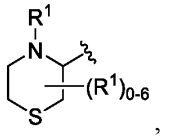
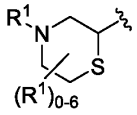
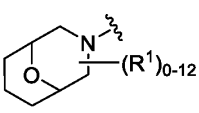
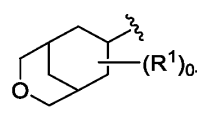
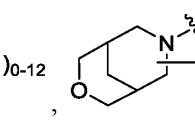


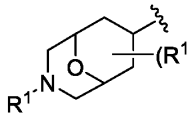
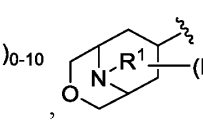
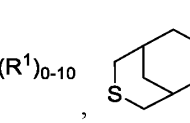
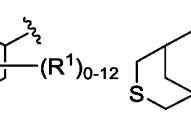
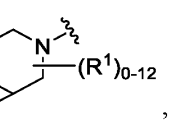


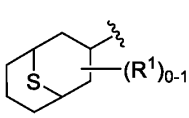
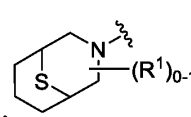
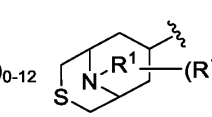
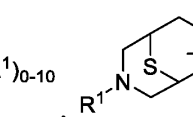
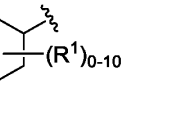
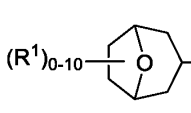
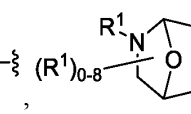
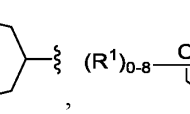
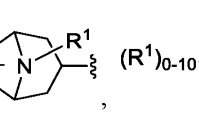
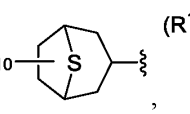


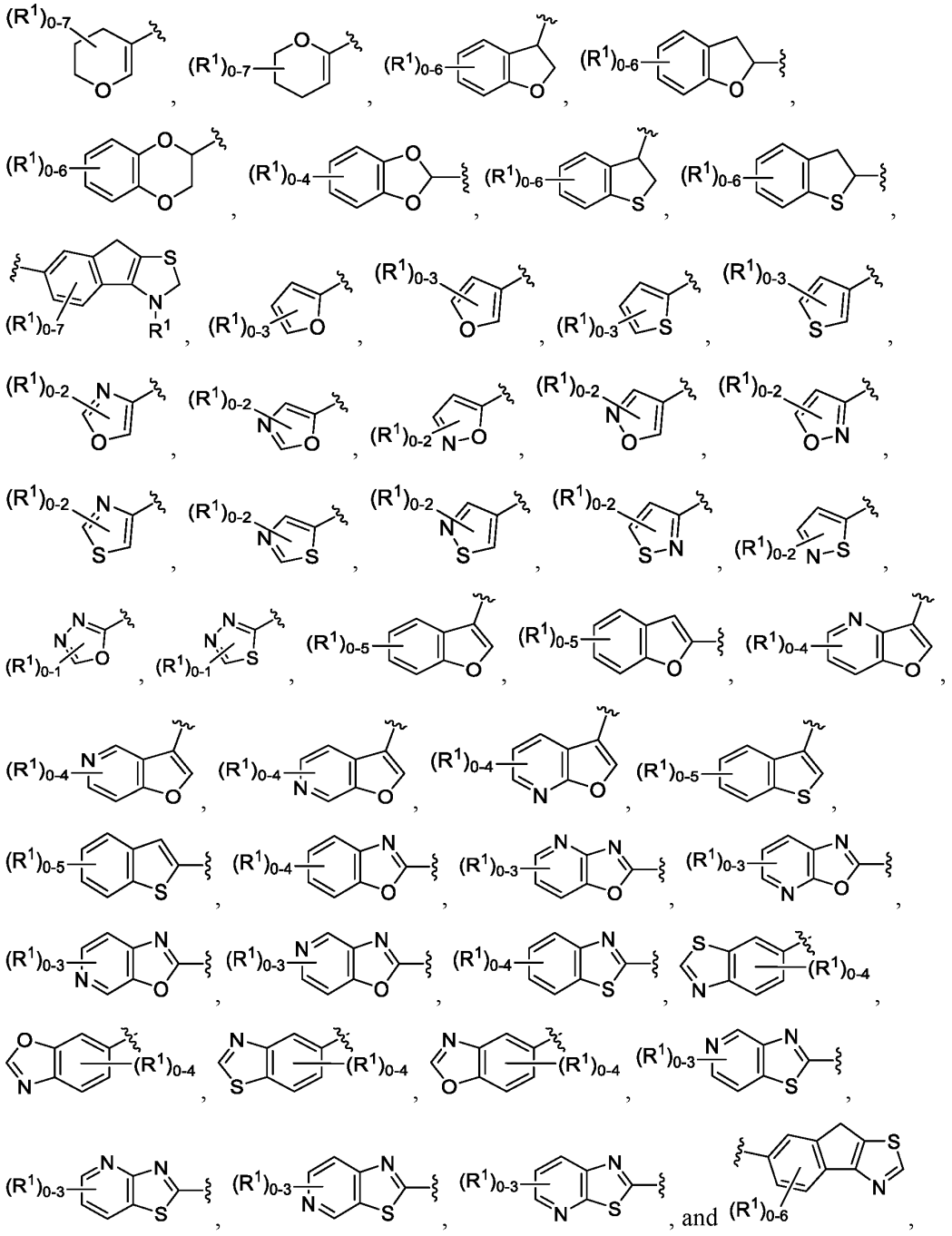







, and  wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described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

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

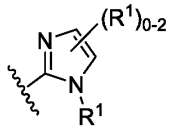
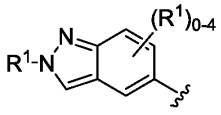
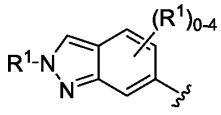
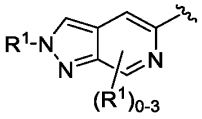
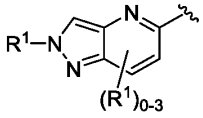
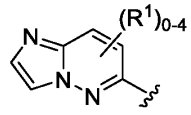
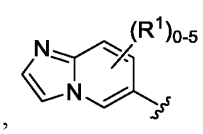
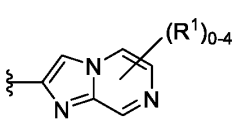
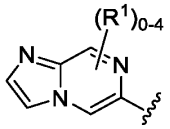
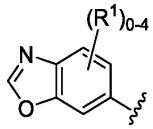
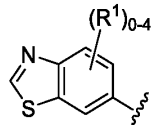
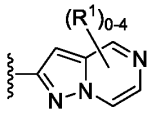
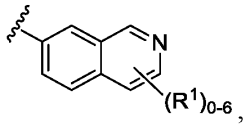
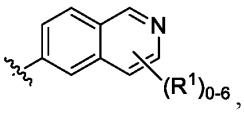
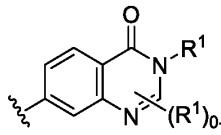
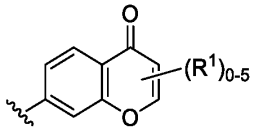
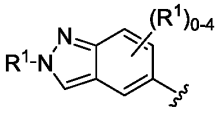
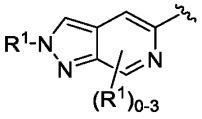
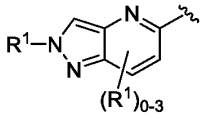
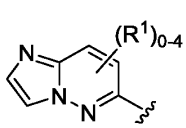
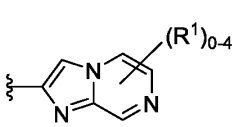
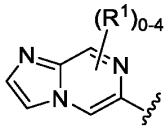
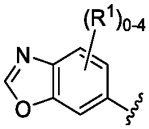
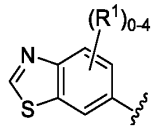






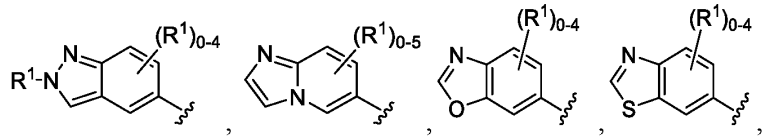











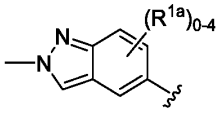
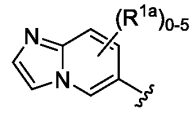
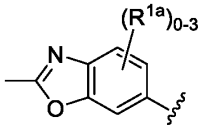
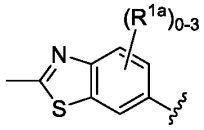
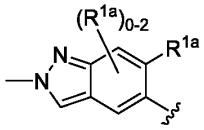
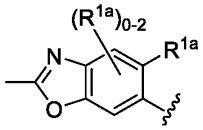


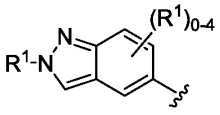
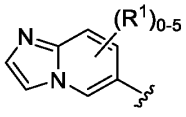
wherein each R^1 is as defined herein. In an embodiment, A and B are each independently a saturated, partially saturated, or unsaturated (e.g., aromatic) derivative of one of the rings

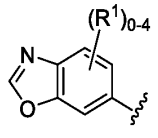
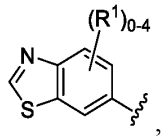
described above. In an embodiment, A and B are each independently a stereoisomer of one of the rings described above.

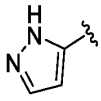
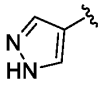
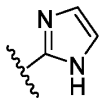
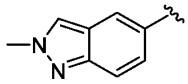
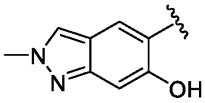
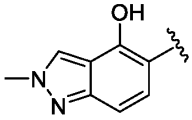
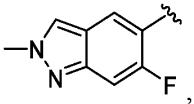
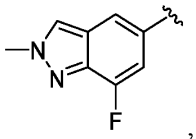
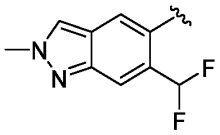
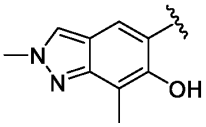
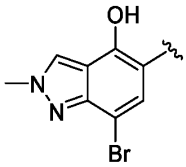
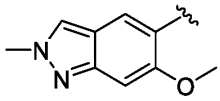
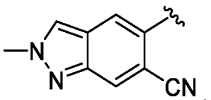
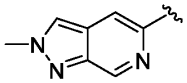
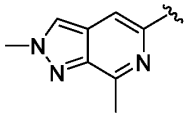
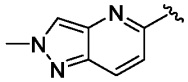
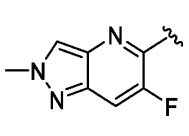
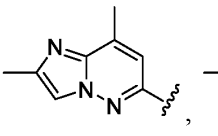
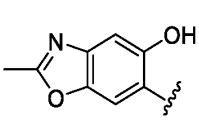
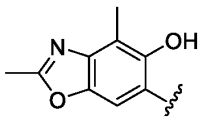
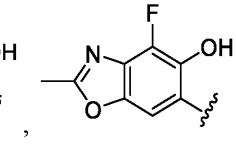
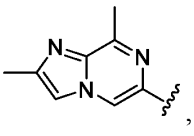
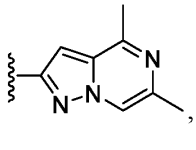
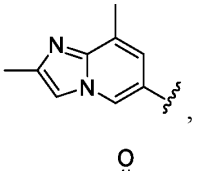
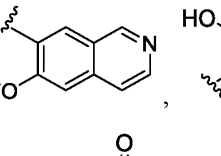
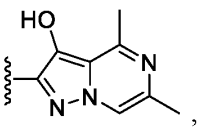
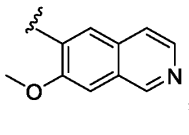
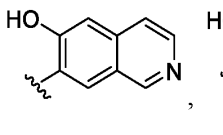
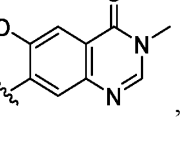
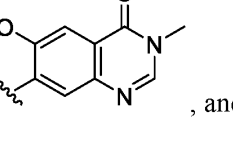
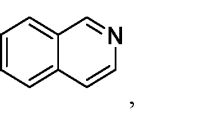
In some embodiments, one of A and B is independently a monocyclic heteroaryl or bicyclic heteroaryl, each of which is optionally substituted with one or more R^1. In some embodiments, one of A and B is independently a bicyclic heteroaryl optionally substituted with one or more R^1. In some embodiments, one of A and B is independently a nitrogen-containing heteroaryl optionally substituted with one or more R^1. In some embodiments, one of A and B is independently a 5-10 membered heteroaryl optionally substituted with one or more R^1. In some embodiments, one of A and B is independently selected from , , , , , , , , , , , , , , , and , wherein R^1 is as described herein. In some embodiments, one of A and B is independently selected from , , , , , , , and , wherein R^1 is as described herein. In some embodiments, one of A and B is independently

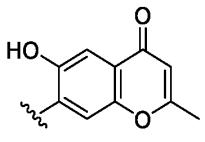
selected from , wherein R^1 is as described herein.

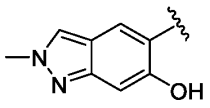
In some embodiments, one of A and B is independently selected from , ,  and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, one of A and B is independently selected from  and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, at least one of R^{1a} is C_1-C_6-alkyl, halo, or $-OR^A$. In some embodiments, R^{1a} is $-OR^A$ and R^A is H.

In some embodiments, one of A or B is , wherein R^1 is as described herein. In some embodiments, one of A or B is , wherein R^1 is as described

herein. In some embodiments, one of A or B is , wherein R^1 is as described herein. In some embodiments, one of A or B is , wherein R^1 is as described herein.

In some embodiments, one of A and B is independently selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and


. In some embodiments, one of A and B is independently selected from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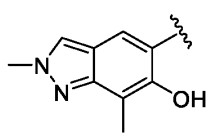
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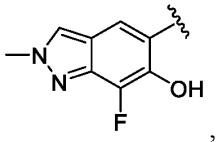
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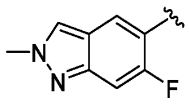
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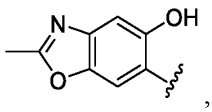
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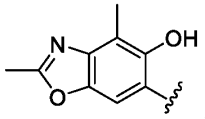
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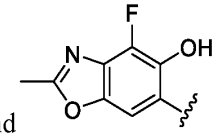
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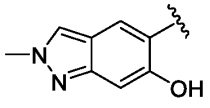
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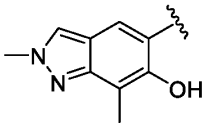
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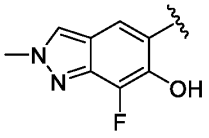
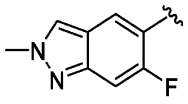

. In some embodiments, one of A or B is

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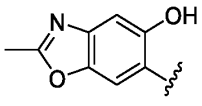
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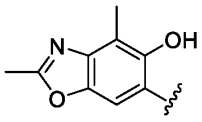
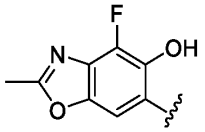
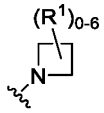
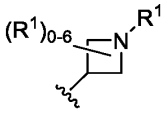
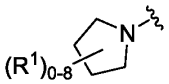
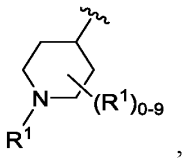
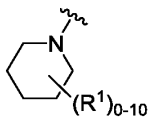
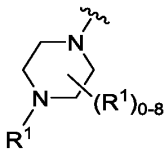
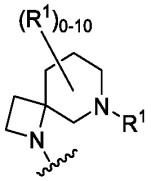
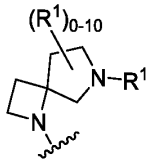
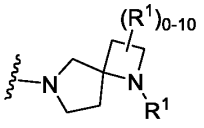
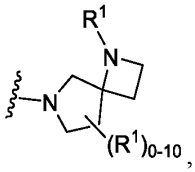
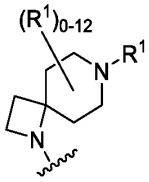
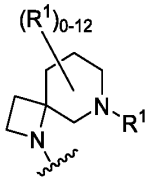
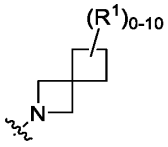
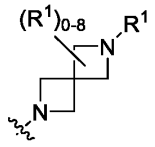
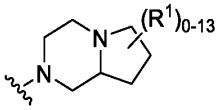
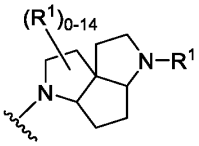
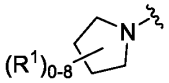
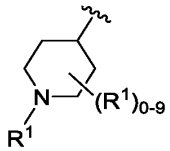
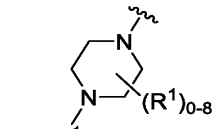
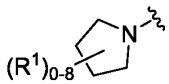
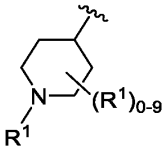
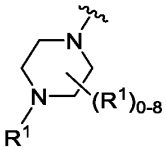
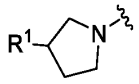
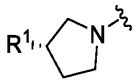
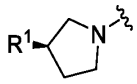
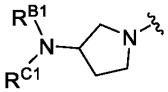

. In some embodiments, one of A or B is

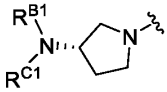
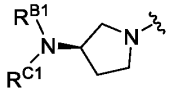

.

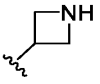
In some embodiments, one of A and B is independently a monocyclic heterocyclyl or bicyclic heterocyclyl, each of which is optionally substituted with one or more R^1. In some embodiments, one of A and B is independently a nitrogen-containing heterocyclyl optionally substituted with one or more R^1. In some embodiments, one of A and B is independently a 4-8 membered heterocyclyl optionally substituted with one or more R^1. In some embodiments, one

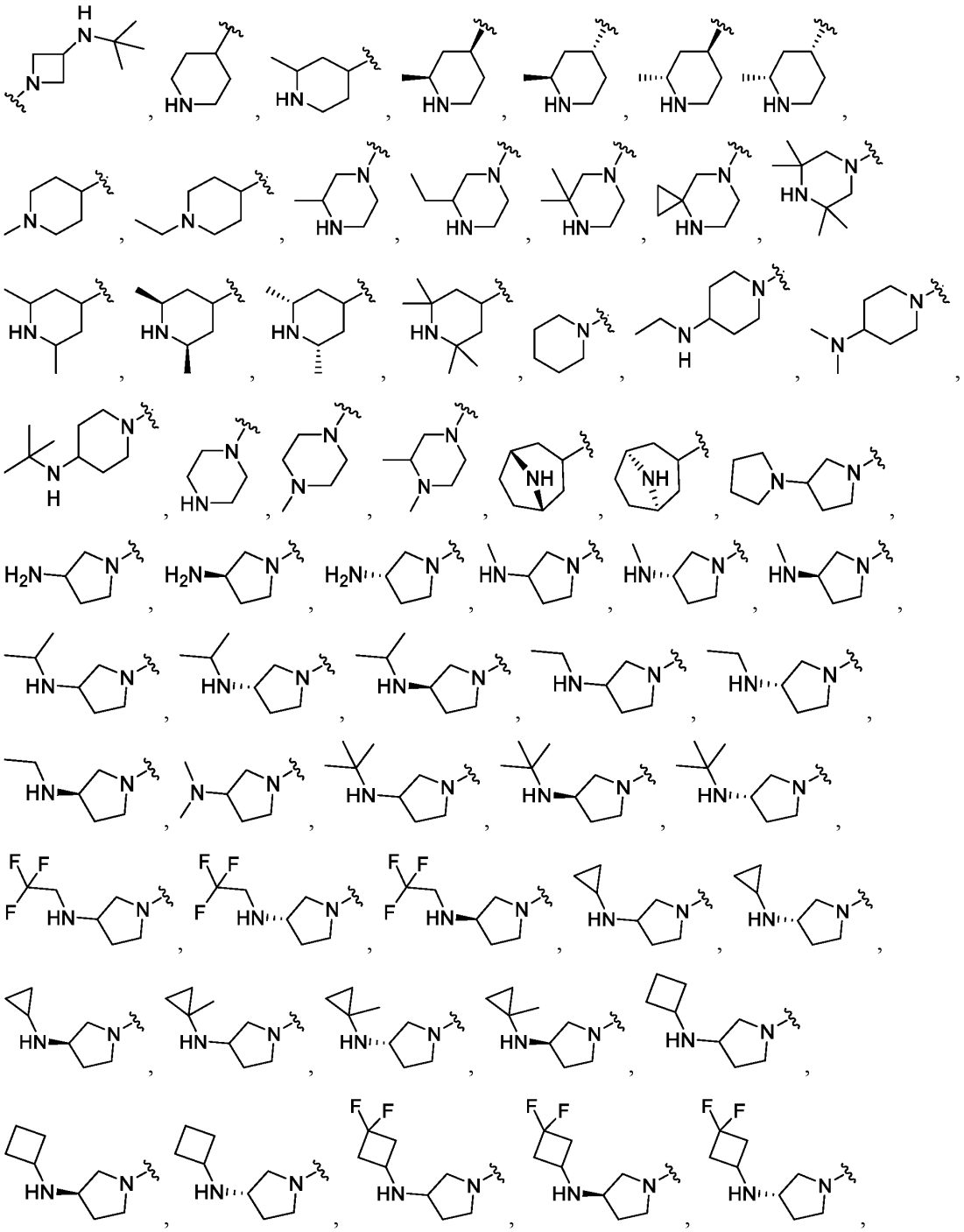
of A and B is independently selected from , , , , , , , , , , , , , , , , and wherein R^1 is as described herein. In some embodiments, one of A and B is independently selected from , , and , wherein R^1 is as described herein. In some embodiments, one of A or B is . In some embodiments, one of A or B is . In some embodiments, one of A or B is .

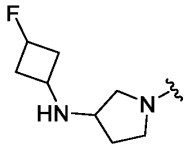
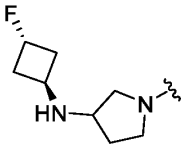
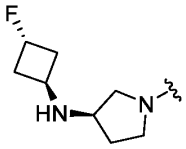
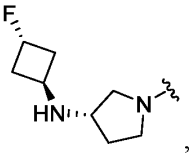
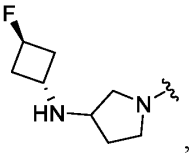
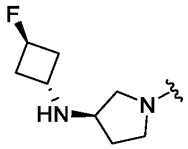
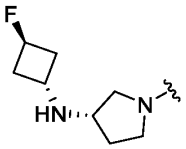
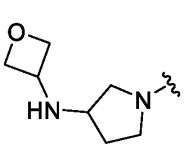
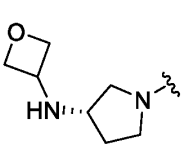
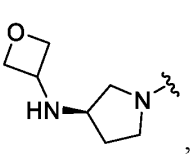
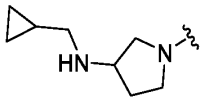
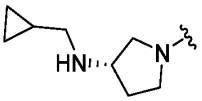
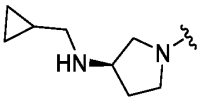
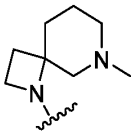
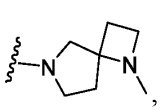
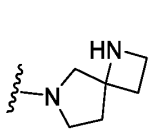
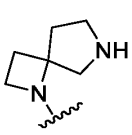
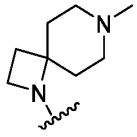
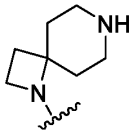
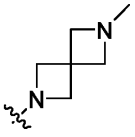
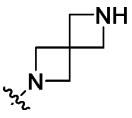
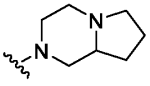
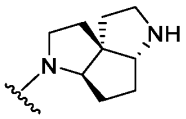
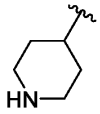
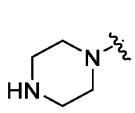
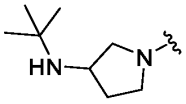
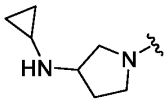
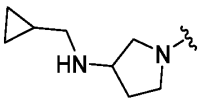
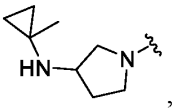
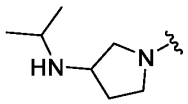
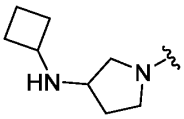
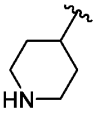
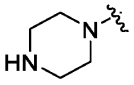
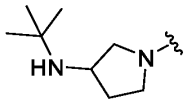
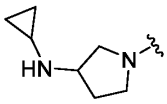
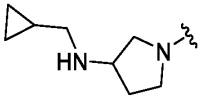
In some embodiments, one of A and B is independently  and R^1 is as described herein. In some embodiments, one of A and B is independently selected from  and , and R^1 is as described herein.

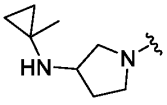
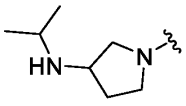
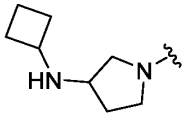
In some embodiments, one of A and B is independently , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

In some embodiments, one of A and B is independently selected from  and , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

In some embodiments, one of A and B is independently is selected from ,

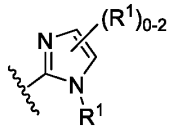
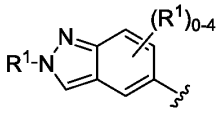
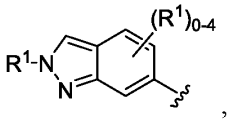
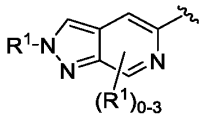
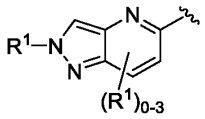
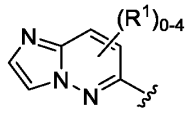
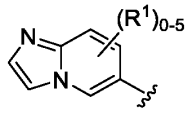
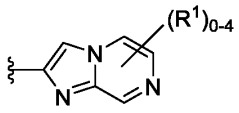
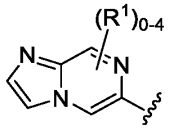
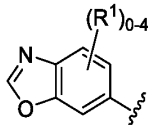
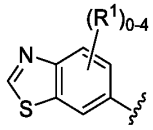
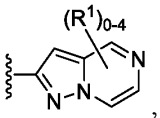
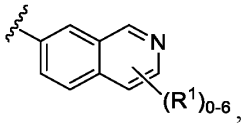
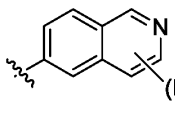
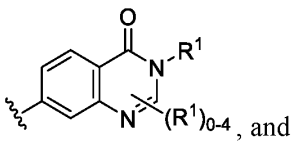
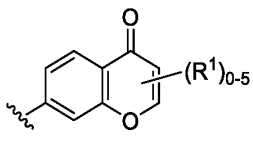


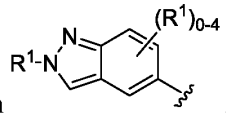






















and . In some embodiments, one of A and B is independently is selected from , , , , , , , and . In some embodiments, one of A or B is . In some embodiments, one of A or B is . In some embodiments, one of A or B is . In some embodiments, one of A or B is . In some embodiments, one of A or B is . In some embodiments, one of A or B is

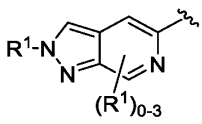
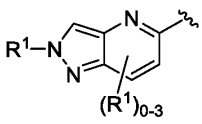
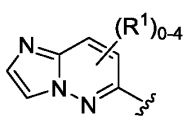
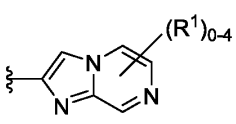
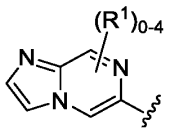

. In some embodiments, one of A or B is 
. In some embodiments, one of A or B is 
.

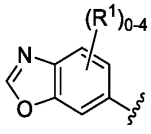
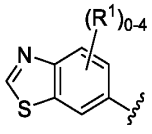
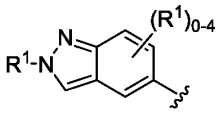
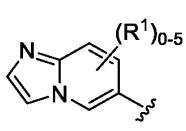
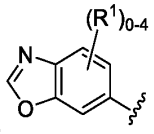
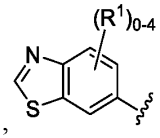
In some embodiments, each of A and B are not independently heteroaryl. In some embodiments, each of A and B are not independently heterocyclyl.

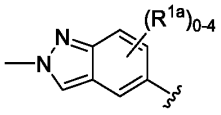
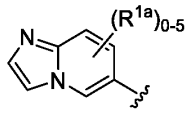
In some embodiments, A is substituted with 0 or 1 R^1. In some embodiments, B is substituted with 0, 1, or 2 R^1. In some embodiments, R^1 is C_1-C_6-alkyl, -OR^A, or halo (e.g., CH_3, OH, or F). In some embodiments, R^1 is CH_3. In some embodiments, R^1 is OH. In some embodiments, R^1 is F.

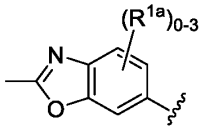
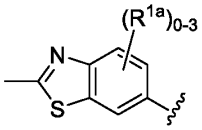
In some embodiments, A is independently a monocyclic heteroaryl or bicyclic heteroaryl, each of which is optionally substituted with one or more R^1. In some embodiments, A is a bicyclic heteroaryl optionally substituted with one or more R^1. In some embodiments, A is a nitrogen-containing heteroaryl optionally substituted with one or more R^1. In some embodiments, A is a 5-10 membered heteroaryl optionally substituted with one or more R^1. In some embodiments, A is selected from 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, and 
, wherein R^1 is as

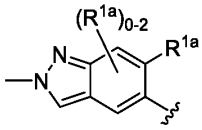
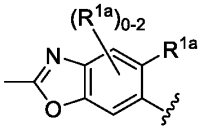
described herein. In some embodiments, A is selected from ,

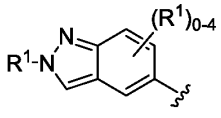
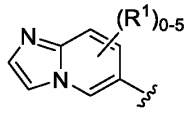
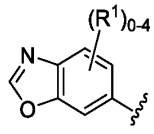
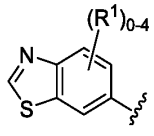
, , , , ,

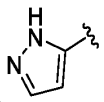
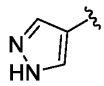
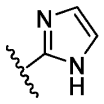
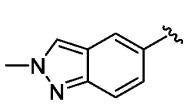
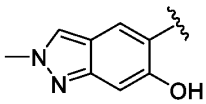
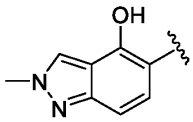
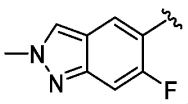
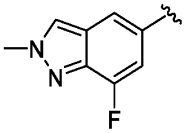
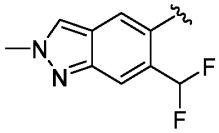
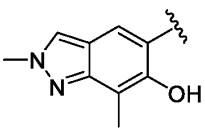
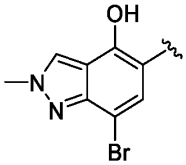
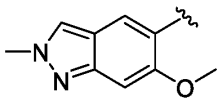
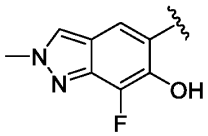
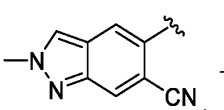
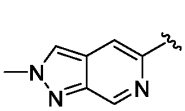
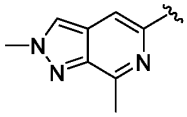
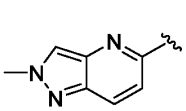
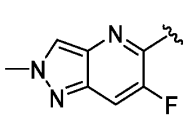
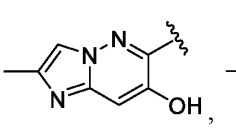
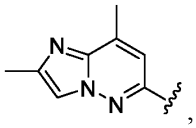
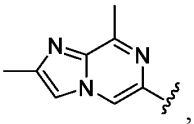
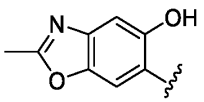
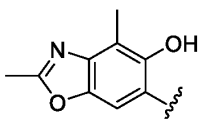
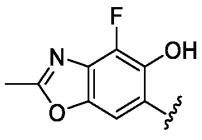
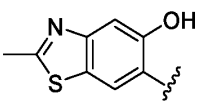
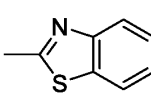
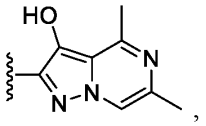
 and , wherein R^1 is as described herein. In some embodiments, A is selected from , , , , wherein R^1 is as described herein.

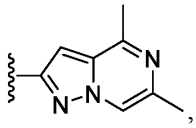
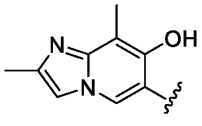
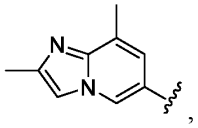
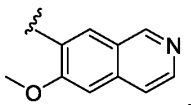
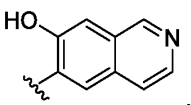
In some embodiments, A is selected from , ,

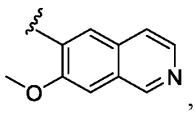
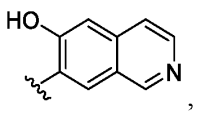
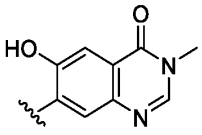
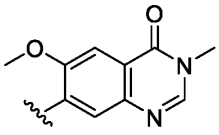
 and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, A is selected from

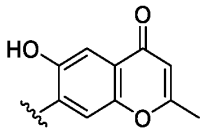
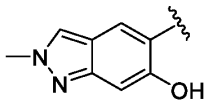
 and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, at least one of R^{1a} is C_1-C_6-alkyl, halo, or $-OR^A$. In some embodiments, R^{1a} is $-OR^A$ and R^A is H.

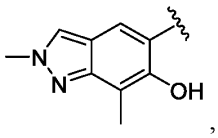
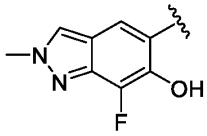
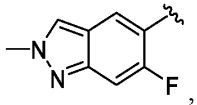
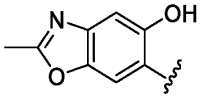
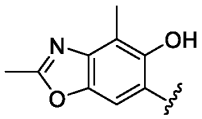
In some embodiments, A is , wherein R^1 is as described herein. In some embodiments, A is , wherein R^1 is as described herein. In some embodiments, A is , wherein R^1 is as described herein. In some embodiments, A is , wherein R^1 is as described herein.

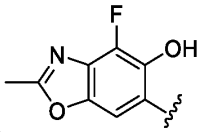
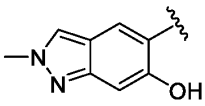
In some embodiments, A is selected from , , , , , , , , , , , , , , , , , , , , , , , , , , .

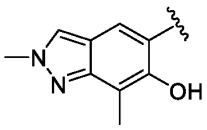
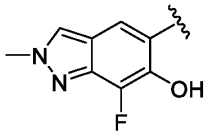
, , , , ,

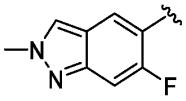
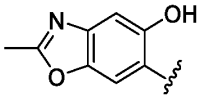
, , , , and

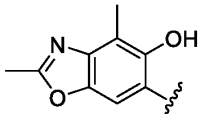
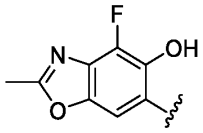
. In some embodiments, A is selected from ,

, , , , ,

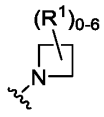
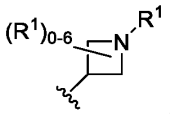
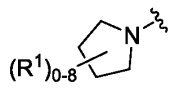
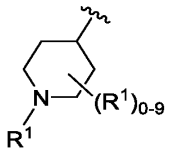
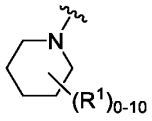
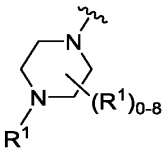
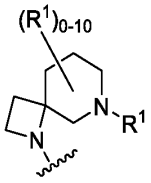
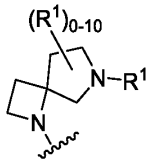
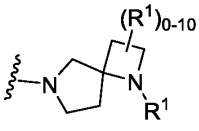
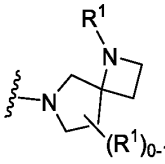
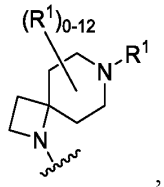
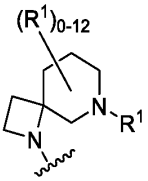
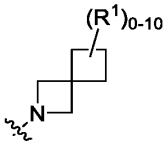
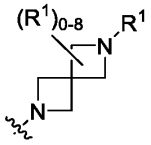
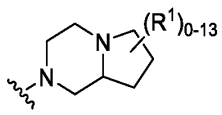
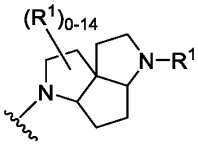
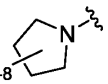
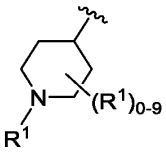
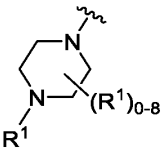
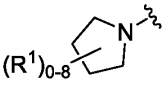
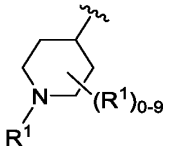
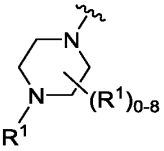
and . In some embodiments, A is . In some embodiments,

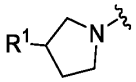
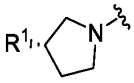
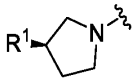
A is .In some embodiments, A is . In some embodiments, A

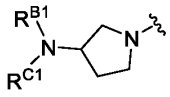
is . In some embodiments, A is . In some embodiments, A is

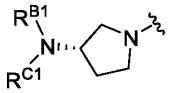
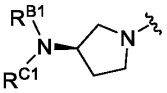
. In some embodiments, A is .

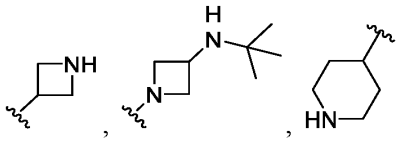
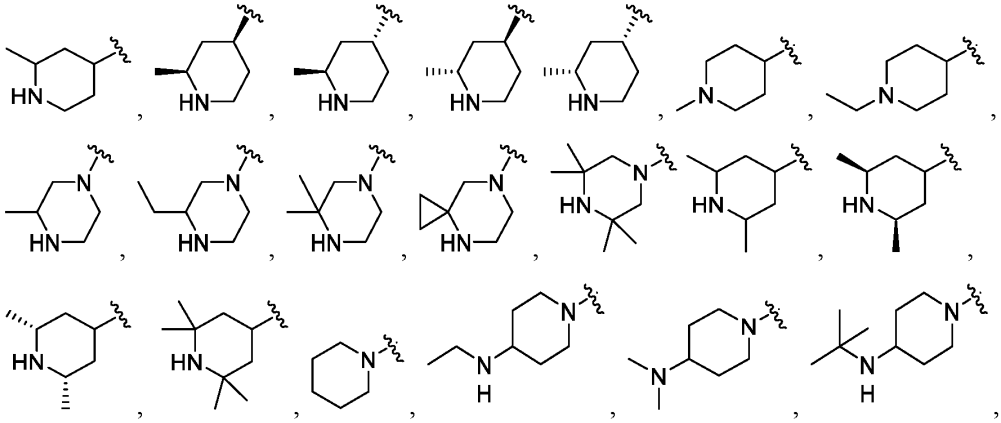
In some embodiments, A is a monocyclic heterocyclyl or bicyclic heterocyclyl, each of which is optionally substituted with one or more R^1. In some embodiments, A is a nitrogen-containing heterocyclyl optionally substituted with one or more R^1. In some embodiments, A is a 4-8 membered heterocyclyl optionally substituted with one or more R^1. In some embodiments,

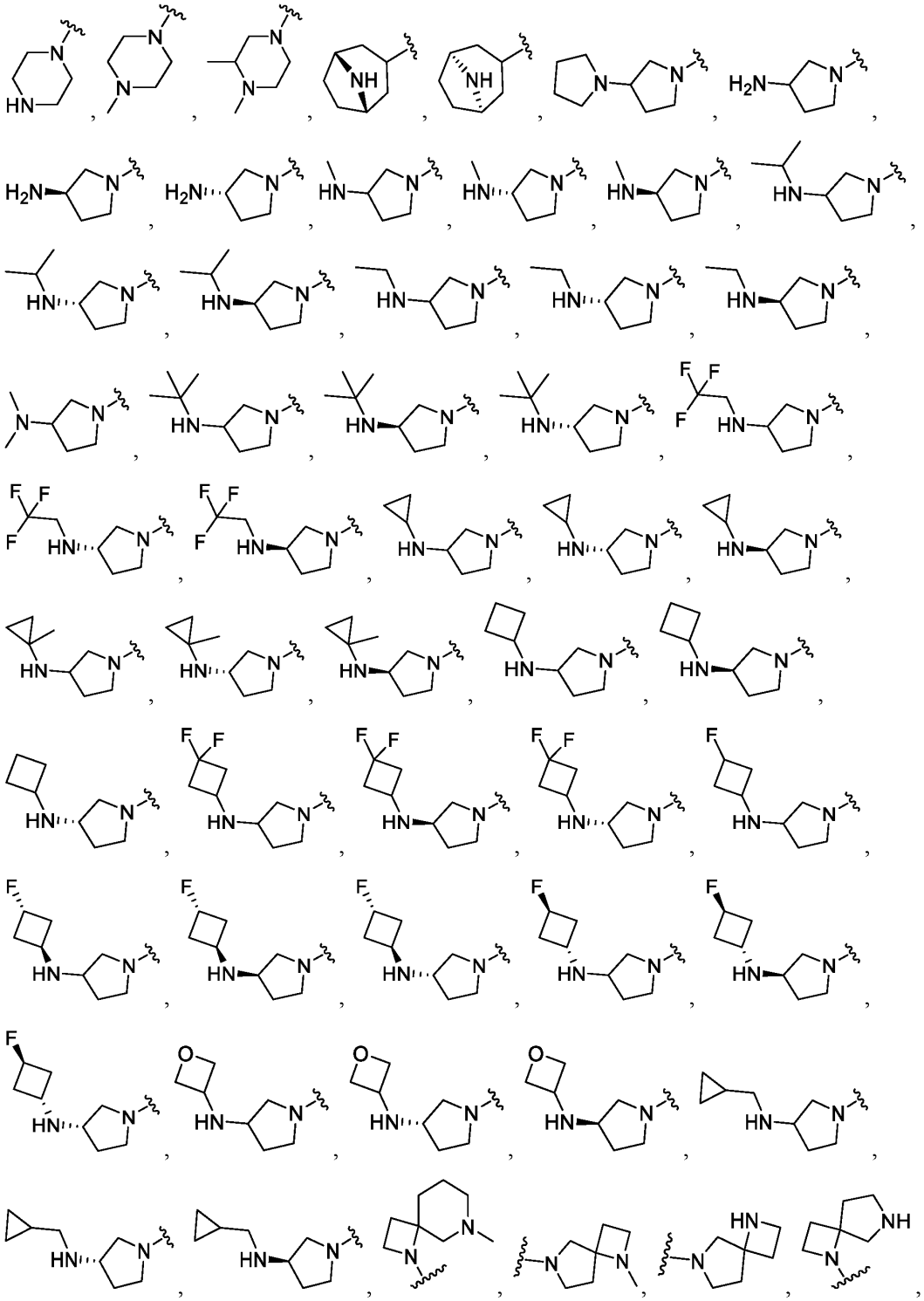
A is selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described herein. In some embodiments, A is selected from , , and , wherein R^1 is as described herein. In some embodiments, A is . In some embodiments, one of A or B is . In some embodiments, A is .

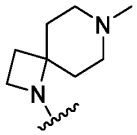
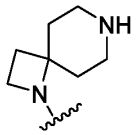
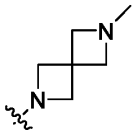
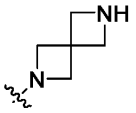
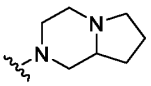
In some embodiments, A is  and R^1 is as described herein. In some embodiments, A is selected from  and , and R^1 is as described herein.

In some embodiments, A is , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

In some embodiments, A is selected from  and , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

In some embodiments, A is selected from , 

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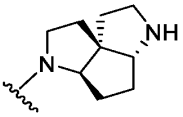
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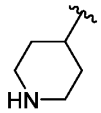
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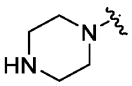
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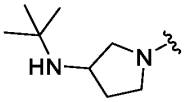
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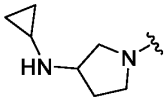
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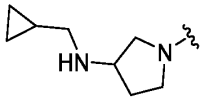
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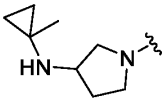
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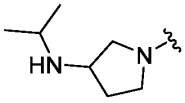
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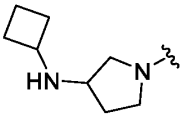
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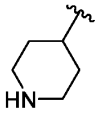
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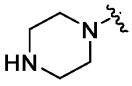
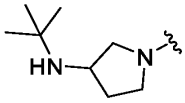

. In some embodiments, A is

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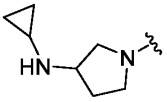
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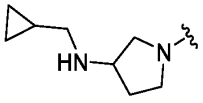
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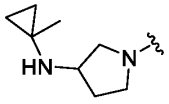
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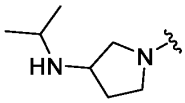
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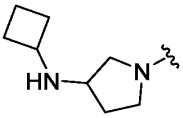
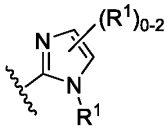

.

In some embodiments, A is not heteroaryl. In some embodiments, A is not heterocyclyl.

In some embodiments, B is a monocyclic heteroaryl or bicyclic heteroaryl, each of which is optionally substituted with one or more R^1. In some embodiments, B is a bicyclic heteroaryl optionally substituted with one or more R^1. In some embodiments, B is a nitrogen-containing heteroaryl optionally substituted with one or more R^1. In some embodiments, B is a 5-10 membered heteroaryl optionally substituted with one or more R^1. In some embodiments, B is selected from

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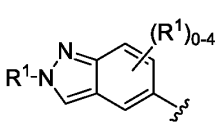
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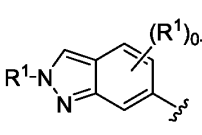
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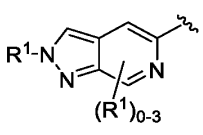
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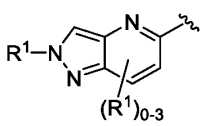
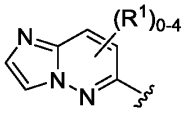
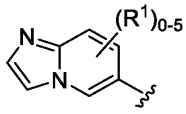
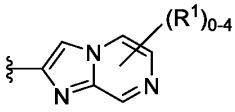
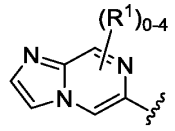
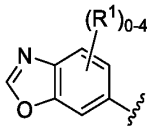
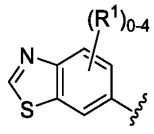
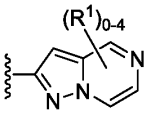
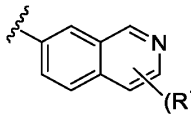
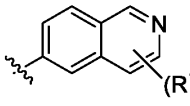
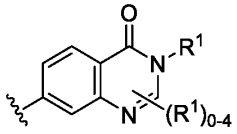
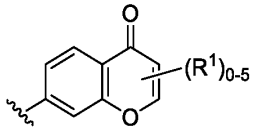
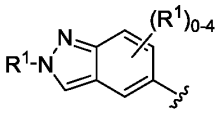
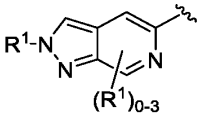
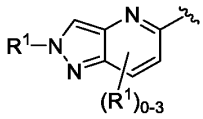
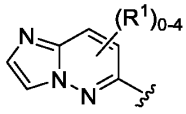
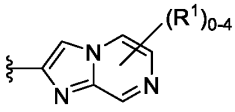
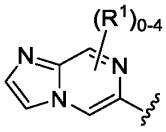
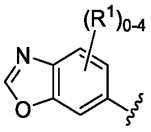
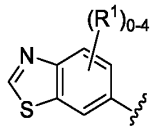
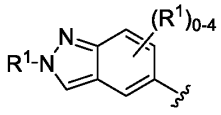
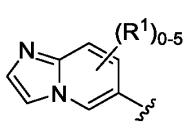
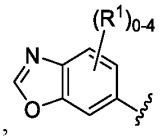
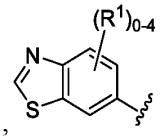
, , , , ,

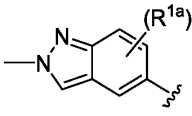
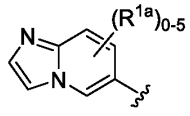
, , , , ,

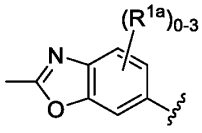
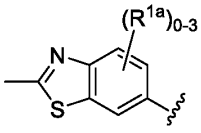
, and , wherein R^1 is as described herein. In some embodiments, B is selected from , , ,

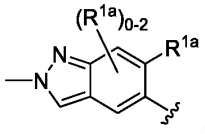
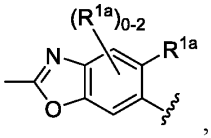
, , , , and ,

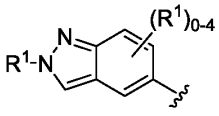
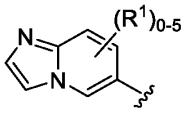
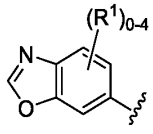
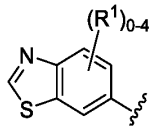
wherein R^1 is as described herein. In some embodiments, B is selected from ,

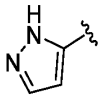
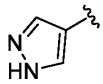
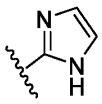
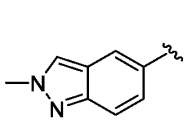
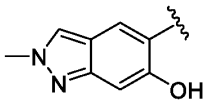
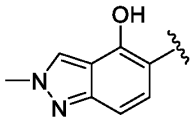
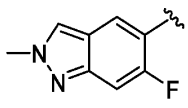
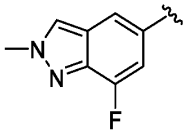
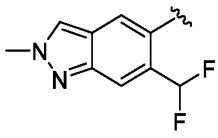
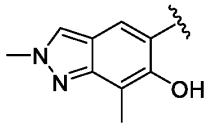
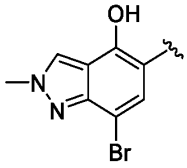
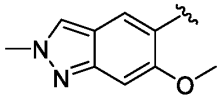
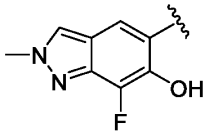
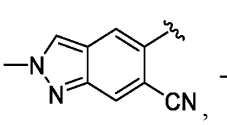
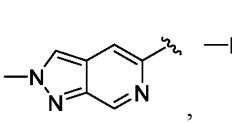
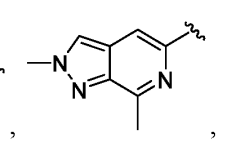
, , , wherein R^1 is as described herein.

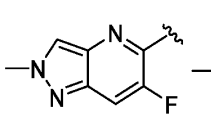
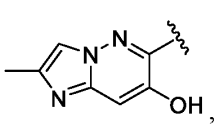
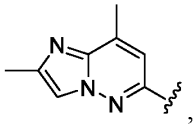
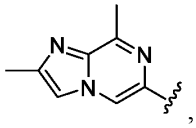
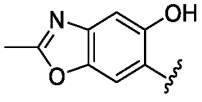
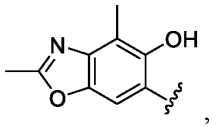
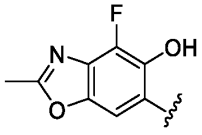
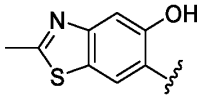
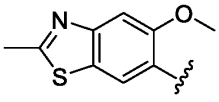
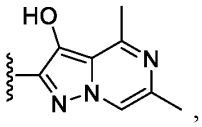
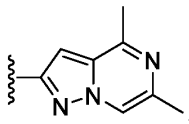
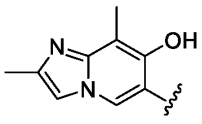
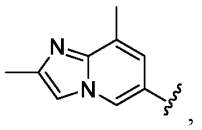
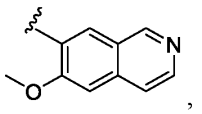
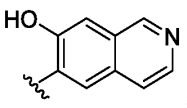
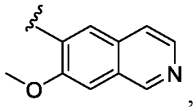
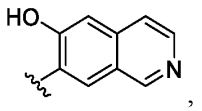
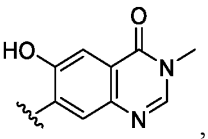
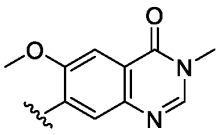
In some embodiments, B is selected from , ,

 and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, B is selected from

 and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7. In some embodiments, at least one of R^{1a} is C_1-C_6-alkyl, halo, or $-OR^A$. In some embodiments, R^{1a} is $-OR^A$ and R^A is H.

In some embodiments, B is , wherein R^1 is as described herein. In some embodiments B is , wherein R^1 is as described herein. In some embodiments, B is , wherein R^1 is as described herein. In some embodiments, B is , wherein R^1 is as described herein.

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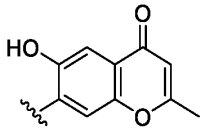
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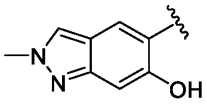
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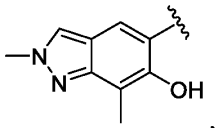
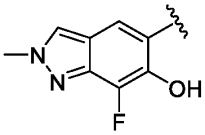
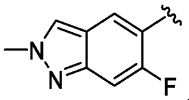
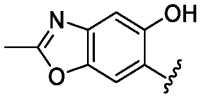
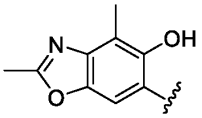
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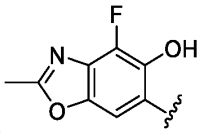
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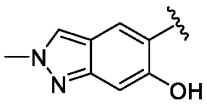
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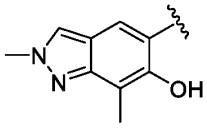
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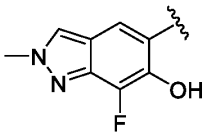
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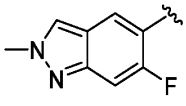
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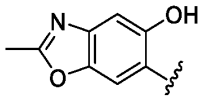
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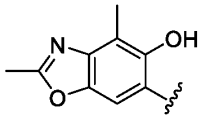
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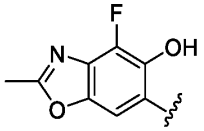
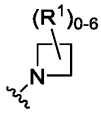
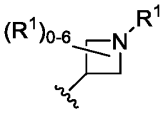
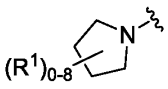
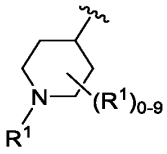
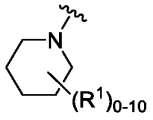
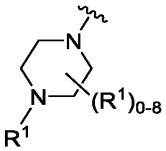
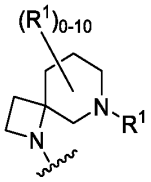
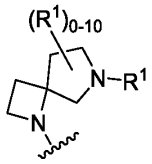
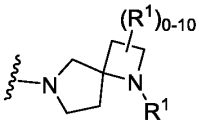
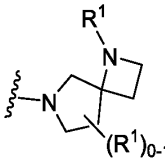
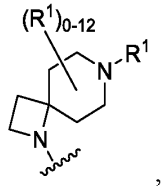
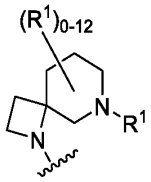
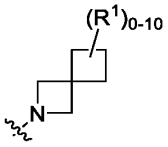
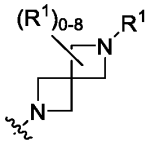
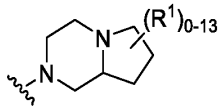
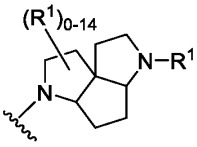
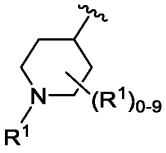
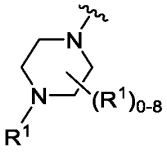
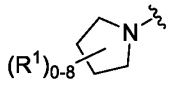
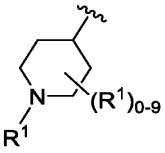
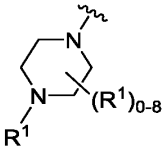
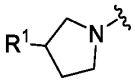
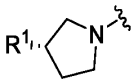
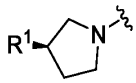
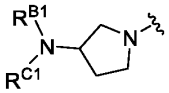
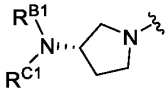
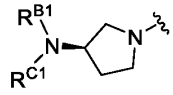
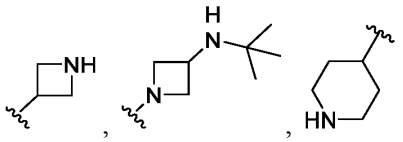
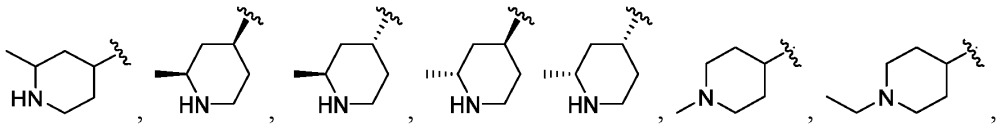

.

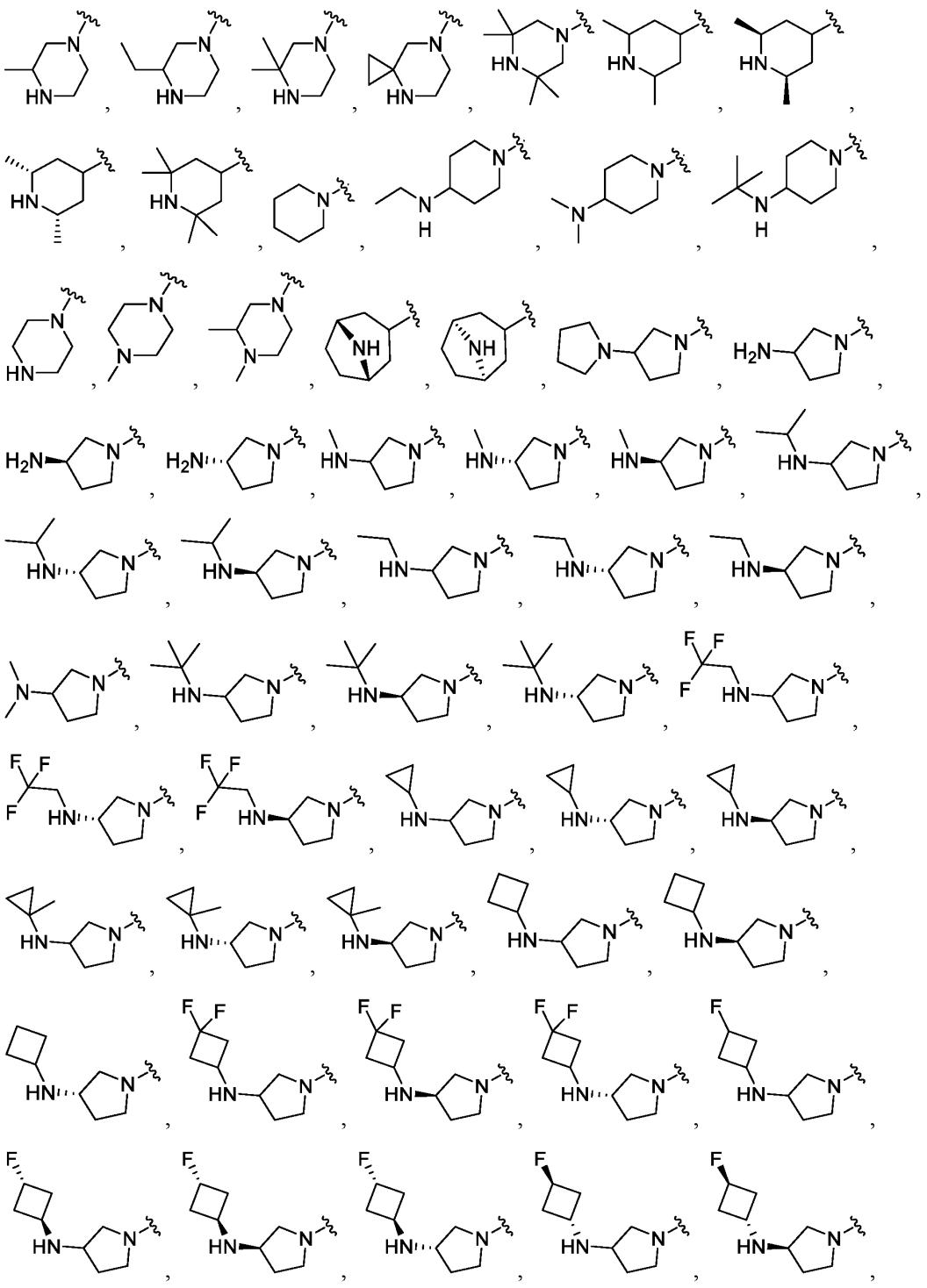
In some embodiments, B is a monocyclic heterocyclyl or bicyclic heterocyclyl, each of which is optionally substituted with one or more R^1. In some embodiments, B is a nitrogen-containing heterocyclyl optionally substituted with one or more R^1. In some embodiments, B is a 4-8 membered heterocyclyl optionally substituted with one or more R^1. In some embodiments, B is selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described herein. In some embodiments, B is selected from , , and , wherein R^1 is as described herein. In some embodiments, B is . In some embodiments B is . In some embodiments, B is .

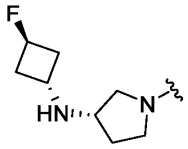
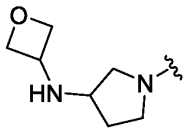
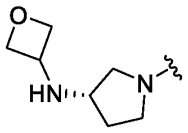
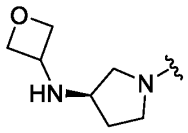
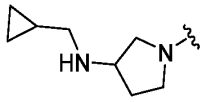
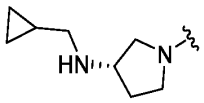
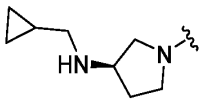
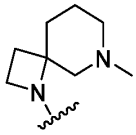
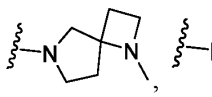
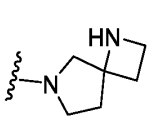
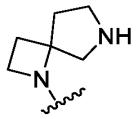
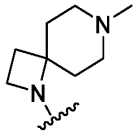
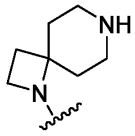
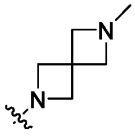
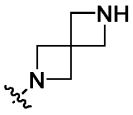
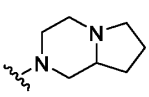
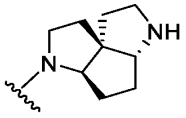
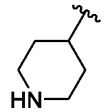
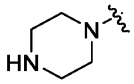
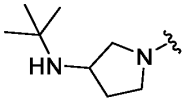
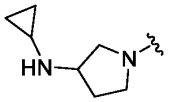
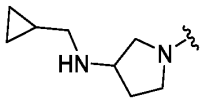
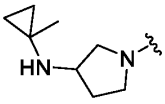
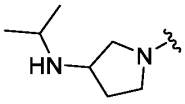
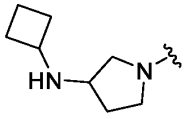
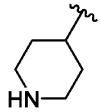
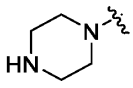
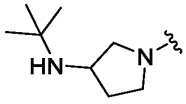
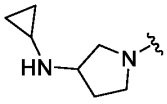
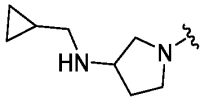
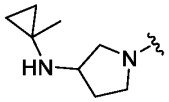
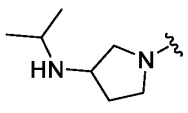
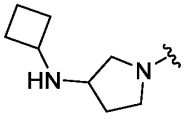
In some embodiments, B is  and R^1 is as described herein. In some embodiments, B is selected from  and , and R^1 is as described herein.

In some embodiments, B is , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

In some embodiments, B is selected from  and , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9. In some embodiments, R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

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 not heteroaryl. In some embodiments, B is not heterocyclyl.

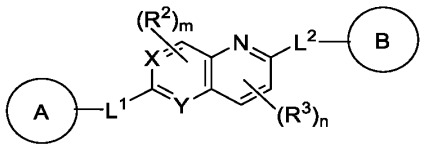
As generally described for Formulas (I) and (II), each of L^1 and L^2 may independently be absent or refer to a C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, -C(O)N(R^4)-, -N(R^4)C(O)N(R^4)-, or C_1-C_6-alkylene-N(R^4)C(O)N(R^4)- group, wherein each alkylene and heteroalkylene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

embodiments, one of L^1 and L^2 is absent or C_1-C_6-heteroalkylene. In some embodiments, one of L^1 and L^2 is independently absent. In some embodiments, L is C_1-C_6-heteroalkylene (e.g., -$N(CH_3)$-). In some embodiments, one of L^1 and L^2 is independently absent and the other of L^1 and L^2 is independently heteroalkylene (e.g., NHC(O)NH or $NHC(O)NHCH_2$, or $N(CH_3)C(O)NH$). In some embodiments, each of L^1 and L^2 is independently absent.

As generally described for Formula (I), each of X, Y, and Z may independently be N or $C(R^6)$. In some embodiments, X is $C(R^6)$ (e.g., CH). In some embodiments, X is N. In some embodiments, Y is $C(R^6)$ (e.g., CH). In some embodiments, Y is N. In some embodiments, Z is $C(R^6)$ (e.g., CH). In some embodiments, Z is N. In some embodiments, each of X and Y is independently $C(R^6)$ (e.g., CH). In some embodiments, each of X and Y is independently N. In some embodiments, each of Y and Z is independently N. In some embodiments, each of X and Z is independently N. In some embodiments, one of X and Y is independently N and Z is N. In some embodiments, X and Z is independent N and Y is N. In some embodiments, each of X, Y, and Z is independently N.

In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, n is 0. In some embodiments, n is 0.

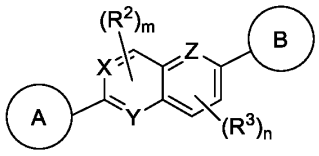
In some embodiments, the compound of Formula (I) is a compound of Formula (I-a):



(I-a), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; L^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -$N(R^4)$-, -$N(R^4)C(O)$-, -$C(O)N(R^4)$-, -$N(R^4)C(O)N(R^4)$-, or C_1-C_6-alkylene-$N(R^4)C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; X and Y are each N or $C(R^6)$; 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, heteroaryl, aryl, C_1-C_6 alkylene-aryl, C_2-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–S(O)_xR^D$; each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, $–OR^A$, or $–NR^BR^C$; each R^6 is independently hydrogen, halo, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $–OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^8; each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, 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, $–OR^A$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; 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^9; each R^D 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, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^9; each R^8 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, halo, cyano, oxo, or $–OR^A$; each R^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $–OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; n is 0, 1, or 2; m is 0 or 1; and x is 0, 1, or 2.

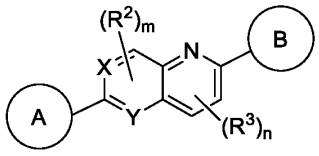
In some embodiments, the compound of Formula (I) is a compound of Formula (I-b):



(I-b), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $–OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or –OR^{A1}; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

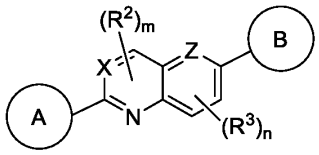
In some embodiments, the compound of Formula (I) is a compound of Formula (I-c):



(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; X, and Y are each N or C(R^6);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, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, or –$S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or –OR^A; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

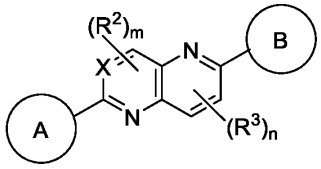
In some embodiments, the compound of Formula (I) is a compound of Formula (I-d):



(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; X and Z are each N or $C(R^6)$;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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

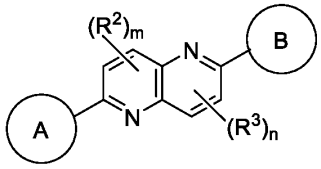
In some embodiments, the compound of Formula (I) is a compound of Formula (I-e):



(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; X is N or $C(R^6)$;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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

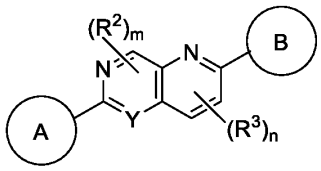
In some embodiments, the compound of Formula (I) is a compound of Formula (I-f):



(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; 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

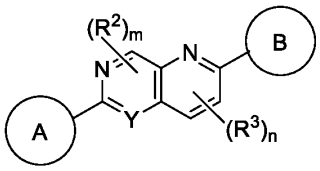
In some embodiments, the compound of Formula (I) is a compound of Formula (I-g):



(I-g), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; Y is N or $C(R^6)$;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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

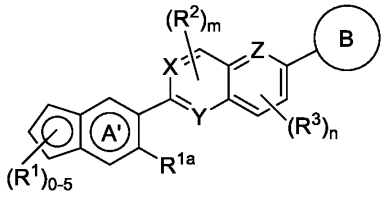
In some embodiments, the compound of Formula (I) is a compound of Formula (I-h):



(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; Y is N or $C(R^6)$; 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, –

$NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

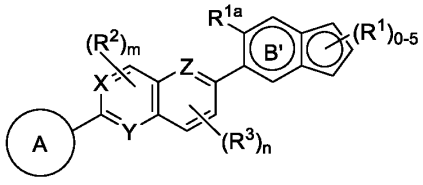
In some embodiments, the compound of Formula (I) is a compound of Formula (I-i):



(I-i), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A' is bicyclic heteroaryl or heterocyclyl; B is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; R^{1a} is C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$,$-C(O)NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

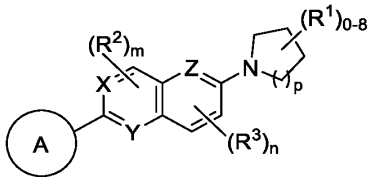
In some embodiments, the compound of Formula (I) is a compound of Formula (I-j):



(I-j), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; B' is bicyclic heteroaryl or heterocyclyl; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; R^{1a} is C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$,$-C(O)NR^BR^C$, $-C(O)R^D$, or $-C(O)OR^D$; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

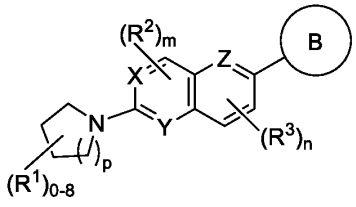
In some embodiments, the compound of Formula (I) is a compound of Formula (I-k):



(I-k), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is 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, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; p is 0, 1, 2, or 3; and x is 0, 1, or 2.

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

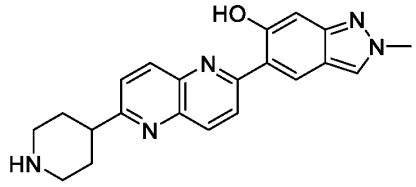
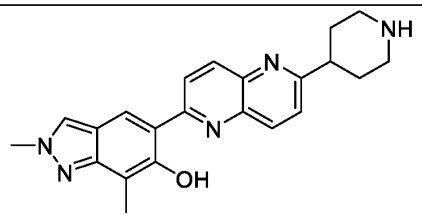
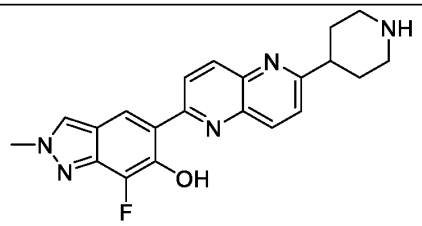
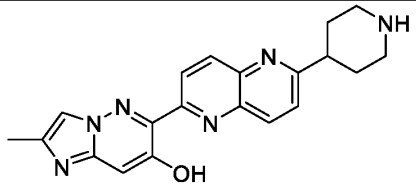
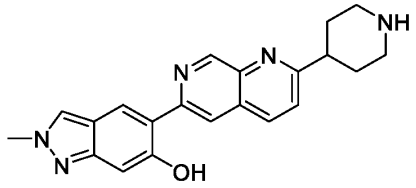
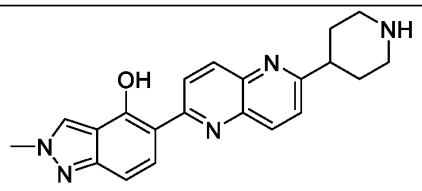


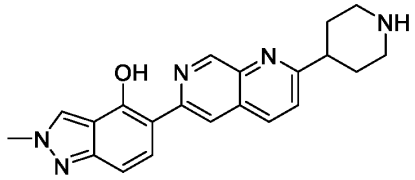
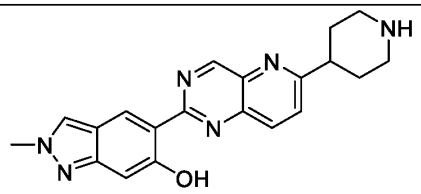
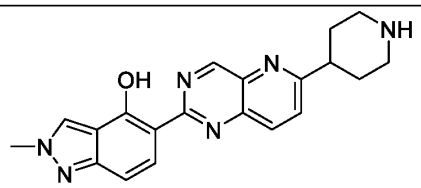
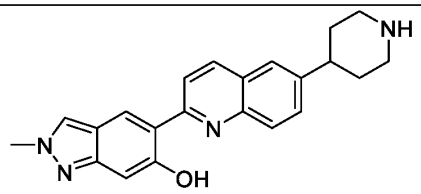
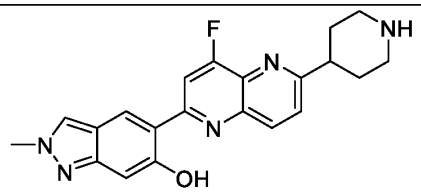
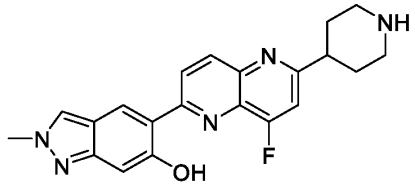
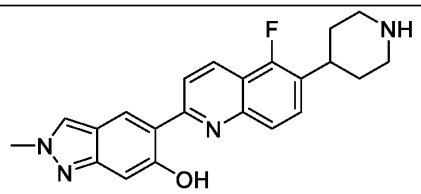
(I-l), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein B is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; X, Y, and Z are each N or $C(R^6)$, wherein at least one of X, Y, and Z is N; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl,

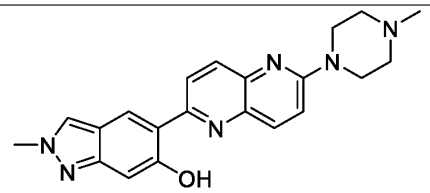
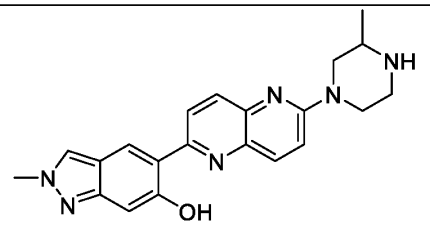
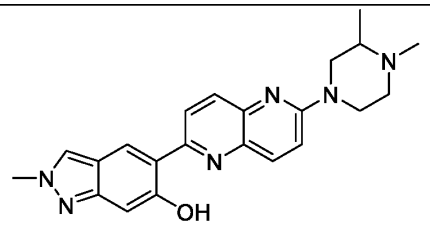
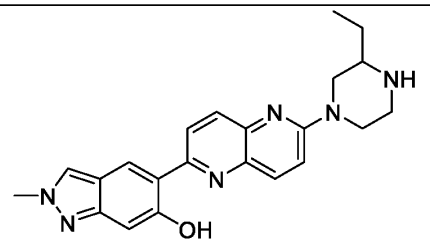
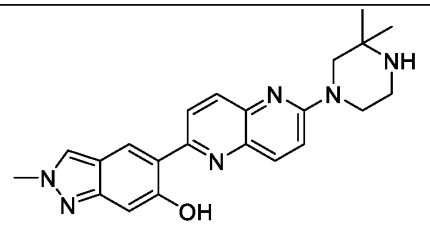
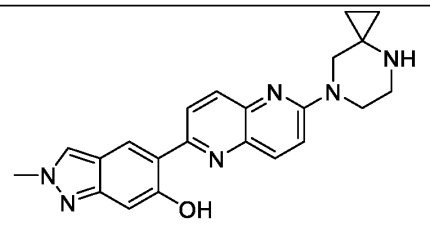
C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; p is 0, 1, 2, or 3; and x is 0, 1, or 2.

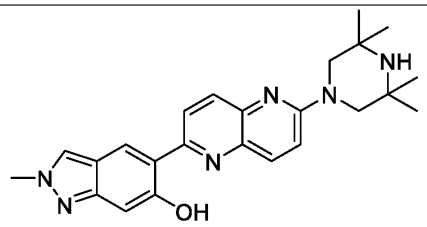
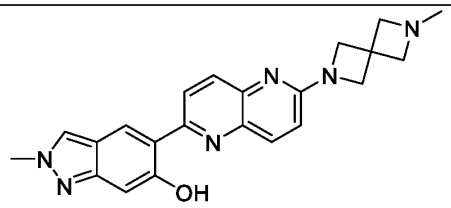
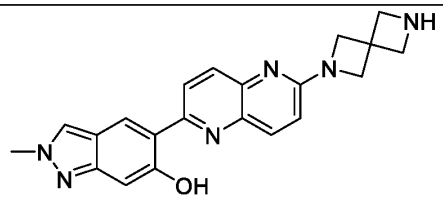
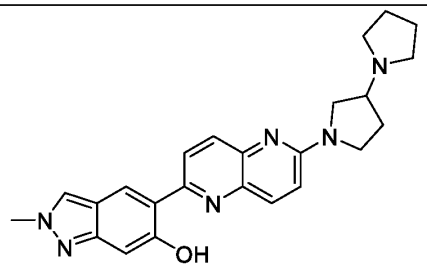
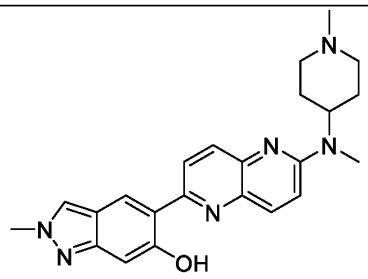
In some embodiments, the compound of Formula (I) is selected from a compound in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

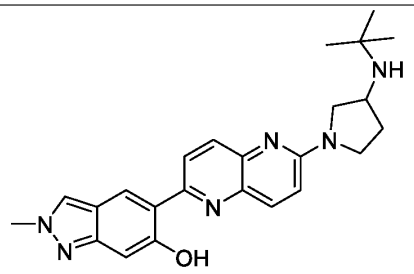
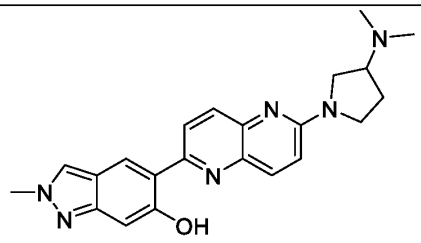
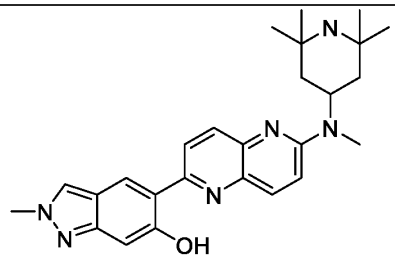
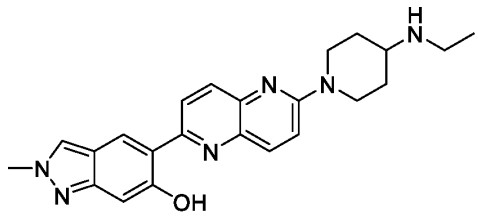
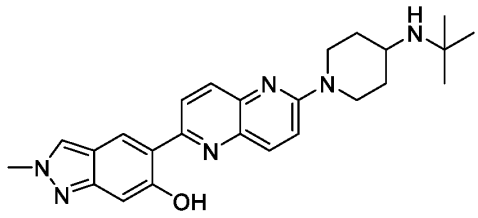
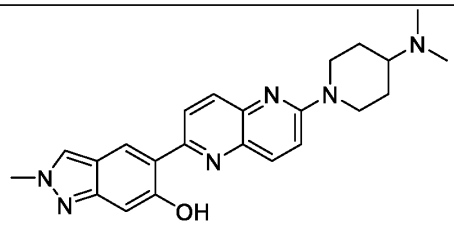
Table 1. Exemplary compounds of Formula (I)

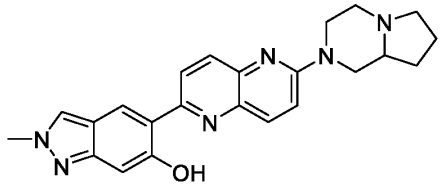
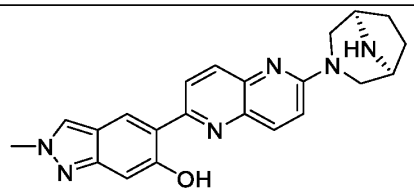
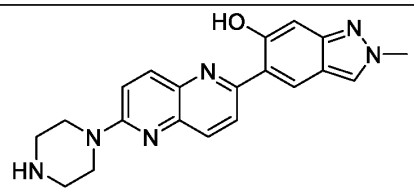
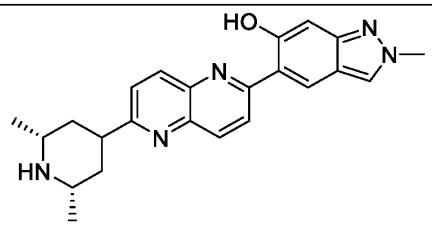
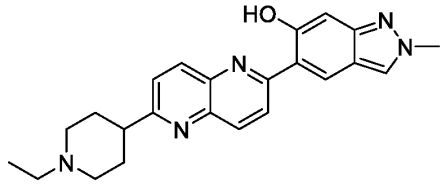
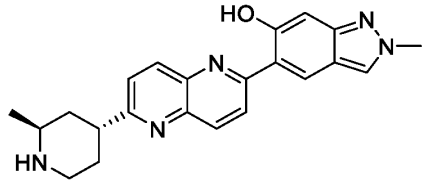
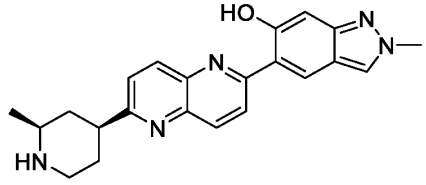
Compound No.	Structure
100	
101	
102	
103	
104	
105	

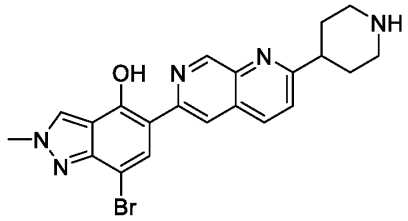
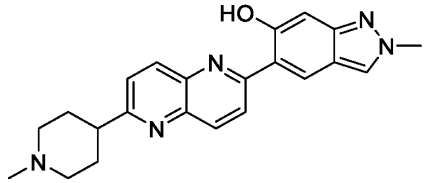
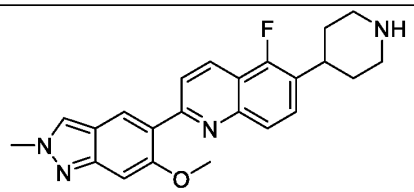
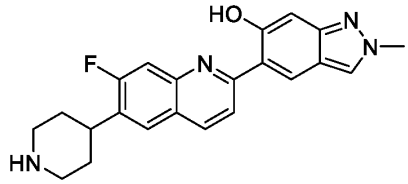
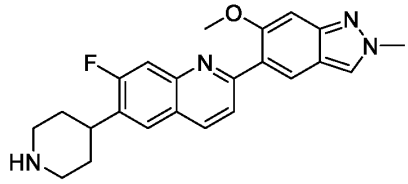
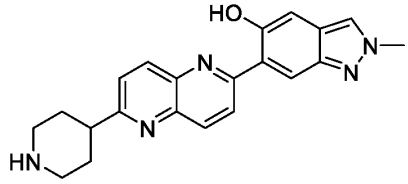
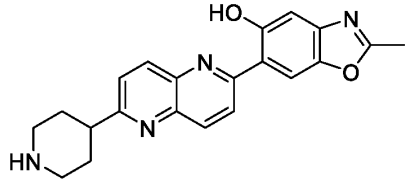
106	
107	
108	
109	
113	
114	
115	

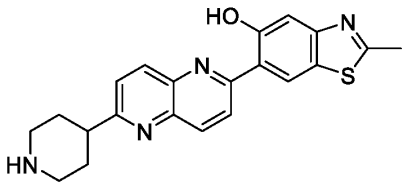
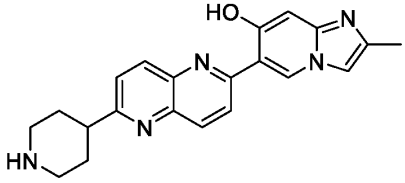
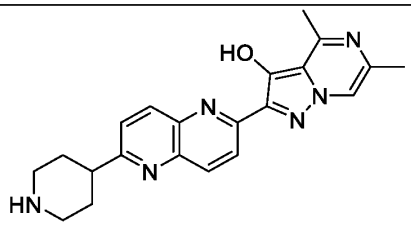
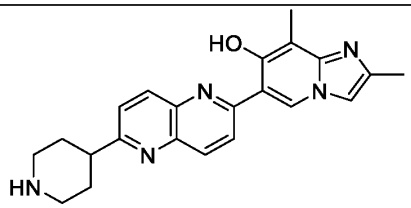
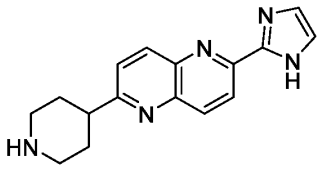
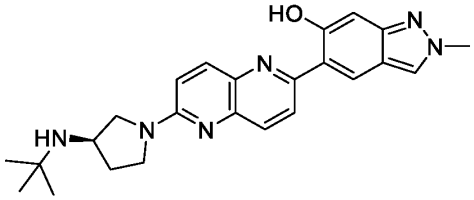
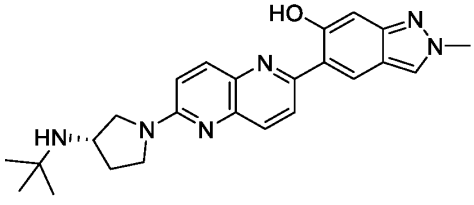
116	
117	
118	
119	
120	
121	

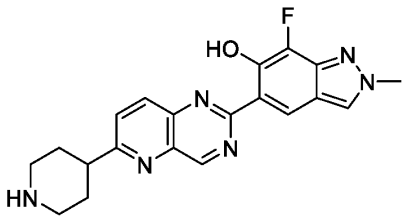
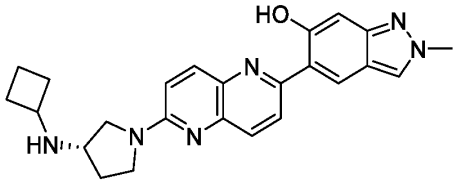
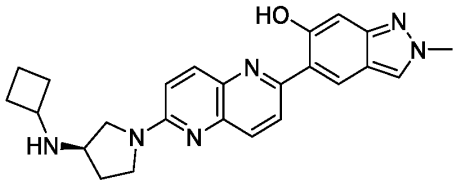
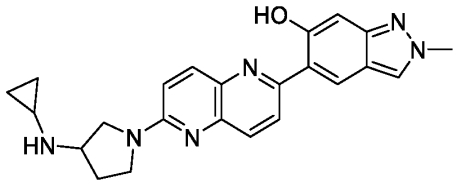
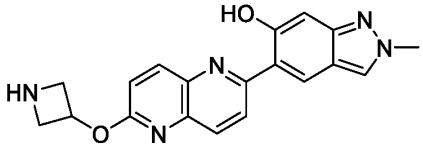
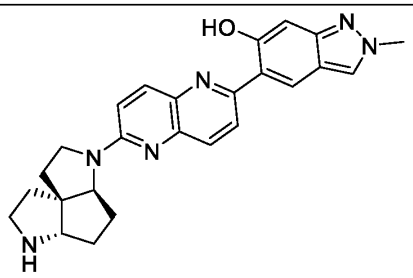
122	
123	
124	
125	
126	

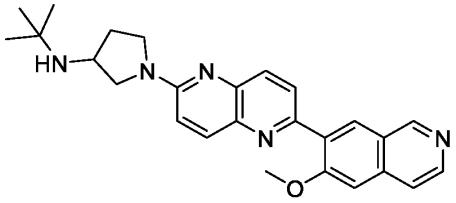
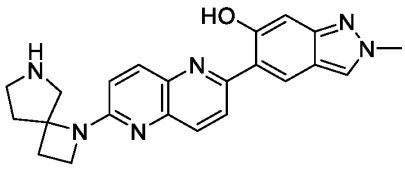
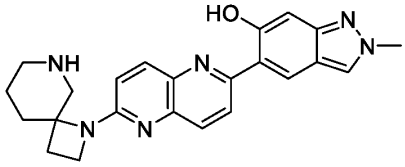
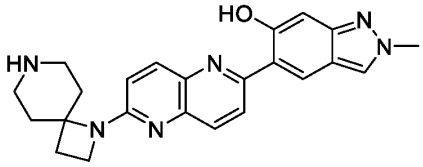
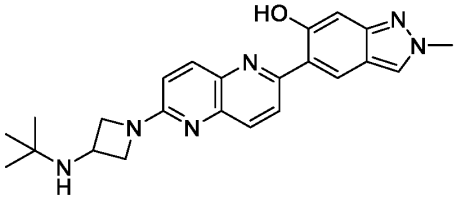
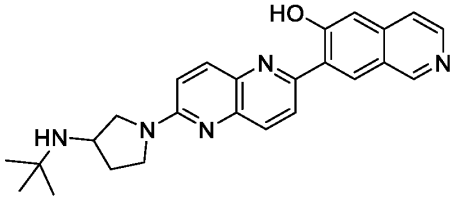
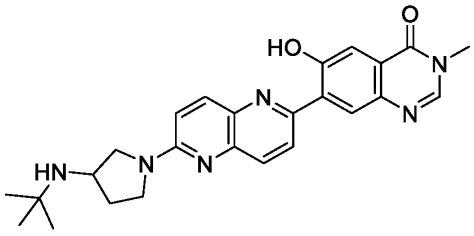
127	
129	
130	
131	
132	
133	

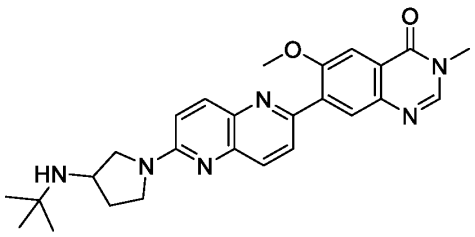
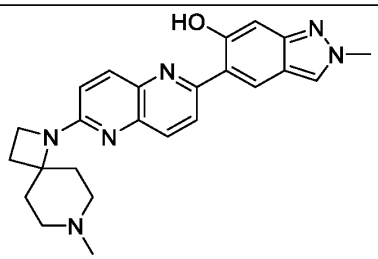
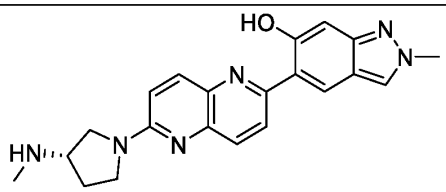
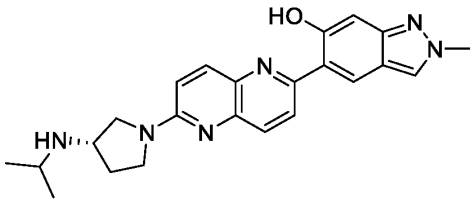
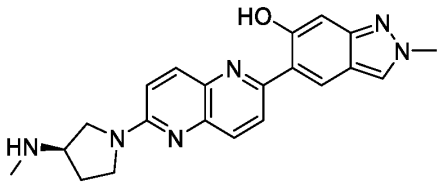
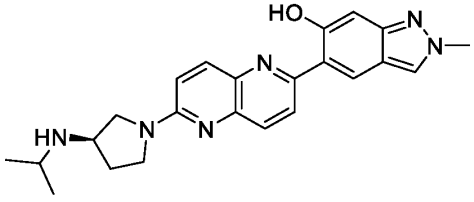
134	
135	
136	
137	
138	
139	
140	

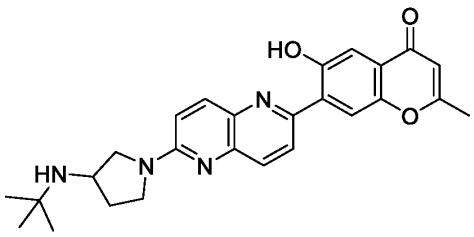
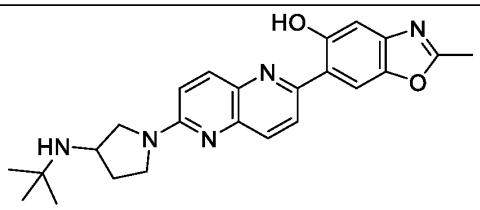
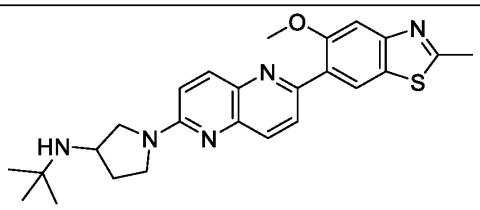
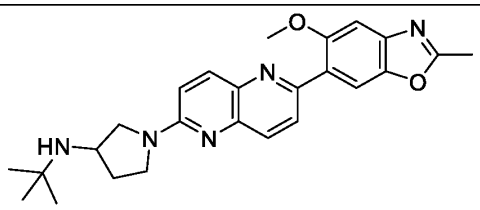
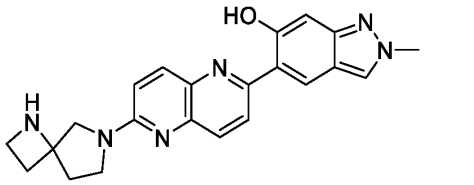
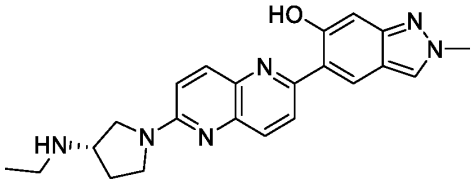
141	
142	
143	
144	
145	
146	
147	

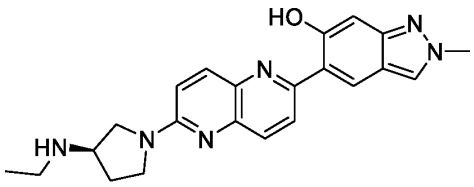
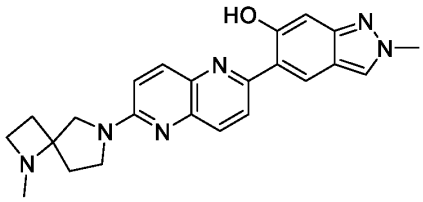
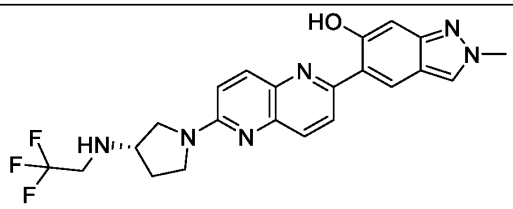
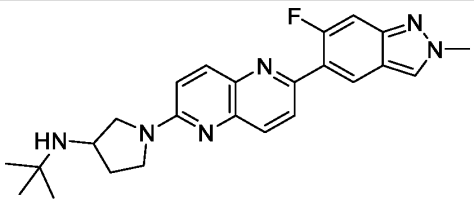
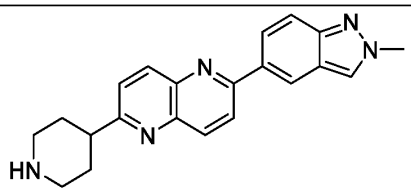
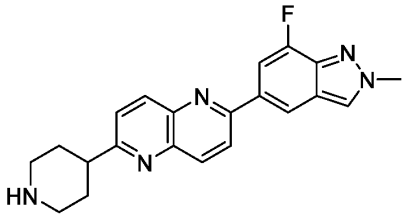
148	
149	
150	
151	
152	
153	
154	

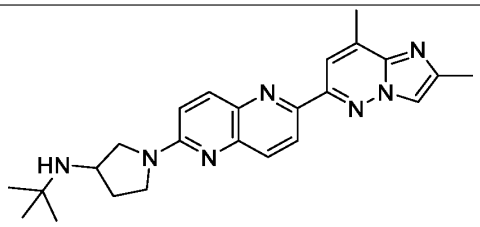
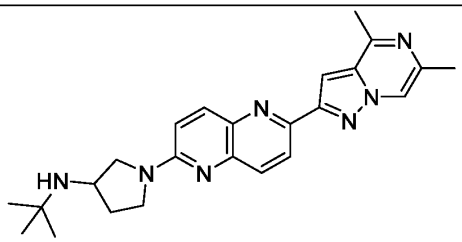
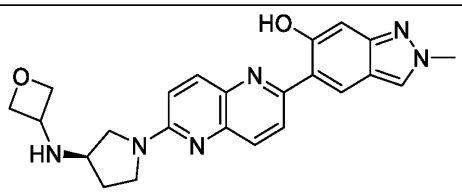
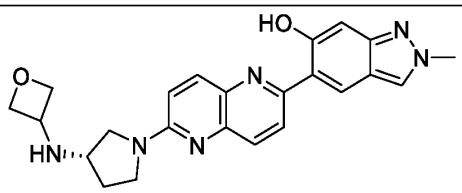
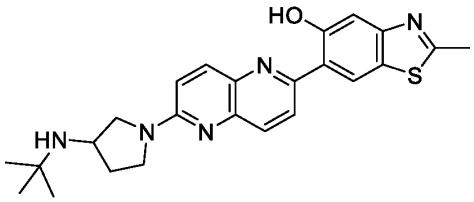
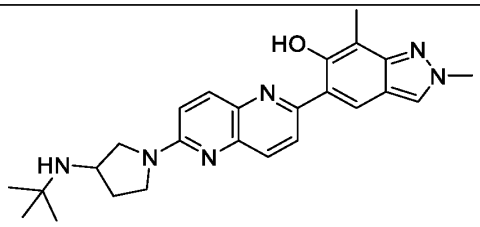
155	
156	
157	
158	
159	
160	

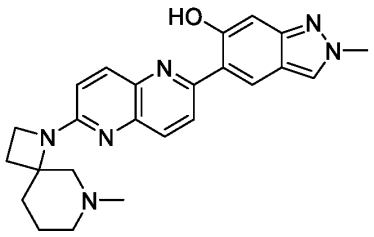
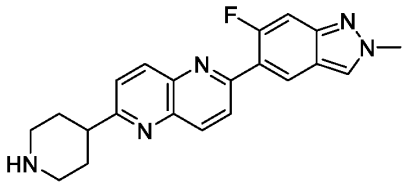
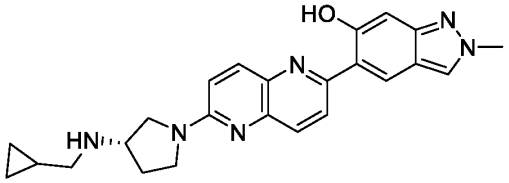
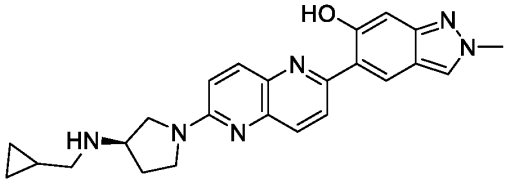
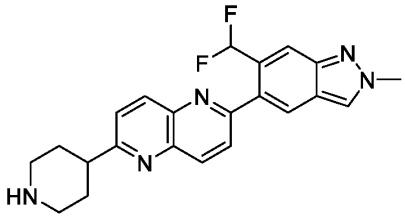
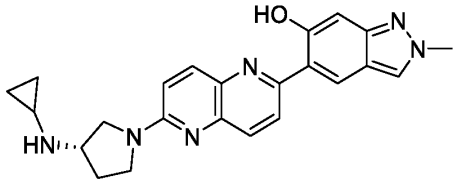
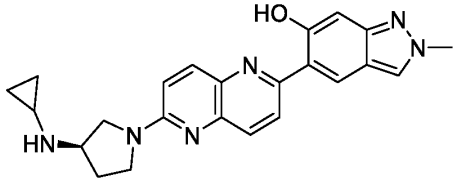
161	
162	
163	
164	
165	
166	
167	

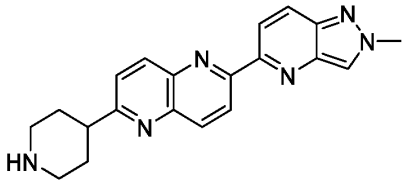
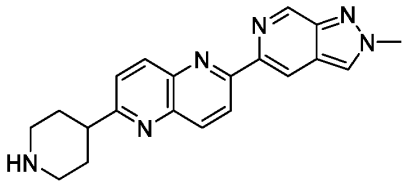
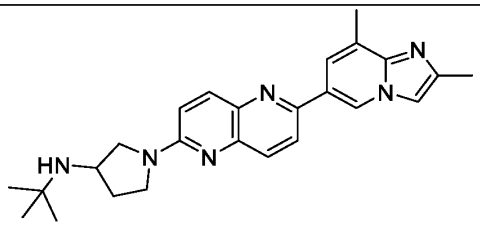
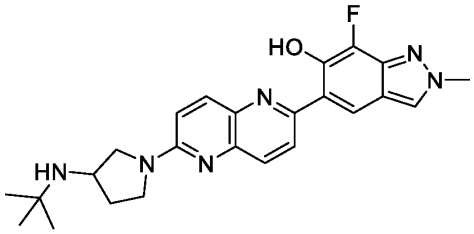
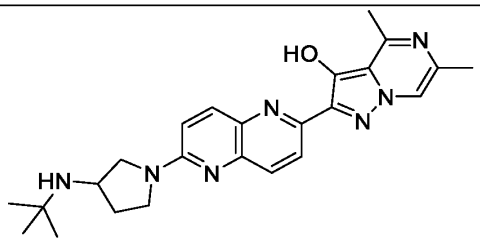
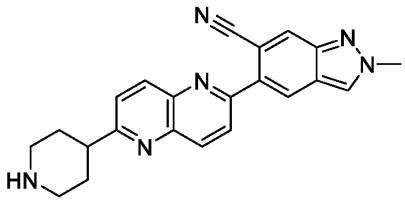
168	
169	
170	
171	
172	
173	

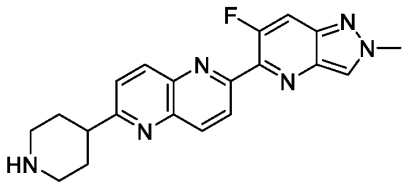
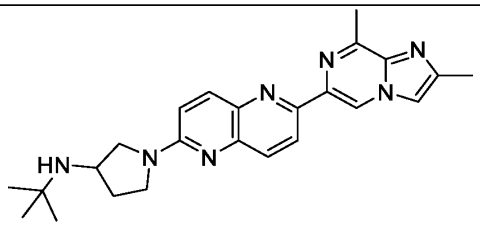
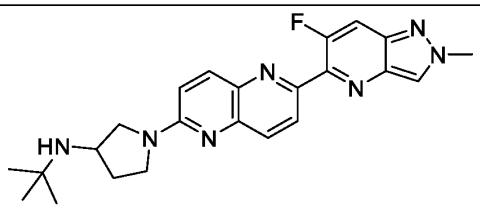
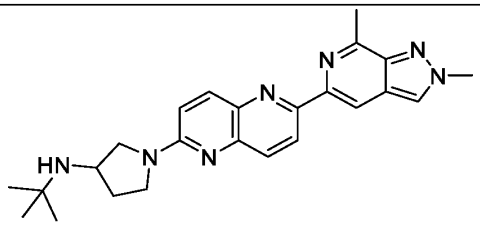
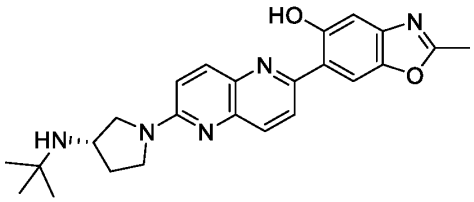
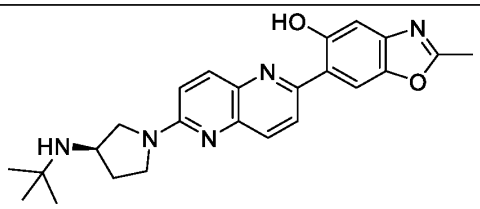
174	
175	
176	
177	
178	
179	

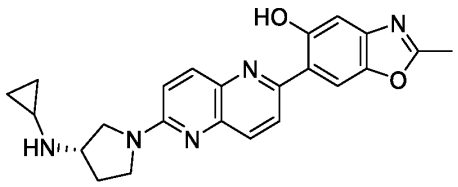
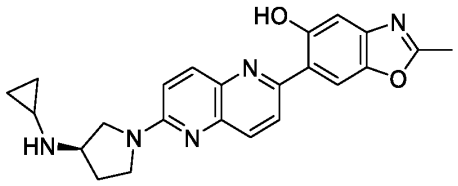
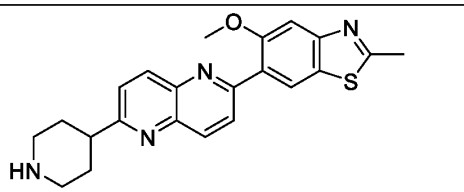
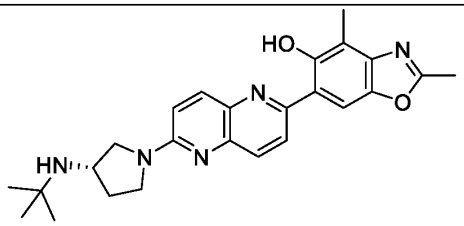
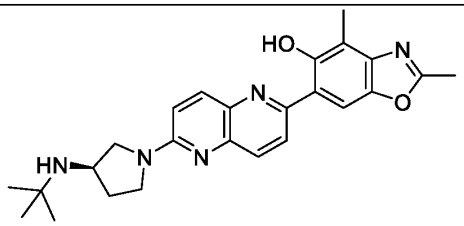
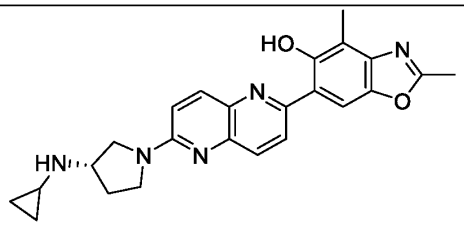
180	
181	
182	
183	
184	
185	

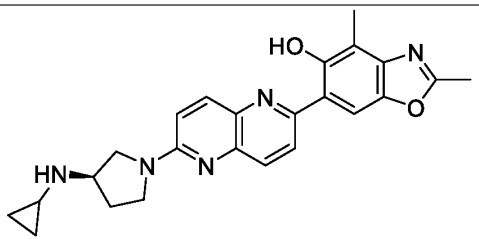
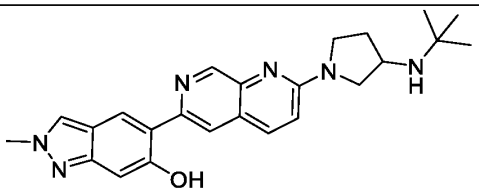
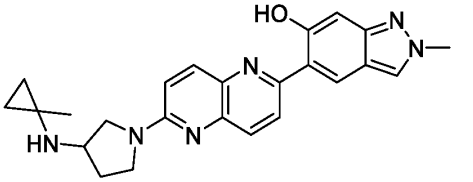
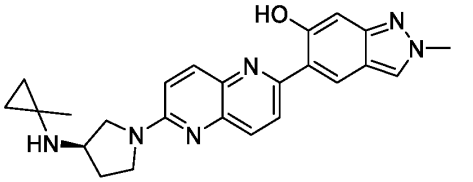
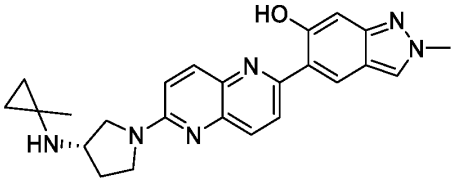
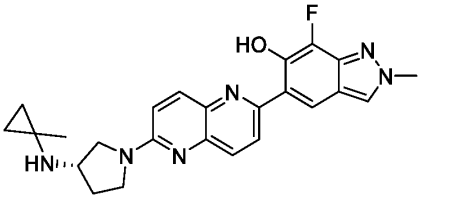
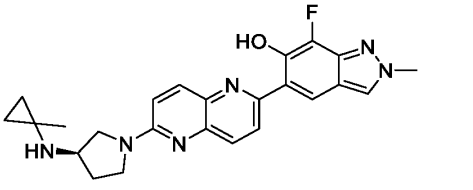
186	
187	
188	
189	
190	
191	

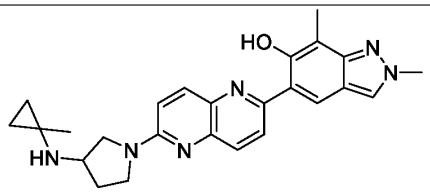
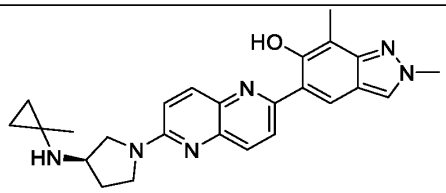
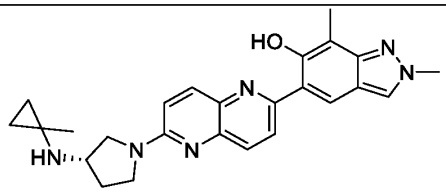
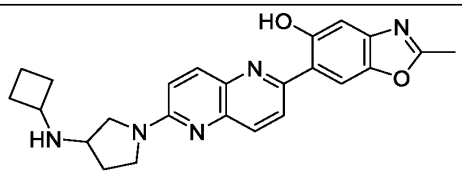
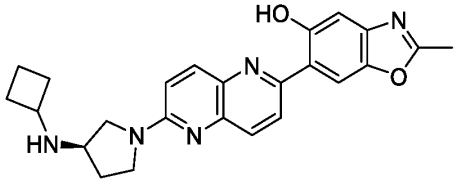
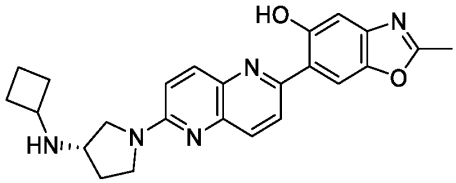
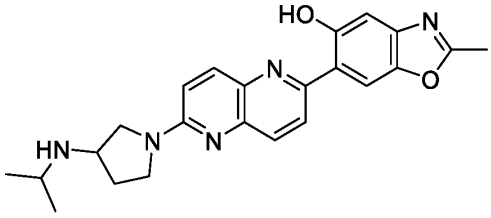
192	
193	
194	
195	
196	
197	
198	

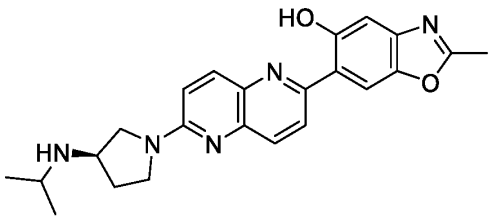
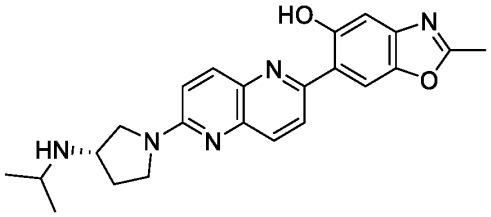
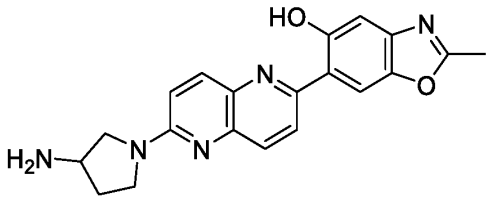
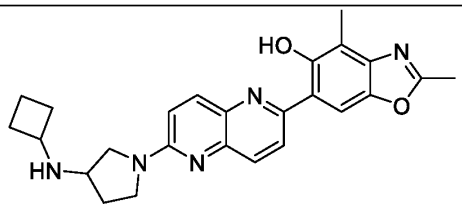
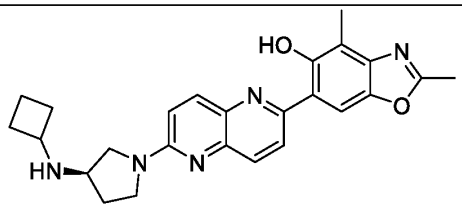
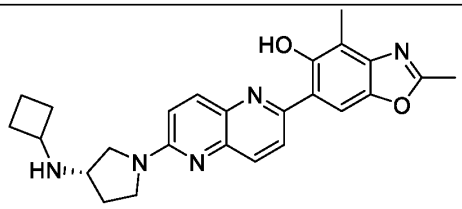
199	
200	
201	
202	
203	
204	

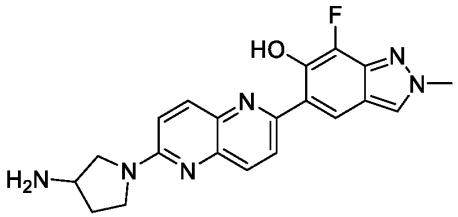
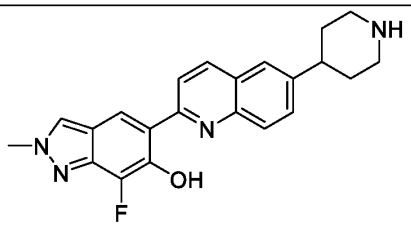
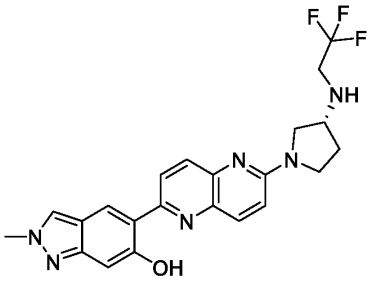
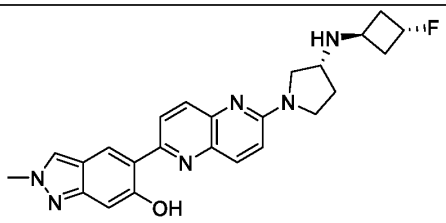
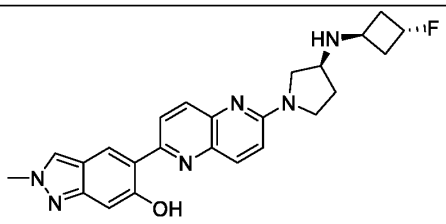
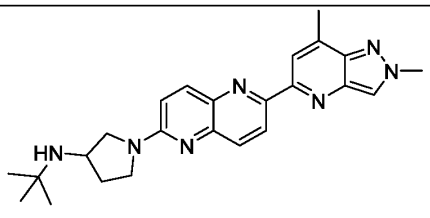
205	
206	
207	
208	
209	
210	

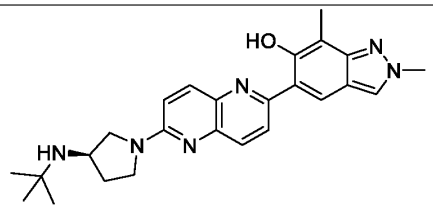
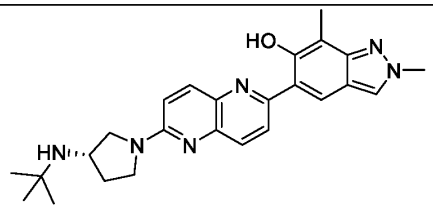
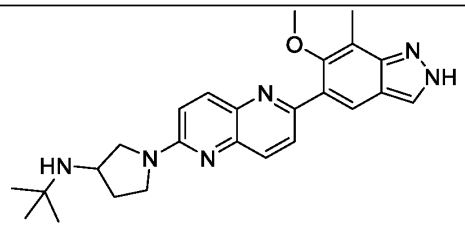
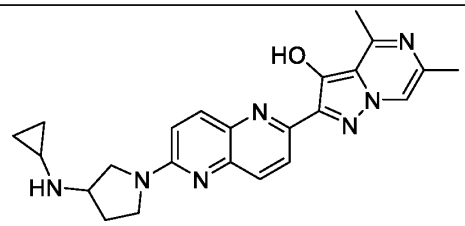
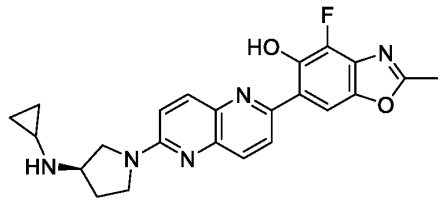
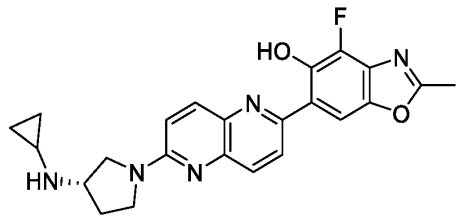
211	
212	
213	
214	
215	
216	

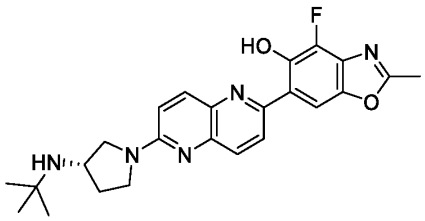
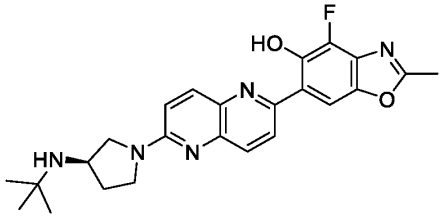
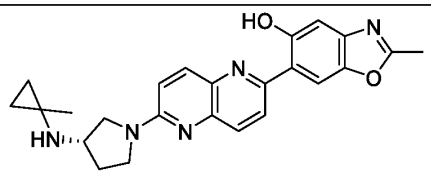
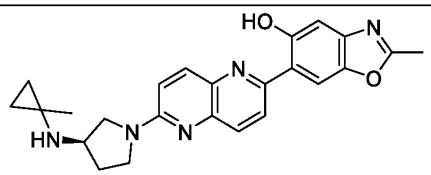
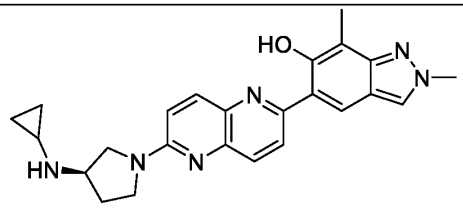
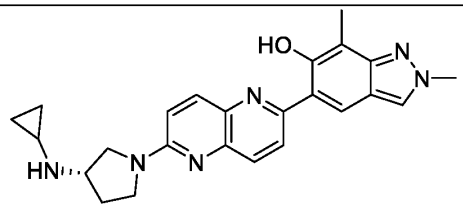
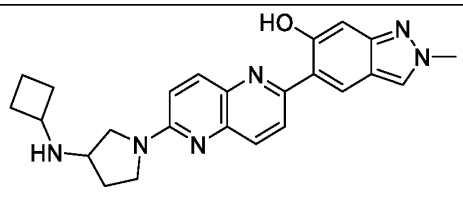
217	
218	
219	
220	
221	
222	
223	

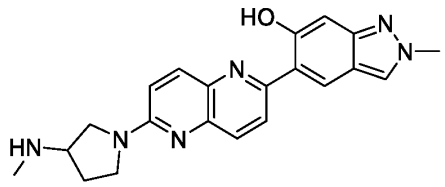
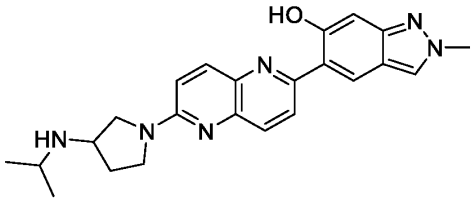
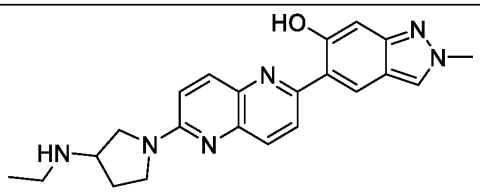
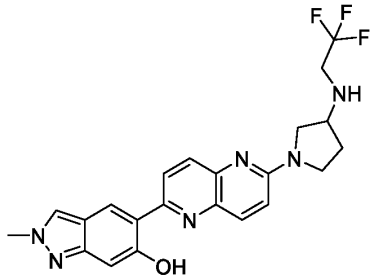
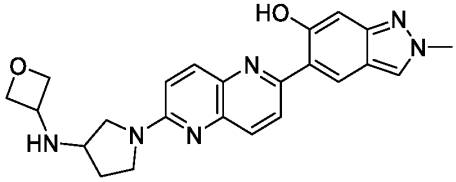
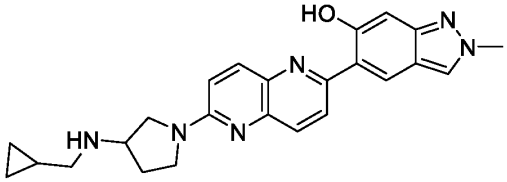
224	
225	
226	
228	
229	
230	
231	

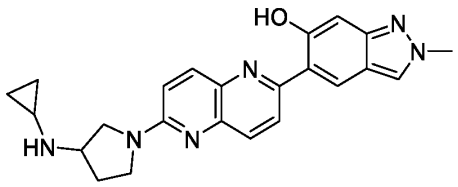
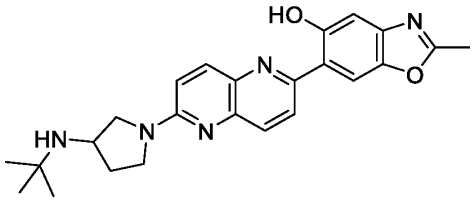
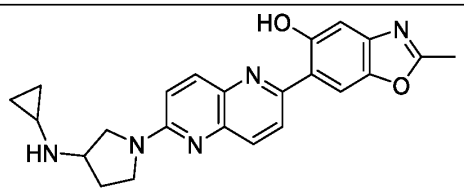
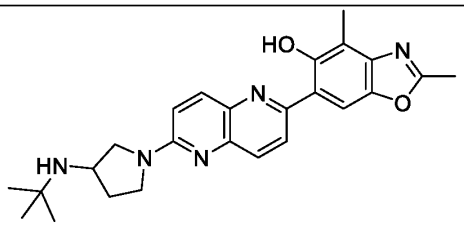
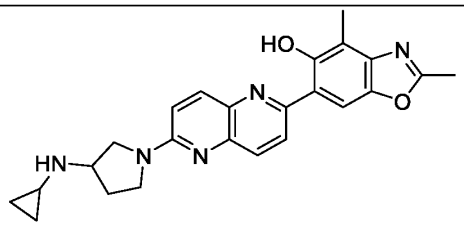
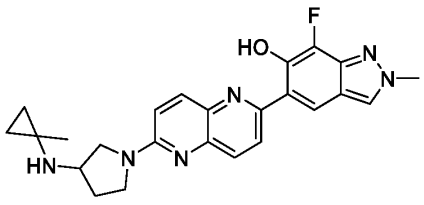
232	
233	
234	
235	
236	
237	

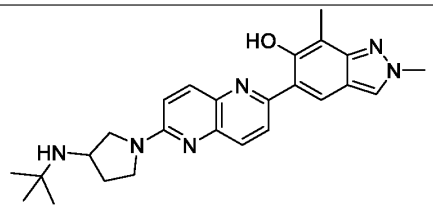
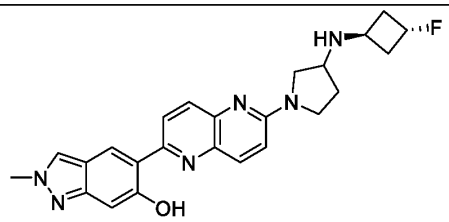
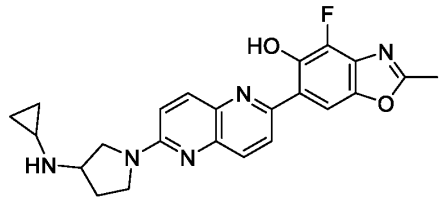
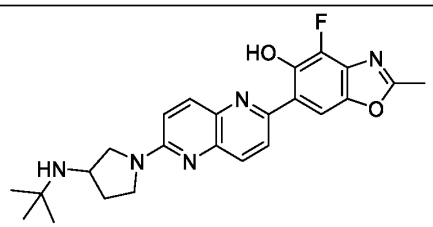
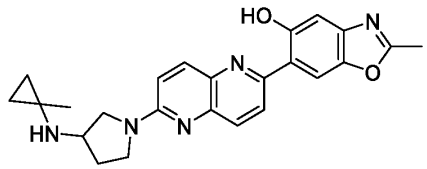
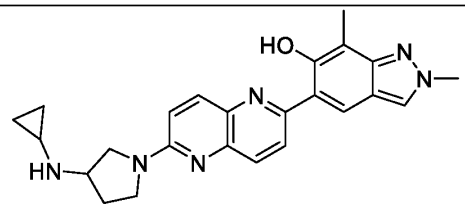
238	
241	
245	
246	
247	
248	

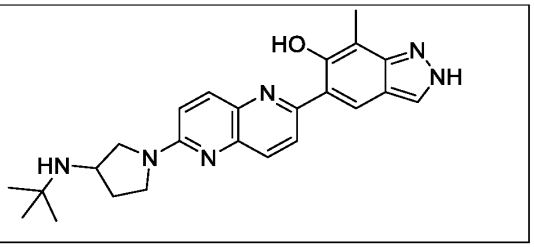
249	
250	
251	
252	
253	
254	

255	
256	
257	
258	
259	
260	
262	

263	
264	
265	
266	
267	
268	

269	
270	
271	
272	
273	
274	

275	
277	
278	
279	
280	
281	

282	

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 100, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2,7-dimethyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 101, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-fluoro-6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 102, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-hydroxy-2-methyl-2H-4λ^4-imidazo[2,1-f]pyridazyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 103, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; Y is $C(R^6)$ (e.g., CH); X and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), 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 heteroaryl (e.g., 4-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 105, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 4-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; Y is $C(R^6)$ (e.g., CH); X and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), 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 bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X, Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 107, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 4-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X, Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (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 heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X and Z are each independently $C(R^6)$ (e.g., CH); Y is N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-c), and (I-d) is Compound 109, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^2 is halo (e.g., F); m is 1; and n is 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 113, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^3 is halo (e.g., F); m is 0; and n is 1. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 114, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y is N; Z is $C(R^6)$ (e.g., CF); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-c), and (I-d) is Compound 115, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1-methylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 116, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2-methylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 117, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1,2-dimethylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 118, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2-ethylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 119, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2,2-dimethylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 120, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 4,7-diazaspiro[2.5]octanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 121, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 122, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2-methyl-2,6-diazaspiro[3.3]heptanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 123, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2,6-diazaspiro[3.3]heptanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 124, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1,3-bipyrrolidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 125, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1-methylpiperadinyl); L^1 is absent; L^2 is -N(R^4)- (e.g., -N(CH_3)-); X is C(R^6) (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I) is Compound 126, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; R^1 is -NR^BR^C (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 127, 153, 154, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; R^1 is -NR^BR^C (e.g., -N($Me)_2$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 129, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2,2,6,6-tetramethylpiperadinyl); L^1 is absent; L^2 is -N(R^4)- (e.g., -N(CH_3)-); X is C(R^6) (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I) is Compound 130, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; R^1 is -NR^BR^C (e.g., -NH(Et)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 131, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; R^1 is -NR^BR^C (e.g., -NH(^{t}Bu));

and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 132, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-N(Me)_2$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 133, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., octahydropyrrolo[1,2-a]pyrazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 134, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 3,8-diazabicyclo[3.2.1]octanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 135, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperazyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 136, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2,6-dimethylpiperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 137, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1-ethylpiperidinyl); L^1 and L^2 are each

absent; X is C(R^6) (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 138, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 2-methylpiperidinyl); L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 139, 140, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-bromo-4-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; Y is C(R^6) (e.g., CH); X and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), and (I-d) is Compound 141, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1-methylpiperidinyl); L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 142, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-methoxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y is N; Z is C(R^6) (e.g., CF); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-c), and (I-d) is Compound 143, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y is N; Z is C(R^6) (e.g., CH); R^3 is halo (e.g., F); m is 0; and n is 1. In some embodiments, the compound of Formula (I), (I-a), (I-c), and (I-d) is Compound 144, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-methoxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is C(R^6) (e.g., CH); Y is N; Z is C(R^6) (e.g., CH); R^3 is halo (e.g., F); m is 0; and n is

1. In some embodiments, the compound of Formula (I), (I-a), (I-c), and (I-d) is Compound 145, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 5-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 146, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 5-hydroxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 147, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 5-hydroxy-2-methylbenzo[d]thiazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 148, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-hydroxy-2-methylimidazo[1,2-a]pyridinyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 149, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 3-hydroxy-4,6-dimethylpyrazolo[1,5-a]pyrazinyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 150, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-hydroxy-2,8-dimethylimidazo[1,2-a]pyridinyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the

compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 151, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is monocyclic heteroaryl (e.g., 1H-imidazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 152, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-fluoro-6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl); L^1 and L^2 are each absent; X, Y, and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 155, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$; R^B is hydrogen; R^C is cycloalkyl (e.g., cyclobutanyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 156, 157, 262, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$; R^B is hydrogen; R^C is cycloalkyl (e.g., cyclopropyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 158, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., azetidinyl); L^1 is absent; L^2 is -O-; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I) is Compound 159, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., decahydrocyclopenta[2,1-b:5,1-

b]dipyrrolyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 160, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-methoxyisoquinolinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 161, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1,6-diazaspiro[3.4]octanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 162, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1,6-diazaspiro[3.5]nonanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 163, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., 1,7-diazaspiro[3.5]nonanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 164, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., azetidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 165, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-isoquinolinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 166, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-3-methylquinazolin-4(3H)-onyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 167, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-methoxy-3-methylquinazolin-4(3H)-onyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 168, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is bicyclic heterocyclyl (e.g., 1,7-diazaspiro[3.5]nonanyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is C_1-C_6 alkyl (e.g., $-CH_3$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 169, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(CH_3)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 170, 172, 263, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^i Pr)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 171, 173, 264, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2-methyl-4H-chromen-4-onyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 174, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 175, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-methoxy-2-methylbenzo[d]thiazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 176, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-methoxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t Bu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 177, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is bicyclic heterocyclyl (e.g., 1,6-diazaspiro[3.4]octanyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 178 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(Et)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 179, 180, 265, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is bicyclic heterocyclyl (e.g., 1,6-diazaspiro[3.4]octanyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is C_1-C_6 alkyl (e.g., $-CH_3$) and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 181 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -$NH(CH_2CF_3)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 182, 245, 266, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 183, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$

(e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 184, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 7-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 185, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2,8-dimethylimidazo[1,2-b]pyridazinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 186, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 4,6-dimethylpyrazolo[1,5-a]pyrazinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 187, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(CHCH_2OCH_2)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 188, 189, 267, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 5-hydroxy-2-methylbenzo[d]thiazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b),

(I-c), and (I-d) is Compound 190, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-2,7-dimethyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(^tBu)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 191, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is bicyclic heterocyclyl (e.g., 1,6-diazaspiro[3.5]nonanyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is C_1-C_6 alkyl (e.g., $-CH_3$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 192, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-fluoro-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 193, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(CH_2CHCH_2CH_2)$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 194, 195, 268, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-(difluoromethyl)-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 196, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-6-hydroxy-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclopropyl)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 197, 198, 269, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-2H-pyrazolo[4,3-b]pyridinyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 199, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2-methyl-2H-pyrazolo[3,4-c]pyridinyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 200, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2,8-dimethylimidazo[1,2-a]pyridinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 201, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-hydroxy-7-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 202, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 3-hydroxy-4,6-dimethylpyrazolo[1,5-a]pyrazinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g.,

-NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 203, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-cyano-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl) L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 204, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-fluoro-2-methyl-2H-pyrazolo[4,3-b]pyridinyl); B is monocyclic heterocyclyl (e.g., piperidinyl) L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 205, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2,8-dimethylimidazo[1,2-a]pyrazinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 206, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 6-fluoro-2-methyl-2H-pyrazolo[4,3-b]pyridinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 207, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g., 2,7-dimethyl-2H-pyrazolo[3,4-c]pyridinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 208, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 209, 210, 270, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclopropyl)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 211, 212, 271, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-methoxy-2-methylbenzo[d]thiazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 213, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2,4-dimethylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}-Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 214, 215, 272, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2,4-dimethylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclopropyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 216, 217, 273, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and

L^2 are each absent; Y is $C(R^6)$ (e.g., CH); X and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}-Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), and (I-d) is Compound 218, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -$NH(C(CH_3)CH_2CH_2)$; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 219, 220, 221, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy- 7-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -$NH(C(CH_3)CH_2CH_2)$; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 222, 223, 274, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2,7-dimethyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -$NH(C(CH_3)CH_2CH_2)$; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 224, 225, 226, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclobutyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 228, 229, 230, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -

NH(isopropyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 231, 232, 233, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH_2$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 234, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 2,4-dimethylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclobutyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 235, 236, 237, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-7-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH_2$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 238, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy- 7-fluoro-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., piperidinyl); L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), and (I-d) is Compound 241, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(CH_2CF_3)$; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is

Compound 245, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., $-NH(CHCH_2CHFCH_2)$; and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 246, 247, 277, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 2,7-dimethyl-2H-pyrazolo[4,3-b]pyridinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t$-Bu); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 248, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy-2,7-dimethyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t$-Bu); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 249, 250, 275, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-methoxy-7-methyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., $-NH(^t$-Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 251, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 3-hydroxy-4,6-dimethylpyrazolo[1,5-a]pyrazinyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., $-NH$(cyclopropyl)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-

a), (I-b), (I-c), and (I-d) is Compound 252, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 4-fluoro-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclopropyl)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 253, 254, 278, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy- 4-fluoro-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X and Z are $C(R^6)$ (e.g., CH); Y is N; R^1 is $-NR^BR^C$ (e.g., -NH(^{t}Bu)); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 255, 256, 279, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

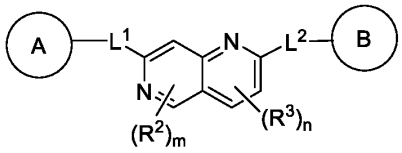
In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 5-hydroxy-2-methylbenzo[d]oxazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH($C(CH_3)CH_2CH_2$); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 257, 258, 280, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (I), A is bicyclic heteroaryl (e.g 6-hydroxy- 2,7-dimethyl-2H-indazolyl); B is monocyclic heterocyclyl (e.g., pyrrolidinyl) substituted with one R^1; L^1 and L^2 are each absent; X is $C(R^6)$ (e.g., CH); Y and Z are N; R^1 is $-NR^BR^C$ (e.g., -NH(cyclopropyl); and m and n are 0. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), and (I-d) is Compound 259, 260, 281, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

As generally described for Formula (II), each of W and Z may independently be N or $C(R^6)$. In some embodiments, W is $C(R^6)$ (e.g., CH). In some embodiments, W is N. In some embodiments, Z is $C(R^6)$ (e.g., CH). In some embodiments, Z is N. In some embodiments, each

of W and Z is independently N. In some embodiments, one of W and Z is independently N and the other of W and Z is C(R^6) (e.g., CH).

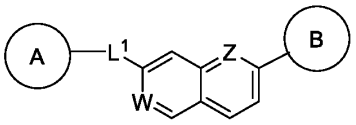
In some embodiments, the compound of Formula (II) is a compound of Formula (II-a):



(II-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^1 and L^2 are each independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, -C(O)N(R^4)-, -N(R^4)C(O)N(R^4)-, or C_1-C_6-alkylene-N(R^4)C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^5; each R^1 is independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, or –$S(O)_xR^D$; each R^4 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl; each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, –OR^A, or –NR^BR^C; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

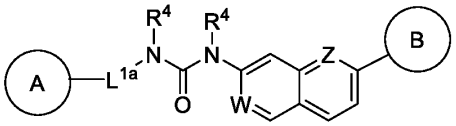
In some embodiments, the compound of Formula (II) is a compound of Formula (II-b):



(II-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; W and Z are each N or $C(R^6)$, wherein at least one of W and Z is 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, , or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

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

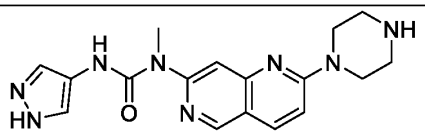
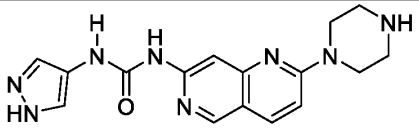
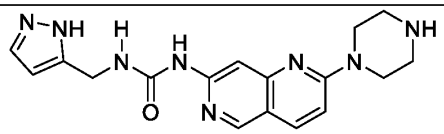


(II-c), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is optionally substituted with one or more R^1; W and Z are each N or $C(R^6)$, wherein at least one of W and Z is N; L^{1a} is absent or C_1-C_6-alkylene; 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^7; 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^7; each R^2 and R^3 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, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, or $-S(O)_xR^D$; each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$; each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8; 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 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^9; each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$; each R^{A1} is hydrogen or C_1-C_6-alkyl; m and n are each independently 0, 1, or 2; and x is 0, 1, or 2.

In some embodiments, the compound of Formula (II) is selected from a compound in Table 2, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

Table 2. Exemplary compounds of Formula (II)

Compound No.	Structure
110	
111	
112	

In some embodiments, for Formula (II), A is monocyclic heteroaryl (e.g., 1H-pyrazolyl); B is monocyclic heterocyclyl (e.g., piperazyl); L^1 is $-N(R^4)C(O)N(R^4)-$ (e.g., $-NHC(O)N(CH_3)-$); L^2 is absent; W and Z are N; and m and n are 0. In some embodiments, the compound of Formula (II), (II-a), (II-b), and (II-c) is Compound 110, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (II), A is monocyclic heteroaryl (e.g., 1H-pyrazolyl); B is monocyclic heterocyclyl (e.g., piperazyl); L^1 is -N(R^4)C(O)N(R^4)- (e.g., -NHC(O)NH-); L^2 is absent; W and Z are N; and m and n are 0. In some embodiments, the compound of Formula (II), (II-a), (II-b), and (II-c) is Compound 111, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some embodiments, for Formula (II), A is monocyclic heteroaryl (e.g., 1H-pyrazolyl); B is monocyclic heterocyclyl (e.g., piperazyl); L^1 is C_1-C_6-alkylene-N(R^4)C(O)N(R^4)- (e.g., -CH_2NHC(O)NH-); L^2 is absent; W and Z are N; and m and n are 0. In some embodiments, the compound of Formula (II), (II-a), (II-b), and (II-c) is Compound 112, 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) or (II), *e.g.*, a compound of Formula (I) or (II) 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 (II) or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (I) or (II) 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) or (II) (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) or (II) 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) or (II) 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) or (II) 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) or (II). 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) or (II). 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 (II), 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,

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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,*

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In some embodiments, the gene encoding a target sequence comprises the HTT gene. In some embodiments, the gene encoding a target sequence comprises the SMN2 gene.

Exemplary genes that may be modulated by the compounds of Formula (I) or (II) 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 (SEQ ID NO: 1), AAAguaaaaa (SEQ ID NO: 2), AAAguaaaau (SEQ ID NO: 3), AAAguaaagu (SEQ

ID NO: 4), AAAguaaaua (SEQ ID NO: 5), AAAguaaaug (SEQ ID NO: 6), AAAguaaauu (SEQ ID NO: 7), AAAguaacac (SEQ ID NO: 8), AAAguaacca (SEQ ID NO: 9), AAAguaacuu (SEQ ID NO: 10), AAAguaagaa (SEQ ID NO: 11), AAAguaagac (SEQ ID NO: 12), AAAguaagag (SEQ ID NO: 13), AAAguaagau (SEQ ID NO: 14), AAAguaagca (SEQ ID NO: 15), AAAguaagcc (SEQ ID NO: 16), AAAguaagcu (SEQ ID NO: 17), AAAguaagga (SEQ ID NO: 18), AAAguaaggg (SEQ ID NO: 19), AAAguaaggu (SEQ ID NO: 20), AAAguaagua (SEQ ID NO: 21), AAAguaaguc (SEQ ID NO: 22), AAAguaagug (SEQ ID NO: 23), AAAguaaguu (SEQ ID NO: 24), AAAguaaucu (SEQ ID NO: 25), AAAguaauua (SEQ ID NO: 26), AAAguacaaa (SEQ ID NO: 27), AAAguaccgg (SEQ ID NO: 28), AAAguacuag (SEQ ID NO: 29), AAAguacugg (SEQ ID NO: 30), AAAguacuuc (SEQ ID NO: 31), AAAguacuug (SEQ ID NO: 32), AAAguagcuu (SEQ ID NO: 33), AAAguaggag (SEQ ID NO: 34), AAAguaggau (SEQ ID NO: 35), AAAguagggg (SEQ ID NO: 36), AAAguaggua (SEQ ID NO: 37), AAAguaguaa (SEQ ID NO: 38), AAAguauauu (SEQ ID NO: 39), AAAguauccu (SEQ ID NO: 40), AAAguaucuc (SEQ ID NO: 41), AAAguaugga (SEQ ID NO: 42), AAAguaugua (SEQ ID NO: 43), AAAguaugug (SEQ ID NO: 44), AAAguauguu (SEQ ID NO: 45), AAAguauugg (SEQ ID NO: 46), AAAguauuuu (SEQ ID NO: 47), AAAgucagau (SEQ ID NO: 48), AAAgucugag (SEQ ID NO: 49), AAAgugaaua (SEQ ID NO: 50), AAAgugagaa (SEQ ID NO: 51), AAAgugagac (SEQ ID NO: 52), AAAgugagag (SEQ ID NO: 53), AAAgugagau (SEQ ID NO: 54), AAAgugagca (SEQ ID NO: 55), AAAgugagcu (SEQ ID NO: 56), AAAgugaggg (SEQ ID NO: 57), AAAgugagua (SEQ ID NO: 58), AAAgugaguc (SEQ ID NO: 59), AAAgugagug (SEQ ID NO: 60), AAAgugaguu (SEQ ID NO: 61), AAAgugcguc (SEQ ID NO: 62), AAAgugcuga (SEQ ID NO: 63), AAAgugggguc (SEQ ID NO: 64), AAAgugggguu (SEQ ID NO: 65), AAAgugguaa (SEQ ID NO: 66), AAAguguaug (SEQ ID NO: 67), AAAgugugug (SEQ ID NO: 68), AAAguguguu (SEQ ID NO: 69), AAAguuaagu (SEQ ID NO: 70), AAAguuacuu (SEQ ID NO: 71), AAAguuagug (SEQ ID NO: 72), AAAguuaugu (SEQ ID NO: 73), AAAguugagu (SEQ ID NO: 74), AAAguuugua (SEQ ID NO: 75), AACguaaaac (SEQ ID NO: 76), AACguaaagc (SEQ ID NO: 77), AACguaaagg (SEQ ID NO: 78), AACguaagca (SEQ ID NO: 79), AACguaaggg (SEQ ID NO: 80), AACguaaguc (SEQ ID NO: 81), AACguaagug (SEQ ID NO: 82), AACguaaugg (SEQ ID NO: 83), AACguaguga (SEQ ID NO: 84), AACguaugua (SEQ ID NO: 85), AACguauguu (SEQ ID NO: 86), AACgugagca (SEQ ID NO: 87), AACgugagga (SEQ ID NO: 88), AACgugauuu (SEQ ID NO: 89), AACgugggau (SEQ ID NO: 90), AACgugggua (SEQ ID

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Additional exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include AAGgcaagau (SEQ ID NO: 96), AUGguaugug (SEQ ID NO: 937), GGGgugaggc (SEQ ID NO: 2281), CAGguaggug (SEQ ID NO: 1222), AAGgucagua (SEQ ID NO: 293), AAGguuagag (SEQ ID NO: 3055), AUGgcacuua (SEQ ID NO: 3056), UAAguaaguc (SEQ ID NO: 2423), UGGgugagcu (SEQ ID NO: 3057), CGAgcugggc (SEQ ID NO: 3058), AAAgcacccc (SEQ ID NO: 3059), UAGgugggggg (SEQ ID NO: 3060), AGAguaacgu (SEQ ID NO: 3061), UCGgugaugu (SEQ ID NO: 3062), AAUgucaguu (SEQ ID NO: 516), AGGgucugag (SEQ ID NO: 3063), GAGgugacug (SEQ ID NO: 3064), AUGguagguu (SEQ ID NO: 3065), GAGgucuguc (SEQ ID NO: 2000), CAGguaugug (SEQ ID NO: 1260), CAAguacugc (SEQ ID NO: 3066), CACgugcgua (SEQ ID NO: 3067), CCGgugagcu (SEQ ID NO: 3068), CAGguacuuc (SEQ ID NO: 3069), CAGgcgagag (SEQ ID NO: 1115), GAAgcaagua (SEQ ID NO: 3070), AGGgugagca (SEQ ID NO: 789), CAGgcaaguc (SEQ ID NO: 3071), AAGgugaggc (SEQ ID NO: 344), CAGguaagua (SEQ ID NO: 1147), CCAguugggu (SEQ ID NO: 3072), AAGgugugggg (SEQ ID NO: 3073), CAGguuggag (SEQ ID NO: 1484), CCGguaugaa (SEQ ID NO: 3074), UGGguaaugu (SEQ ID NO: 2845), CAGgugaggu (SEQ ID NO: 1344), AGAguaauag (SEQ ID NO: 3075), CAGguaugag (SEQ ID NO: 1249), AUGguaaguu (SEQ ID NO: 901), UUGgugggguc (SEQ ID NO: 3015), UUUguaagca (SEQ ID NO: 3036), CUCguaugcc (SEQ ID NO: 3076),

UAGguaagag (SEQ ID NO: 2483), UAGgcaaguu (SEQ ID NO: 3077), GGAguuaagu (SEQ ID NO: 3078), GAGguaugcc (SEQ ID NO: 1959), AAGguguggu (SEQ ID NO: 402), CAGgugggug (SEQ ID NO: 1415), UUAguaagua (SEQ ID NO: 2933), AAGguuggcu (SEQ ID NO: 3079), UGAguaugug (SEQ ID NO: 3080), CCAgccuucc (SEQ ID NO: 3081), CCUguacgug (SEQ ID NO: 3082), CCUguaggua (SEQ ID NO: 1601), CAGguacgcu (SEQ ID NO: 3083), GAGguucuuc (SEQ ID NO: 3084), AAGguugccu (SEQ ID NO: 3085), CGUguucacu (SEQ ID NO: 3086), CGGgugggga (SEQ ID NO: 3087), UAGgugggau (SEQ ID NO: 2614), CGGguaagga (SEQ ID NO: 3088), AAGguacuau (SEQ ID NO: 195), GGGguaagcu (SEQ ID NO: 2248), ACGguagagc (SEQ ID NO: 3089), CAGgugaaga (SEQ ID NO: 1318), GCGguaagag (SEQ ID NO: 3090), CAGguguugu (SEQ ID NO: 3091), GAAguuugug (SEQ ID NO: 3092), AUGgugagca (SEQ ID NO: 955), CGGguucgug (SEQ ID NO: 3093), AUUguccggc (SEQ ID NO: 3094), GAUgugugug (SEQ ID NO: 3095), AUGgucuguu (SEQ ID NO: 3096), AAGguaggau (SEQ ID NO: 219), CCGguaagau (SEQ ID NO: 1575), AAGguaaaga (SEQ ID NO: 126), GGGgugaguu (SEQ ID NO: 2285), AGGguuggug (SEQ ID NO: 808), GGAgugagug (SEQ ID NO: 2228), AGUguaagga (SEQ ID NO: 3097), UAGguaacug (SEQ ID NO: 2480), AAGgugaaga (SEQ ID NO: 3098), UGGguaagug (SEQ ID NO: 2843), CAGguaagag (SEQ ID NO: 1140), UAGgugagcg (SEQ ID NO: 3099), GAGguaaaaa (SEQ ID NO: 1865), GCCguaaguu (SEQ ID NO: 3100), AAGguuuugu (SEQ ID NO: 473), CAGgugagga (SEQ ID NO: 1341), ACAgcccaug (SEQ ID NO: 3101), GCGgugagcc (SEQ ID NO: 3102), CAGguaugca (SEQ ID NO: 1251), AUGguaccua (SEQ ID NO: 3103), CAAguaugua (SEQ ID NO: 1050), AUGguggugc (SEQ ID NO: 3104), UAAguggcag (SEQ ID NO: 3105), UAGguauagu (SEQ ID NO: 3106), CUGguauuua (SEQ ID NO: 3107), AGGguaaacg (SEQ ID NO: 3108), AUAguaagug (SEQ ID NO: 850), UUGguacuga (SEQ ID NO: 3109), GGUguaagcc (SEQ ID NO: 2303), GAGguggaua (SEQ ID NO: 3110), GAUguaagaa (SEQ ID NO: 3111), ACGgucaguu (SEQ ID NO: 3112), UAAguaaaca (SEQ ID NO: 3113), AAGguaucug (SEQ ID NO: 251), AGGguauuug (SEQ ID NO: 3114), AAGgugaaug (SEQ ID NO: 328), CUGgugaauu (SEQ ID NO: 1749), CAGguuuuuu (SEQ ID NO: 1514), CAUguaugug (SEQ ID NO: 1534), UUGguagagg (SEQ ID NO: 2973), AAGguaugcc (SEQ ID NO: 258), CAGgugccac (SEQ ID NO: 3115), UCGguauuga (SEQ ID NO: 2727), AAGguuugug (SEQ ID NO: 468), AAUguacagg (SEQ ID NO: 3116), CAUguggguu (SEQ ID NO: 1545), CAUgugaguu (SEQ ID NO: 1542), UUGguaaugu (SEQ ID NO: 2968), AGUguaggug (SEQ ID NO: 3117), GAGguaacuc (SEQ ID NO: 3118), GAGguggcgc (SEQ ID NO: 3119), CUGguaauug

(SEQ ID NO: 3120), GAGguuugcu (SEQ ID NO: 3121), UGUguacgug (SEQ ID NO: 3122), UAGguaaaga (SEQ ID NO: 2468), CUAguaggca (SEQ ID NO: 3123), UCUgugaguc (SEQ ID NO: 2761), UCUguaaggc (SEQ ID NO: 3124), CAGguuugug (SEQ ID NO: 1509), GAGguagggc (SEQ ID NO: 1935), AAGguaacca (SEQ ID NO: 3125), ACUgugaguu (SEQ ID NO: 646), UAGguaauag (SEQ ID NO: 2495), AAAguaagcu (SEQ ID NO: 17), AUGgugagug (SEQ ID NO: 963), UAGguuugug (SEQ ID NO: 2645), AACguaggac (SEQ ID NO: 3126), GUAgcaggua (SEQ ID NO: 3127), GAGgucagac (SEQ ID NO: 3128), AGGguaugaa (SEQ ID NO: 3129), GAGguuagug (SEQ ID NO: 2089), CAGgcacgug (SEQ ID NO: 3130), GGGgcaagac (SEQ ID NO: 3131), CAGgugugc (SEQ ID NO: 1441), CAGguauuga (SEQ ID NO: 1265), CAGguauguc (SEQ ID NO: 1259), AAGgcaaggu (SEQ ID NO: 3132), UUGgugagaa (SEQ ID NO: 3133), AAGguaaaau (SEQ ID NO: 122), GGGguaagua (SEQ ID NO: 2251), AAGguaucuu (SEQ ID NO: 252), GACgugaguc (SEQ ID NO: 3134), UAUguaugcu (SEQ ID NO: 3135), AAGguacugu (SEQ ID NO: 199), CAGgugaacu (SEQ ID NO: 3136), CACguaaaug (SEQ ID NO: 3137), AAGgugugau (SEQ ID NO: 3138), GAAguauuug (SEQ ID NO: 3139), AAGgucugug (SEQ ID NO: 3140), AAGguggagg (SEQ ID NO: 3141), AAGguauaug (SEQ ID NO: 244), CAGguucuua (SEQ ID NO: 1477), AGGguaacca (SEQ ID NO: 730), CAGgugucac (SEQ ID NO: 1423), AAAguucugu (SEQ ID NO: 3142), UUGgugaguu (SEQ ID NO: 3007), CAAgugaguc (SEQ ID NO: 1067), UAGguagguc (SEQ ID NO: 2525), GCGgugagcu (SEQ ID NO: 2180), AUUgugagga (SEQ ID NO: 3143), CAGgugcaca (SEQ ID NO: 1361), CAGguuggaa (SEQ ID NO: 3144), CUGgucacuu (SEQ ID NO: 3145), GGAguaagug (SEQ ID NO: 2214), GAGgugggcu (SEQ ID NO: 2059), AAGguacuug (SEQ ID NO: 201), AGGguaggau (SEQ ID NO: 3146), AAUguguguu (SEQ ID NO: 3147), ACAguuaagu (SEQ ID NO: 568), GAGgugugug (SEQ ID NO: 2078), AAGgcgggcu (SEQ ID NO: 3148), AUAgcaagua (SEQ ID NO: 3149), AAGguuguua (SEQ ID NO: 454), CAAgcaaggc (SEQ ID NO: 3150), GUGguaauua (SEQ ID NO: 3151), UCUguucagu (SEQ ID NO: 3152), AGGguaggcc (SEQ ID NO: 754), AAGguaucau (SEQ ID NO: 3153), UAGguaccuu (SEQ ID NO: 2509), AAGguaugac (SEQ ID NO: 254), GGAguaggua (SEQ ID NO: 2219), UAAguuggca (SEQ ID NO: 3154), AGUgugaggc (SEQ ID NO: 3155), GAGguuugug (SEQ ID NO: 3156), UGGgucugcu (SEQ ID NO: 3157), CAGgugaucc (SEQ ID NO: 1350), CAGgucagug (SEQ ID NO: 1283), AAGguaaggg (SEQ ID NO: 151), CAGgugcagu (SEQ ID NO: 3158), GAGguggguc (SEQ ID NO: 2064), GCUgugagug (SEQ ID NO: 2206), AAGguggagu (SEQ ID NO: 3159), GGGgucaguu (SEQ ID NO: 3160),

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CUGguacuaa (SEQ ID NO: 1721), GAGguagcug (SEQ ID NO: 1929), CUUgucagcu (SEQ ID NO: 4408), UAGguaaggc (SEQ ID NO: 2489), CUGguauuac (SEQ ID NO: 4409), UAAguacguc (SEQ ID NO: 4410), AAGguaagcc (SEQ ID NO: 146), ACGgugaaag (SEQ ID NO: 4411), CCAgccaaua (SEQ ID NO: 4412), CAGguuuguc (SEQ ID NO: 4413), AAGguauaau (SEQ ID NO: 239), AAGgucuuag (SEQ ID NO: 4414), AGGgugagcu (SEQ ID NO: 791), AAGguuaggg (SEQ ID NO: 4415), CGGguaaauu (SEQ ID NO: 4416), CAGguaacgg (SEQ ID NO: 4417), AGAgugugua (SEQ ID NO: 4418), ACAguaaguu (SEQ ID NO: 549), GAUguaauuu (SEQ ID NO: 4419), GAGguaggga (SEQ ID NO: 1934), UUGgcaagug (SEQ ID NO: 2945), AAAgugagga (SEQ ID NO: 4420), AAGguagugc (SEQ ID NO: 234), AGAguaauuc (SEQ ID NO: 674), GGAguaaaua (SEQ ID NO: 4421), GUGguaccca (SEQ ID NO: 4422), CAGguauugc (SEQ ID NO: 4423), GAUgugaggg (SEQ ID NO: 4424), CAAguaaauc (SEQ ID NO: 1017), CAGgugucuc (SEQ ID NO: 1428), AAGguaacag (SEQ ID NO: 4425), UUGguaaaag (SEQ ID NO: 4426), CAGguaucau (SEQ ID NO: 1240), ACGgugagac (SEQ ID NO: 4427), CUGguaugac (SEQ ID NO: 4428), CAGguucacu (SEQ ID NO: 4429), GAGgugauca (SEQ ID NO: 4430), AGUguaaguc (SEQ ID NO: 4431), AACguaagua (SEQ ID NO: 4432), AAAgugagug (SEQ ID NO: 60), GAGguacagg (SEQ ID NO: 4433), CAAguaauga (SEQ ID NO: 4434), GAUguaagga (SEQ ID NO: 4435), UCAguucccc (SEQ ID NO: 4436), GCGguaagga (SEQ ID NO: 4437), UAGguacuaa (SEQ ID NO: 4438), AAGgugaaag (SEQ ID NO: 321), ACUguaagug (SEQ ID NO: 4439), UGGguaugug (SEQ ID NO: 2862), AUGguaacag (SEQ ID NO: 884), CAGguagggu (SEQ ID NO: 1219), ACAguaagug (SEQ ID NO: 548), AAGgugcucc (SEQ ID NO: 366), AAGgugugcu (SEQ ID NO: 4440), AAGgugguga (SEQ ID NO: 4441), ACGgugcgcc (SEQ ID NO: 4442), AAGguauugc (SEQ ID NO: 4443), GGGguaugug (SEQ ID NO: 2267), CAGgugggcu (SEQ ID NO: 1408), GAGguauguu (SEQ ID NO: 1968), AACgugaaua (SEQ ID NO: 4444), CAGguaaugg (SEQ ID NO: 1154), UAGguaugau (SEQ ID NO: 4445), CAGgcaggug (SEQ ID NO: 1108), GGGguugguc (SEQ ID NO: 4446), AAGguauggg (SEQ ID NO: 262), UAAgugaggc (SEQ ID NO: 4447), CAAgugaucg (SEQ ID NO: 4448), AAAguacggg (SEQ ID NO: 4449), AGAgcuacag (SEQ ID NO: 4450), GAGgugggaa (SEQ ID NO: 2054), CAGguacuuu (SEQ ID NO: 1195), GAGgugagag (SEQ ID NO: 2016), CAGguagguc (SEQ ID NO: 1221), UGGguacagc (SEQ ID NO: 4451), AAGgugucag (SEQ ID NO: 396), AAGgcaagaa (SEQ ID NO: 4452), GAGguaaaca (SEQ ID NO: 4453), AAGguaaagu (SEQ ID NO: 129), AAGguaguca (SEQ ID NO: 4454), CUGguauguc (SEQ ID NO: 4455), GAGguauggg (SEQ ID

NO: 1963), AAGguauugu (SEQ ID NO: 273), CUGguacuga (SEQ ID NO: 4456), GAGguaagcu (SEQ ID NO: 1888), UGGgugggua (SEQ ID NO: 2883), CAGguucgug (SEQ ID NO: 4457), AAGguauggu (SEQ ID NO: 4458), CAGgugagca (SEQ ID NO: 1337), UGGguaaauu (SEQ ID NO: 2827), UGUguaggug (SEQ ID NO: 4459), UGUgugagcc (SEQ ID NO: 2921), CUGguaauau (SEQ ID NO: 4460), AAAguauguu (SEQ ID NO: 45), UGUguaagaa (SEQ ID NO: 2903), CUAgugagaa (SEQ ID NO: 4461), AGGguagguc (SEQ ID NO: 757), AAGgugggug (SEQ ID NO: 385), UCGguaagug (SEQ ID NO: 4462), AGUguaaaua (SEQ ID NO: 812), GAUguaagug (SEQ ID NO: 2122), AAGguuagug (SEQ ID NO: 424), UAGguaagca (SEQ ID NO: 2485), CAAgugagaa (SEQ ID NO: 1061), AGUguaagua (SEQ ID NO: 819), CAGgugaauc (SEQ ID NO: 1321), UGGgugagac (SEQ ID NO: 2868), AAGguagggc (SEQ ID NO: 224), CUGguuugug (SEQ ID NO: 1788), GCGguagggc (SEQ ID NO: 4463), GAGguaaucc (SEQ ID NO: 4464), AUUguaauaa (SEQ ID NO: 4465), CUGgugaaua (SEQ ID NO: 1748), AAGguuuaaa (SEQ ID NO: 4466), CCUguacugu (SEQ ID NO: 4467), GCGgugagcg (SEQ ID NO: 4468), AAGguaaucc (SEQ ID NO: 162), UAUgugagua (SEQ ID NO: 2671), CCCgugagug (SEQ ID NO: 1573), CAGgugcaga (SEQ ID NO: 1363), CAGgucaguu (SEQ ID NO: 1284), CAGguaggcu (SEQ ID NO: 4469), AAAguaagug (SEQ ID NO: 23), UAGguugguc (SEQ ID NO: 4470), CAGguugccu (SEQ ID NO: 4471), AAGguaugga (SEQ ID NO: 260), GGUguggacg (SEQ ID NO: 4472), AAAgugagaa (SEQ ID NO: 51), AGGgugagag (SEQ ID NO: 788), GAUguggcau (SEQ ID NO: 4473), UCGguaaggu (SEQ ID NO: 4474), GAGgugcguc (SEQ ID NO: 4475), CGGgugaguc (SEQ ID NO: 4476), AAGguacggg (SEQ ID NO: 190), GAGguucuug (SEQ ID NO: 4477), AAGgugcuug (SEQ ID NO: 4478), UAGguaugua (SEQ ID NO: 2551), AUGgucagca (SEQ ID NO: 4479), CGGguacuca (SEQ ID NO: 4480), AGGgugagga (SEQ ID NO: 792), AUCgugagua (SEQ ID NO: 869), UCAguaagua (SEQ ID NO: 2689), UAGguaaaua (SEQ ID NO: 2469), AAGguaauug (SEQ ID NO: 170), GAAgucagug (SEQ ID NO: 1835), CAGguacaaa (SEQ ID NO: 1160), AAAguuaauc (SEQ ID NO: 4481), AGCgugagcg (SEQ ID NO: 4482), CCGgcuggug (SEQ ID NO: 4483), AGUguaauuu (SEQ ID NO: 4484), UGAgccacuc (SEQ ID NO: 4485), GGGgucugua (SEQ ID NO: 4486), AUGgcauguc (SEQ ID NO: 4487), CGGguaaaga (SEQ ID NO: 4488), AGGguagcau (SEQ ID NO: 4489), CGGguaggag (SEQ ID NO: 1631), GAGguucgug (SEQ ID NO: 4490), UAAguuauuc (SEQ ID NO: 4491), UAUguaagau (SEQ ID NO: 2650), AAGguaguuu (SEQ ID NO: 237), CAGgugguau (SEQ ID NO: 4492), GUGguaauga (SEQ ID NO: 2355), AAGgugauuu (SEQ ID NO: 359), CAGgugaagu

(SEQ ID NO: 4493), GUAguaauua (SEQ ID NO: 4494), AUGguuggug (SEQ ID NO: 4495), CCAguaagug (SEQ ID NO: 1557), UAGgugagag (SEQ ID NO: 2589), AUGgugaggc (SEQ ID NO: 959), AAAguuagug (SEQ ID NO: 72), AAGgugccuu (SEQ ID NO: 4496), UAGguaugag (SEQ ID NO: 2546), CAGgugugac (SEQ ID NO: 1431), CUGgugggguu (SEQ ID NO: 1774), AUGguaagga (SEQ ID NO: 896), UCUguaagaa (SEQ ID NO: 2740), UCCgugaguu (SEQ ID NO: 4497), AAAgcaggua (SEQ ID NO: 4498), UAUgugagug (SEQ ID NO: 2672), CAGguggagg (SEQ ID NO: 4499), CAGguuagac (SEQ ID NO: 4500), AUAguaagac (SEQ ID NO: 846), AAGguguugu (SEQ ID NO: 4501), GAGgucugug (SEQ ID NO: 4502), AAGguaagau (SEQ ID NO: 144), CAUguaaguu (SEQ ID NO: 1524), CUGguaauua (SEQ ID NO: 4503), CAGguaggcg (SEQ ID NO: 4504), AGAguaaguc (SEQ ID NO: 669), UGGgugagga (SEQ ID NO: 2872), AAUguaggua (SEQ ID NO: 4505), UAGguuagca (SEQ ID NO: 4506), GGGguaggua (SEQ ID NO: 2258), GAGguauugc (SEQ ID NO: 4507), AUUguacaca (SEQ ID NO: 4508), GAAguaggua (SEQ ID NO: 4509), GGAguaagcu (SEQ ID NO: 2212), UAGguaugug (SEQ ID NO: 2553), GAGgugaaua (SEQ ID NO: 2007), GAGgugggau (SEQ ID NO: 2056), AAGguaaucu (SEQ ID NO: 163), GGUgugaguu (SEQ ID NO: 4510), AACgugaguu (SEQ ID NO: 4511), GAGguaaccg (SEQ ID NO: 4512), UAGguaagga (SEQ ID NO: 2488), AUUguaagaa (SEQ ID NO: 4513), UGGgugagca (SEQ ID NO: 2870), AAGguaaggc (SEQ ID NO: 150), CCAguaucgu (SEQ ID NO: 4514), CCGgugggug (SEQ ID NO: 4515), GAGguagugu (SEQ ID NO: 4516), ACGgugggaa (SEQ ID NO: 4517), GAGgugaccu (SEQ ID NO: 2011), CACguaugua (SEQ ID NO: 4518), AGGgugggga (SEQ ID NO: 799), AAUguaaguc (SEQ ID NO: 490), AAAguuaagu (SEQ ID NO: 70), CAUgugagug (SEQ ID NO: 1541), AGAguauguc (SEQ ID NO: 694), GCGguaugac (SEQ ID NO: 4519), CGGgugaguu (SEQ ID NO: 1643), CCGguauuuu (SEQ ID NO: 4520), GAGguagaac (SEQ ID NO: 4521), UAGguaugaa (SEQ ID NO: 2545), CAGgcgcgug (SEQ ID NO: 4522), CAAguaaguc (SEQ ID NO: 1027), AGUguaagau (SEQ ID NO: 816), AAGguucuac (SEQ ID NO: 4523), CCAguaagua (SEQ ID NO: 1555), GAGguagcag (SEQ ID NO: 4524), CAGgucuguu (SEQ ID NO: 1312), CAGguacaau (SEQ ID NO: 1162), CCGguaaaga (SEQ ID NO: 1574), UAAgugcugu (SEQ ID NO: 4525), AGGgugagaa (SEQ ID NO: 786), CUCguaaggu (SEQ ID NO: 4526), CAGgucagcu (SEQ ID NO: 4527), CAGguaaggc (SEQ ID NO: 1144), AGGgugcagg (SEQ ID NO: 4528), GAGgugaaac (SEQ ID NO: 4529), AGGguaagua (SEQ ID NO: 740), AAUguaugcc (SEQ ID NO: 4530), AAGguaagca (SEQ ID NO: 145), ACGguacggu (SEQ ID NO: 587), AAGguaauga (SEQ ID NO: 164),

UCUgcucaau (SEQ ID NO: 4531), ACGguaaugu (SEQ ID NO: 4532), AAGguaguug (SEQ ID NO: 4533), ACGguaagug (SEQ ID NO: 580), CAGgugauga (SEQ ID NO: 4534), GAGguaacac (SEQ ID NO: 4535), GAGguaggua (SEQ ID NO: 1937), CAGguaccuu (SEQ ID NO: 1179), CAGguaauaa (SEQ ID NO: 1150), UUGgugggug (SEQ ID NO: 3016), CUGguaauga (SEQ ID NO: 1710), UAGguaaguc (SEQ ID NO: 2492), AGGgugugac (SEQ ID NO: 4536), GAGgcaauaa (SEQ ID NO: 4537), GUGguaaagc (SEQ ID NO: 4538), CUGgugggcg (SEQ ID NO: 4539), GAUguauguu (SEQ ID NO: 2128), AGGgugagac (SEQ ID NO: 787), UCGgucagca (SEQ ID NO: 4540), AUGgugauua (SEQ ID NO: 4541), CGAgugugua (SEQ ID NO: 4542), CAGguuggug (SEQ ID NO: 1488), AGCgcaagua (SEQ ID NO: 4543), UGGguacguu (SEQ ID NO: 4544), GAGguauuug (SEQ ID NO: 1974), AGUguacaua (SEQ ID NO: 4545), AUGguaagua (SEQ ID NO: 898), ACAguagguu (SEQ ID NO: 4546), AAGgugagag (SEQ ID NO: 337), UUGgugaagu (SEQ ID NO: 4547), AAAguaugua (SEQ ID NO: 43), UGGguaagga (SEQ ID NO: 4548), UAGgugccuu (SEQ ID NO: 4549), and CCUgugggug (SEQ ID NO: 4550).

Additional exemplary gene sequences and splice site sequences (e.g., 5' splice site sequences) include UCCguaaguu (SEQ ID NO: 4551), GUGguaaacg (SEQ ID NO: 4552), CGGgugcggu (SEQ ID NO: 4553), CAUguacuuc (SEQ ID NO: 4554), AGAguaaagg (SEQ ID NO: 4555), CGCgugagua (SEQ ID NO: 4556), AGAgugggca (SEQ ID NO: 4557), AGAguaagcc (SEQ ID NO: 4558), AGAguaaaca (SEQ ID NO: 4559), GUGguuauga (SEQ ID NO: 4560), AGGguaauaa (SEQ ID NO: 4561), UGAguaagac (SEQ ID NO: 4562), AGAguuuguu (SEQ ID NO: 4563), CGGgucugca (SEQ ID NO: 4564), CAGguaaguc (SEQ ID NO: 4565), AAGguagaau (SEQ ID NO: 4566), CAGgucccuc (SEQ ID NO: 4567), AGAguaaugg (SEQ ID NO: 4568), GAGgucuaag (SEQ ID NO: 4569), AGAguagagu (SEQ ID NO: 4570), AUGgucagua (SEQ ID NO: 4571), GAGgccuggg (SEQ ID NO: 4572), AAGguguggc (SEQ ID NO: 4573), AGAgugaucu (SEQ ID NO: 4574), AAGguaucca (SEQ ID NO: 4575), UUCguaagua (SEQ ID NO: 4576), UAAgugggug (SEQ ID NO: 4577), GCCgugaacg (SEQ ID NO: 4578), GAGguugugg (SEQ ID NO: 4579), UAUguaugca (SEQ ID NO: 4580), UGUguaacaa (SEQ ID NO: 4581), AGGguauuag (SEQ ID NO: 4582), UGAguauauc (SEQ ID NO: 4583), AGAguuugug (SEQ ID NO: 4584), GAGgucgcug (SEQ ID NO: 4585), GAGgucaucg (SEQ ID NO: 4586), ACGguaaagc (SEQ ID NO: 4587), UGAguacuug (SEQ ID NO: 4588), CGAgucgccg (SEQ ID NO: 4589), CUGguacguc (SEQ ID NO: 4590), AGGguauugc (SEQ ID NO: 4591), GAAgugaaug (SEQ ID NO: 4592), CAGaugaguc (SEQ ID NO: 4593), UGGguauugg (SEQ ID

NO: 4594), UGAguaaaga (SEQ ID NO: 4595), GUGguuccug (SEQ ID NO: 4596), UGAgcaagua (SEQ ID NO: 4597), UAUguaagag (SEQ ID NO: 4598), AAGgucuugc (SEQ ID NO: 4599), AAAgcaugug (SEQ ID NO: 4600), AGAguacagu (SEQ ID NO: 4601), GUGguaaucc (SEQ ID NO: 4602), CAGguagagg (SEQ ID NO: 4603), AAGguacaac (SEQ ID NO: 4604), UGGgcagcau (SEQ ID NO: 4605), CCGgucauca (SEQ ID NO: 4606), CCGguuugua (SEQ ID NO: 4607), UGAguaaggg (SEQ ID NO: 4608), GAAguaugua (SEQ ID NO: 4609), GGGguagcuc (SEQ ID NO: 4610), GCUguacaua (SEQ ID NO: 4611), CUGgucucuu (SEQ ID NO: 4612), GUGguaaaug (SEQ ID NO: 4613), AUCguaagug (SEQ ID NO: 4614), GAGgcaugua (SEQ ID NO: 4615), AAGgucuccc (SEQ ID NO: 4616), UGGgugcguu (SEQ ID NO: 4617), UGUguagguu (SEQ ID NO: 4618), GAAgugagca (SEQ ID NO: 4619), GGUguaauuu (SEQ ID NO: 4620), CUGgugaaau (SEQ ID NO: 4621), AUCguaaguc (SEQ ID NO: 4622), AGAguaaucc (SEQ ID NO: 4623), GGAguagguc (SEQ ID NO: 4624), GAGguaccaa (SEQ ID NO: 4625), CUUguaggug (SEQ ID NO: 4626), AAGguauaag (SEQ ID NO: 4627), AGAguuggua (SEQ ID NO: 4628), AUGguuugug (SEQ ID NO: 4629), UGGgucagau (SEQ ID NO: 4630), AGAguaggac (SEQ ID NO: 4631), AGAguagugu (SEQ ID NO: 4632), AGAguaggag (SEQ ID NO: 4633), CAGgucucua (SEQ ID NO: 4634), AAGguggaug (SEQ ID NO: 4635), UGGguaucaa (SEQ ID NO: 4636), GAUguaugga (SEQ ID NO: 4637), AAGguguuuc (SEQ ID NO: 4638), GCAguguaaa (SEQ ID NO: 4639), UUAguaugua (SEQ ID NO: 4640), UCUguaugca (SEQ ID NO: 4641), AAUguaaaau (SEQ ID NO: 4642), AGAguaaauu (SEQ ID NO: 4643), GGGguacuuu (SEQ ID NO: 4644), GAAguuugau (SEQ ID NO: 4645), AAAguagauu (SEQ ID NO: 4646), UGUguagagu (SEQ ID NO: 4647), UGGguaagcg (SEQ ID NO: 4648), CGGguucagg (SEQ ID NO: 4649), AGGguacgac (SEQ ID NO: 4650), UCGguaagaa (SEQ ID NO: 4651), AGGguuggca (SEQ ID NO: 4652), AAAguacagu (SEQ ID NO: 4653), UAAguuaagg (SEQ ID NO: 4654), AUGguaaugu (SEQ ID NO: 4655), GUGguuuuac (SEQ ID NO: 4656), AGAguaacaa (SEQ ID NO: 4657), AAGguagccc (SEQ ID NO: 4658), GCGgugaggc (SEQ ID NO: 4659), AUGguucagc (SEQ ID NO: 4660), AAGguacuua (SEQ ID NO: 4661), AAGguccgug (SEQ ID NO: 4662), UAGguaagcg (SEQ ID NO: 4663), AUGguaccuu (SEQ ID NO: 4664), GCCguggugg (SEQ ID NO: 4665), CUGgugcguc (SEQ ID NO: 4666), CAGguggaaa (SEQ ID NO: 4667), AAAgucugua (SEQ ID NO: 4668), GAGguaaccc (SEQ ID NO: 4669), AGAguauggg (SEQ ID NO: 4670), UAUgccccug (SEQ ID NO: 4671), AAGgugccag (SEQ ID NO: 4672), ACGgugcggc (SEQ ID NO: 4673), AGGguacuga (SEQ ID NO: 4674), AGAguaagcg (SEQ ID NO: 4675), CUGgcaaggg

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UUUguaaaaa (SEQ ID NO: 5403), GAAguuugua (SEQ ID NO: 5404), CUAguaaucu (SEQ ID NO: 5405), AAGguuuuua (SEQ ID NO: 5406), GAGgugcguu (SEQ ID NO: 5407), UAGgcgagua (SEQ ID NO: 5408), ACCgugagua (SEQ ID NO: 5409), CAGgucccga (SEQ ID NO: 5410), AUGguacugg (SEQ ID NO: 5411), UGAguucagu (SEQ ID NO: 5412), AAUguguggu (SEQ ID NO: 5413), UCCguugguu (SEQ ID NO: 5414), CAGgucagag (SEQ ID NO: 5415), CAGgucccua (SEQ ID NO: 5416), UAGguagacu (SEQ ID NO: 5417), CAAguuaagg (SEQ ID NO: 5418), GAGgugugcg (SEQ ID NO: 5419), GAAgcugccc (SEQ ID NO: 5420), CGAguacgug (SEQ ID NO: 5421), CGGguaggua (SEQ ID NO: 5422), UUGguauuga (SEQ ID NO: 5423), AUUguaugau (SEQ ID NO: 5424), UUGguaugaa (SEQ ID NO: 5425), GAGgugguca (SEQ ID NO: 5426), GCUguaugaa (SEQ ID NO: 5427), CAGguguugc (SEQ ID NO: 5428), CAGguaaaac (SEQ ID NO: 5429), AUAguaaggu (SEQ ID NO: 5430), CUGguuagag (SEQ ID NO: 5431), AGCgugugag (SEQ ID NO: 5432), AAGguuaucu (SEQ ID NO: 5433), CACgugagua (SEQ ID NO: 5434), AGGgucagua (SEQ ID NO: 5435), GAGguauaau (SEQ ID NO: 5436), CAGguuauuu (SEQ ID NO: 5437), AGGguggacu (SEQ ID NO: 5438), AUUguaauuc (SEQ ID NO: 5439), UUUguggguu (SEQ ID NO: 5440), AUGguacgug (SEQ ID NO: 5441), AAGguguucc (SEQ ID NO: 5442), CAGgugacgc (SEQ ID NO: 5443), GAGguacuaa (SEQ ID NO: 5444), ACAguucagu (SEQ ID NO: 5445), GAGgucacgg (SEQ ID NO: 5446), CAAguaaggc (SEQ ID NO: 5447), AAGguuuggg (SEQ ID NO: 5448), AAAgugggcu (SEQ ID NO: 5449), GCGguucuug (SEQ ID NO: 5450), GAGguggagc (SEQ ID NO: 5451), UGAgucagug (SEQ ID NO: 5452), CAGgucaagg (SEQ ID NO: 5453), AGUguaagcu (SEQ ID NO: 5454), GAGgcagaaa (SEQ ID NO: 5455), AAGgucacac (SEQ ID NO: 5456), GAAguagguu (SEQ ID NO: 5457), GUCguaaguu (SEQ ID NO: 5458), AGAguaugca (SEQ ID NO: 5459), CCUgugcaaa (SEQ ID NO: 5460), ACGgugaaaa (SEQ ID NO: 5461), CAGguacgaa (SEQ ID NO: 5462), CAUgugagga (SEQ ID NO: 5463), AGCgugagua (SEQ ID NO: 5464), GGUguguagg (SEQ ID NO: 5465), AACgugagcu (SEQ ID NO: 5466), GAGgugaacu (SEQ ID NO: 5467), AGAguucagu (SEQ ID NO: 5468), AACgugugua (SEQ ID NO: 5469), CAGguugugg (SEQ ID NO: 5470), AAGguacuag (SEQ ID NO: 5471), UCAgugaaaa (SEQ ID NO: 5472), AAUgucuggu (SEQ ID NO: 5473), ACGguaaaau (SEQ ID NO: 5474), CUGguguaag (SEQ ID NO: 5475), GAGgugcgaa (SEQ ID NO: 5476), AGGguuucuc (SEQ ID NO: 5477), CAGguagccc (SEQ ID NO: 5478), AUUguauugg (SEQ ID NO: 5479), AUGguacuua (SEQ ID NO: 5480), GAGgcccgac (SEQ ID NO: 5481), UCGguaagac (SEQ ID NO: 5482), CGGgcuguag

(SEQ ID NO: 5483), UAUgugugug (SEQ ID NO: 5484), UAGguagaaa (SEQ ID NO: 5485), GUGgucauua (SEQ ID NO: 5486), UAGgugaaag (SEQ ID NO: 5487), ACUguaauuc (SEQ ID NO: 5488), GCAguacagg (SEQ ID NO: 5489), UCGgugaguc (SEQ ID NO: 5490), UAUguaggga (SEQ ID NO: 5491), AUGguauguc (SEQ ID NO: 5492), GUGgugugug (SEQ ID NO: 5493), CUGgugaccu (SEQ ID NO: 5494), AAUgugaaua (SEQ ID NO: 5495), UAGgucucac (SEQ ID NO: 5496), GAGguuauug (SEQ ID NO: 5497), UGAguaggcu (SEQ ID NO: 5498), CGGgcacgua (SEQ ID NO: 5499), GCAguaaaua (SEQ ID NO: 5500), CCGgugagag (SEQ ID NO: 5501), UAAguugguc (SEQ ID NO: 5502), CCGgugagcc (SEQ ID NO: 5503), AAGguuguca (SEQ ID NO: 5504), CUGguauuau (SEQ ID NO: 5505), GGGguauggg (SEQ ID NO: 5506), AAAgucagua (SEQ ID NO: 5507), UUUguaugua (SEQ ID NO: 5508), UAAguacugc (SEQ ID NO: 5509), CAGguaccaa (SEQ ID NO: 5510), GAAguucaga (SEQ ID NO: 5511), AUGgugcggu (SEQ ID NO: 5512), GUGgugaggu (SEQ ID NO: 5513), UGAguaagcc (SEQ ID NO: 5514), UAUguaaggg (SEQ ID NO: 5515), GUGguggaaa (SEQ ID NO: 5516), GAGgugauug (SEQ ID NO: 5517), GGAguuugua (SEQ ID NO: 5518), AAGgucacga (SEQ ID NO: 5519), GUGguagagg (SEQ ID NO: 5520), UAAguauauc (SEQ ID NO: 5521), AAGgugucca (SEQ ID NO: 5522), UAUgugguau (SEQ ID NO: 5523), GAGguacaau (SEQ ID NO: 5524), AAGgugggggg (SEQ ID NO: 5525), GGAguaggug (SEQ ID NO: 5526), and UAGgugacuu (SEQ ID NO: 5527).

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 (SEQ ID NO: 667).

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) or (II) 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) or (II) 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 (II) 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 (II) 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 (II) 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) or (II). 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 (II), 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 (II) 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) or (II) 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 (II), 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 (II), 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) or (II) 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) or (II) 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 (II), 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 (II), 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. In some embodiments, the neurological disease comprises spinal muscular atrophy (SMA). 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 (II), 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 (II), 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 (II), 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 (II), 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 (II), 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 (II), 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 (II), 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) or (II) increases expression of the haploinsufficient gene locus. In an embodiment, a compound of Formula (I) or (II) 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 (II), 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) or (II) 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 (II), 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) or (II) 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). In some embodiments, absolute stereochemistry of chiral compounds provided herein is arbitrarily assigned.

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.)

Reverse flash chromagraphy: Column: C18 silica gel.

Condition 1: Mobile Phase A: water; Mobile Phase B: methanol. Gradient 1: 10% B to 50% B in 10 min.

Condition 2: Mobile Phase A: methanol; Mobile Phase B: dichloromethane. Gradient 1: 0% B to 10% B in 10 min.

Condition 3: Mobile Phase A: water (10 mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Gradient 1: 20% B to 40% B in 30 min; Gradient 2: 10% B to 30% B in 20 min.

Condition 4: Mobile Phase A: water (0.1% TFA); Mobile Phase B: acetonitrile; Gradient 1: 12% B to 51% B in 12 min.

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 on a Waters-2545 or Shimadzu, using column: X-Select CSH C18 OBD (130Å, 5 μm, 30 mm x 150 mm), XBridge Prep OBD C18 (30 x 150mm, 5μm), or XBridge Prep C18 OBD (5um, 19 mm x 150 mm).

Condition 1: Column: XBridge Prep OBD C18, 30*150 mm, 5 μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 45% B to 95% B in 8 min; Gradient 2: 5% B to 50% B in 8 min; Gradient 3: 5% B to 45% B in 8 min; Gradient 4: 5% B to 55% B in 8 min; Gradient 5: 5% B to 42% B in 8 min; Gradient 6: 5% B to 35% B in 8 min; Gradient 7: 5% B to 30% B in 8 min; Gradient 8: 20% B to 66% B in 8 min; Gradient 9: 10% B to 55% B in 8 min; Gradient 10: 5% B to 40% B in 8 min; Gradient 11: 10% B in 50% B in 8 min; Gradient 12: 20% B to 50% B in 8 min; Gradient 13: 25% B to 65% B in 8 min; Gradient 14: 5% B to 85% B in 8 min; Gradient 15: 10% B to 40% B in 8 min; Gradient 16: 5% B to 37% B; Gradient 17: 5% B to 38% B in 8 min; Gradient 18: 5% B to 45% B; Gradient 19: 10% B to 46% B in 8 min; Gradient 20: 10% B to 45% B in 10 min; Gradient 21: 15% B to 60% B in 8 min; Gradient 22: 35% B to 55% B in 10 min; Gradient 23: 10% B to 55% B in 8 min; Gradient 24: 20% B to 65% B in 8 min; Gradient 25: 25% B to 70% B in 8 min; Gradient 26: 10% B to 30% B in 10 min.

Condition 2: Column: Xselect CSH OBD; Mobile Phase A: water (10 mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Gradient 1: 5% B to 35% B in 8 min; Gradient 2: 10% B to 50% B in 8 min; Gradient 3: 5% B to 45% B in 8 min; Gradient 4: 10% B to 90% B in 8

min; Gradient 5: 15% B to 75% B in 8 min; Gradient 6: 25% B to 75% B in 8 min; Gradient 7: 15% B to 50% B in 8 min; Gradient 8: 3% B to 20% B in 8 min; Gradient 9: 5% B to 65% B in 8 min.

Condition 3: Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3); Mobile Phase B: acetonitrile; Flow rate: 60 mL/min; Gradient 1: 10% B to 65% B in 8 min; Gradient 2: 5% B to 60% B in 8 min; Gradient 3: 5% B to 43% B in 8 min; Gradient 4: 5% B to 40% B in 8 min; Gradient 5: 5% B to 38% B in 8 min; Gradient 6: 5% B to 35% B in 8 min; Gradient 7: 5% B to 37% B in 8 min; Gradient 8: 5% B to 50% B in 8 min; Gradient 9: 5% B to 75% B in 8 min; Gradient 10: 5% B to 30% B in 8 min; Gradient 11: 3% B to 3% B in 2 min; Gradient 12: 3% B to 43% B in 8 min; Gradient 13: 15% B to 65% B in 8 min; Gradient 14: 40% B to 76% B in 8 min; Gradient 15: 10% B to 45% B in 8 min; Gradient 16: 5% B to 55% B in 8 min; Gradient 17: 5% B to 45% B in 8 min; Gradient 18: 10% B to 50% B in 8 min; Gradient 19: 5% B to 57% B in 8 min; Gradient 20: 15% B to 80% B in 8 min.

Condition 4: Column: Xselect CSH OBD; Mobile Phase A: water (0.05% HCl); Mobile Phase B: acetonitrile; Gradient 1: 5% B to 30% B in 8 min; Gradient 2: 10% B to 50% B in 8 min; Gradient 3: 3% B to 43% B in 6 min.

Condition 5: Column: SunFire Prep C18 OBD Column19*150 mm, 5μm 10 nm; Mobile Phase A: water (0.05%TFA), Mobile Phase B: acetonitrile; Gradient 1: 10% to 20% B in 7 min.

Condition 6: Column: C18 silica gel, XBridge, 19*150 mm; Mobile Phase A: water (0.05% NH_3H_2O), Mobile Phase B: acetonitrile; Gradient 1: 30% to 70% B in 7 min; Gradient 2: 24% B to 54% B in 7 min; Gradient 3: 25% B to 55% B in 7 min; Gradient 4: 20% B to 58% B in 8 min; Gradient 5: 22% B to 62% B in 8 min.

Condition 7: Column: Weich UItimate XB-C18 50*250mm 10um; Mobile Phase A: water (0.1% TFA), Mobile Phase B: acetonitrile; Flow rate: 90mL/min; Gradient 1: 12% B to 47% B in 12 min; Gradient 2: 10% B to 45% B in 12 min.

Condition 8: Column: SunFire Prep C18 OBD 19*150 mm, 5μm 10 nm, Mobile Phase A: water (0.05% HCl), Mobile Phase B: acetonitrile; Gradient 1: 10% to 20% B in 12 min.

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

Condition 1: Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.1% DEA); Mobile Phase B: EtOH; Flow rate: 20 mL/min; Gradient 1: 30% B to 30% B

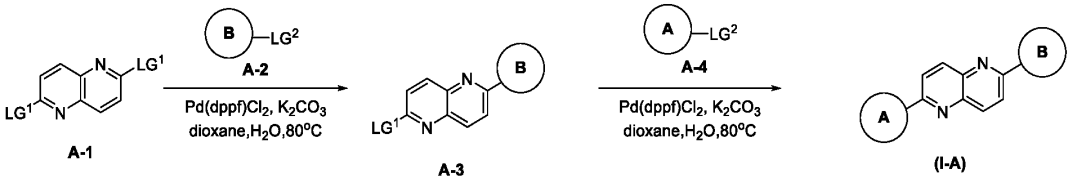
in 7 min; Gradient 2: 15% B to 15% B in 7 min; Gradient 3: 0% B to 0% B; Gradient 4: 15% B to 15% B in 10 min; Gradient 5: 15% B to 15%B in 8 min; Gradient 6: 15% B to 15% B in 8.5 min; Gradient 7: 30% B to 30% B in 7 min; Gradient 8: 30% B to 30% B in 6.5 min; Gradient 9: 30% B to 30% B in 10.5 min; Gradient 10: 15% B to 15% B in 11 min; Gradient 11: 20% B to 20% B in 7.5 min; Gradient 12: 20% B to 20% B in 6.5 min; Gradient 13: 10% B to 10% B in 7.5 min.

Condition 2: Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.1% DEA); Mobile Phase B: EtOH; Flow rate 1: 20 mL/min; Flow rate 2: Gradient 1: 20% B to 20% B in 15 min; Gradient 2: 0% B to 0% B.

Condition 3: Column: CHIRALPAK IA-3, 4.6*50mm, 3 μm; Mobile Phase A: MtBE (0.1%DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient 1: 0% B to 0% B.

General Schemes

Compounds of the present disclosure may be prepared using a synthetic protocol illustrated below in Schemes A, B, and C.

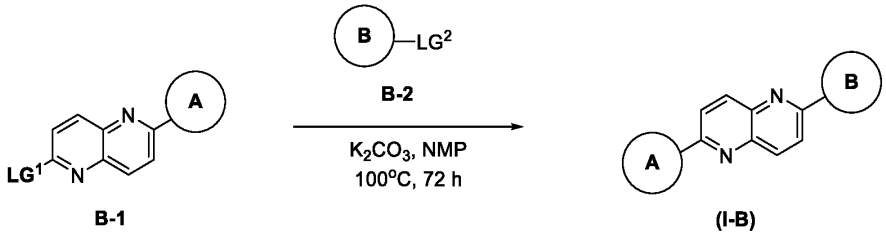


Scheme A. An exemplary method of preparing a representative compound of Formula (I-A); wherein A, and B are as defined herein, LG^1 and LG^2 are each independently a leaving group (e.g., halo); and $-B(OR^{12})_2$ is a boronic ester (e.g., Bpin), wherein each R^{12} may be C_1-C_6-alkyl, C_2-C_6-heteroalkyl,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

An exemplary method of preparing a compound of Formula (I-A) is provided in Scheme A. In this scheme, A-3 is prepared by incubating A-1 with A-2 in the presence of a base, for example, potassium carbonate (K_2CO_3) in dioxane and water or another suitable reagent. In some instances, A-3 is prepared by heating the reaction to a suitable temperature, for example, 80°C. Step 1 may also be carried out using an alternative catalyst to $Pd_2(dba)_3$, such as another palladium catalyst, for example, [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (Pd(dtbpf)Cl_2) or chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhos-Pd-G2). The reaction may be conducted in DMF or

a similar solvent, at 100 °C or a temperature sufficient to provide Fragment A-3, for example, 80 °C, 90 °C, 110 °C, or 120°C. The reaction may be conducted in a microwave reactor.

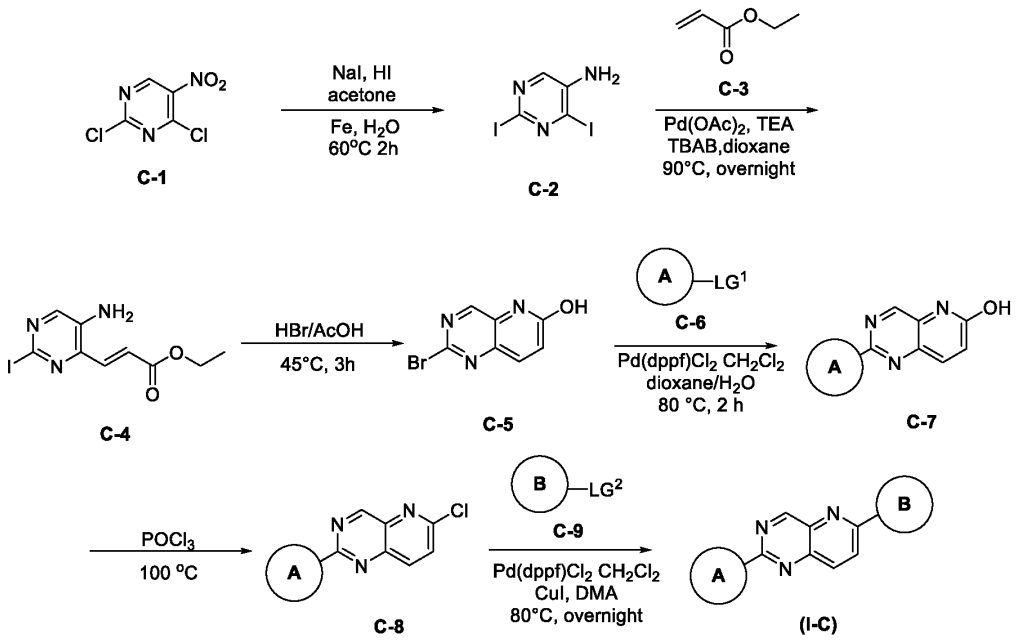
In Step 2, A-3 and A-4 are coupled to provide a compound of Formula (I). This coupling reaction may be conducted in the presence of $Pd(dppf)Cl_2$, and K_2CO_3 or a similar reagent, for example tripotassium carbonate (K_3PO_4). As in Step 1, alternative catalysts to $Pd(dppf)Cl_2$ may be used, such as any suitable palladium catalyst, for example, tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) or chloro(2-dicyclohexylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)[2-(2′-amino-1,1′-biphenyl)]palladium(II) (XPhos-Pd-G2). The reaction of Step 2 is conducted in dioxane or a mixture of dioxane and water, or other suitable solvents, and the mixture is heated to 80 °C or a temperature sufficient to provide the compound of Formula (I-A) or a precursor to the compound of Formula (I-A) with one or more protecting group(s), for example, 100 °C. Compounds of Formula (I-A) may be purified using standard techniques and characterized using any method known in the art, such as nuclear magnetic resonance spectroscopy (NMR) or mass spectrometry (MS).



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

An exemplary method of preparing a compound of Formula (I-B) is provided in Scheme B. In this scheme, the compound of Formula (I-B) is prepared by incubating A-1 with A-2 in the presence of a base, for example, potassium carbonate (K_2CO_3) or another suitable reagent. In some instances, A-3 is prepared by heating the reaction to a suitable temperature, for example, 100°C. The reaction may be conducted in DMF or a similar solvent, at 100 °C or a temperature sufficient to provide the compound of Formula (I-B), for example, 80 °C, 90 °C, 110 °C, or 120°C to provide the compound of Formula (I-B) or a precursor to the compound of Formula (I-

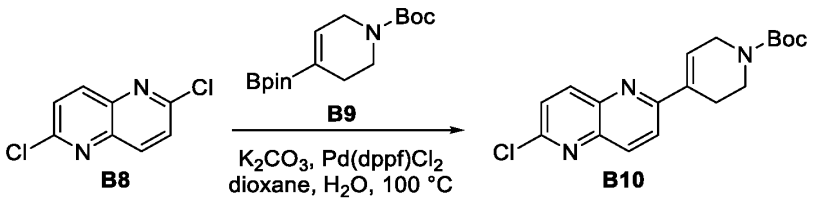
B) with one or more protecting group(s), for example, 100 °C. Compounds of Formula (I-B) may be purified using standard techniques and characterized using any method known in the art, such as nuclear magnetic resonance spectroscopy (NMR) or mass spectrometry (MS). The reaction may be conducted in a microwave reactor.



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

Example 1: Synthesis of Compound 100

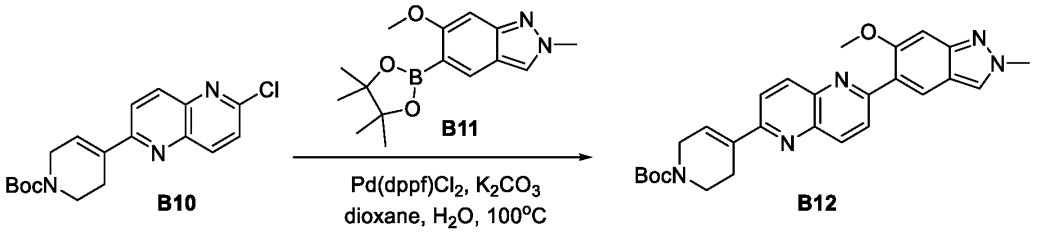
Synthesis of Intermediate B10



Potassium carbonate (1.9 g, 14 mmol) and $Pd(dppf)Cl_2$ (349 mg, 0.5 mmol) were added in portions to a mixture of 2,6-dichloro-1,5-naphthyridine (B8; 950 mg, 4.7 mmol) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B9; 1.78 g, 5.7

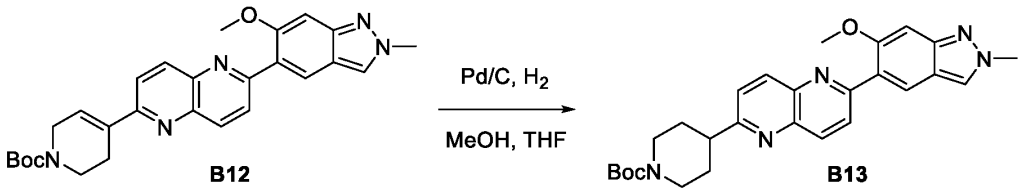
mmol) in dioxane (20 mL) and H_2O (4 mL) at room temperature, and the resulting mixture was stirred for 2 h at 100 °C under a nitrogen atmosphere. The reaction was quenched with water at room temperature, and the resulting mixture was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with brine, 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 (3:1), to afford tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B10; 1 g) as a solid. **LCMS** (ES, *m/z*): 346 $[M+H]^+$.

Synthesis of Intermediate B12



Potassium carbonate (599 mg, 4.3 mmol) and $Pd(dppf)Cl_2$ (105 mg, 0.1 mmol) were added in portions to a mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B10; 500 mg, 1.5 mmol) and 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (B11; 458 mg, 1.6 mmol) in dioxane (15 mL) and H_2O (3 mL) at room temperature under a nitrogen atmosphere. The resulting mixture was stirred for 2 h at 100 °C, and then quenched with water at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with brine, 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 (2:1) to afford tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (B12; 450 mg) as a solid.

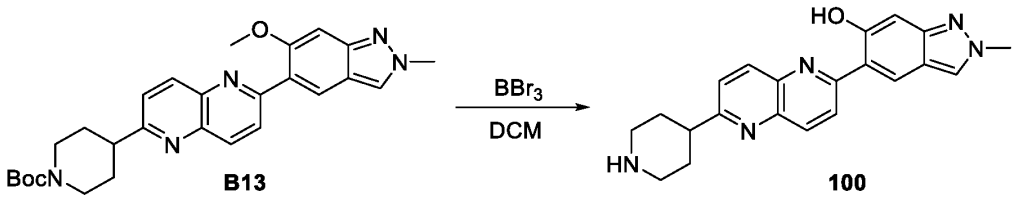
Synthesis of Intermediate B13



Palladium on carbon (80 mg) was added in portions to a mixture of tert-butyl 4-[6-(6-methoxy-2-

methylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (B12; 400 mg) in methanol (20 mL) and tetrahydrofuran (4 mL) at room temperature, and the resulting mixture was stirred overnight at room temperature under a hydrogen atmosphere. The mixture was then filtered, the filter cake was washed with methanol (3x30 mL), and the filtrate was concentrated under reduced pressure. The crude product (B13) was used in the next step directly without further purification. **LCMS** (ES, *m/z*): 474[M+H]$^+$.

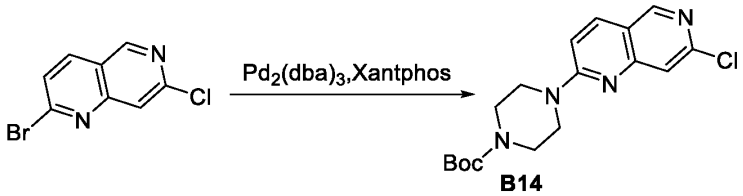
Synthesis of Compound 100



Boron tribromide (1.11 g, 4.4 mmol) was added in portions to a solution of tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (B13; 350 mg, 0.7 mmol) in dichloromethane (5 mL) at room temperature, and the resulting mixture was stirred for 5 h. The reaction was then cooled to 0 °C and quenched by the addition of methanol (20 mL). The residue was purified by reverse flash chromatography using a C18 silica gel column, eluting with acetonitrile in water (10% to 50% gradient over 10 min), to afford 2-methyl-5-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (Compound 100; 17.9 mg) as a solid. **LCMS** (ES, *m/z*): 360 [M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.63 (s, 1H), 8.70 (s, 1H), 8.62 (d, *J* = 9.2 Hz, 1H), 8.48 (d, *J* = 9.2 Hz, 1H), 8.45 – 8.35 (m, 2H), 7.78 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 4.14 (s, 3H), 3.14 – 2.98 (m, 3H), 2.73 – 2.61 (m, 2H), 1.88 (d, *J* = 12.6 Hz, 2H), 1.76 (qd, *J* = 12.3, 4.0 Hz, 2H).

Example 2: Synthesis of Compound 111

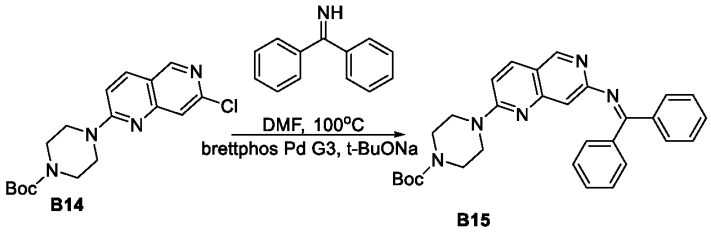
Synthesis of Intermediate B14



To a solution of 2-bromo-7-chloro-1,6-naphthyridine (1700 mg, 6.982 mmol, 1.00 equiv) and tert-butyl piperazine-1-carboxylate (1300 mg, 6.982 mmol, 1.00 equiv) in dioxane (20 mL) was

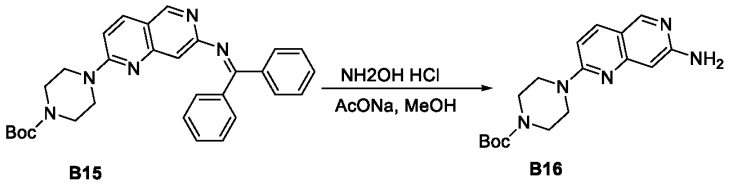
added $Pd_2(dba)_3$ (1278 mg, 1.396 mmol, 0.20 equiv) and XantPhos (807 mg, 1.396 mmol, 0.20 equiv) and Cs_2CO_3 (6824 mg, 20.945 mmol, 3.00 equiv). After stirring for 2h at 100°C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (1:2) to afford tert-butyl 4-(7-chloro-1,6-naphthyridin-2-yl)piperazine-1-carboxylate (B14; 1700 mg, 69.80%) as a solid. **LCMS** (ES, *m/z*): 349 $[M+H]^+$ **1H NMR** (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.20 (d, *J* = 9.3 Hz, 1H), 7.43 (s, 1H), 7.36 (d, *J* = 9.4 Hz, 1H), 3.82 (t, *J* = 5.3 Hz, 4H), 3.47 (dd, *J* = 6.4, 3.8 Hz, 4H), 1.44 (s, 9H).

Synthesis of Intermediate B15



To a solution of B14 (1000 mg, 2.867 mmol, 1.00 equiv) and diphenylmethanimine (519 mg, 2.867 mmol, 1.00 equiv) in dioxane (15 mL) were added BrettPhos Pd G3 (519 mg, 0.573 mmol, 0.20 equiv) and t-BuONa (826 mg, 8.600 mmol, 3.00 equiv). After stirring for 2h at 100°C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE:EA (1:2) to afford B15, tert-butyl 4-[7-[(diphenylmethylidene)amino]-1,6-naphthyridin-2-yl]piperazine-1-carboxylate (850 mg, 60.07%) as a solid. **1H NMR** (400 MHz, Chloroform-d) δ 8.65 (s, 1H), 7.87 – 7.80 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.26 (s, 5H), 6.85 (d, *J* = 9.2 Hz, 1H), 6.78 (s, 1H), 3.78 (dd, *J* = 6.7, 3.9 Hz, 4H), 3.57 (dd, *J* = 6.4, 4.0 Hz, 4H), 1.51 (s, 9H).

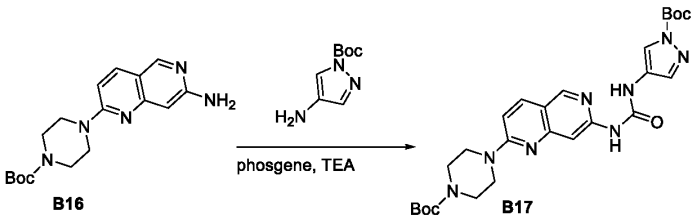
Synthesis of Intermediate B16



To a stirred solution of B15 (850 mg, 1.722 mmol, 1.00 equiv) in MeOH (20 mL) was added $NH_2OH.HCl$ (239 mg, 3.444 mmol, 2.00 equiv) and NaOAc (353 mg, 4.305 mmol, 2.50 equiv)

at room temperature. The mixture was stirred 1h at same temperature. The residue was purified by silica gel column chromatography, eluted with DCM:MeOH (10:1) to afford B16, tert-butyl 4-(7-amino-1,6-naphthyridin-2-yl)piperazine-1-carboxylate (540 mg, 95.20%) as a solid. **LCMS** (ES, *m/z*): 330 [M+H] $^+$ **1H NMR** (400 MHz, Chloroform-d) δ 8.48 (d, *J* = 0.8 Hz, 1H), 7.79 (dd, *J* = 9.2, 0.8 Hz, 1H), 6.73 (d, *J* = 9.2 Hz, 1H), 6.58 (d, *J* = 0.8 Hz, 1H), 3.84 – 3.77 (m, 4H), 3.58 (dd, *J* = 6.6, 4.0 Hz, 4H), 1.52 (s, 9H).

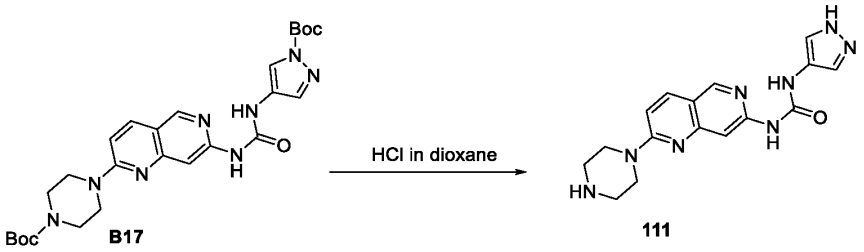
Synthesis of Intermediate B17



B16 B17

To a stirred solution of B16 (200 mg, 0.607 mmol, 1.00 equiv) in DCM (10 mL) was added TEA (184 mg, 1.821 mmol, 3.00 equiv) and triphosgene (72 mg, 0.243 mmol, 0.40 equiv) at room temperature. The mixture was stirred 30min, then tert-butyl 4-aminopyrazole-1-carboxylate (111 mg, 0.607 mmol, 1.00 equiv) was added and stirred for 1h at room temperature. The residue was purified by reverse flash chromatography to afford B17, tert-butyl 4-[7-([[1-(tert-butoxycarbonyl)pyrazol-4-yl]carbamoyl]amino)-1,6-naphthyridin-2-yl]piperazine-1-carboxylate (100 mg, 30.58%) as a solid. **LCMS** (ES, *m/z*): 539 [M+H] $^+$

Synthesis of Compound 111

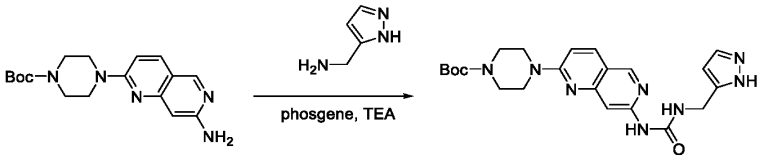


B17 111

To a stirred solution of B17 (100 mg, 0.186 mmol, 1.00 equiv) in MeOH (5 mL) was added HCl(gas)in 1,4-dioxane (2 mL) at room temperature. The mixture was stirred 1h at room temperature, then the crude product was purified by prep-HPLC to afford Compound 111, 1-[2-(piperazin-1-yl)-1,6-naphthyridin-7-yl]-3-(1H-pyrazol-4-yl)urea (18.8 mg, 29.92%) as a solid. **LCMS** (ES, *m/z*): 339 [M+H] $^+$

Example 3: Synthesis of Compound 112

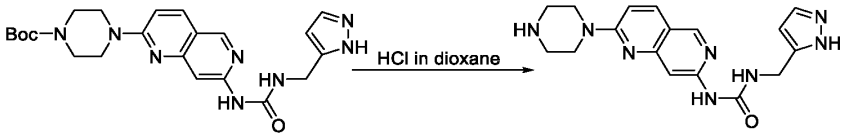
Synthesis of Intermediate B18



B16 B18

To a stirred solution of B16 (58 mg, 0.607 mmol, 1.00 equiv) and TEA (184 mg, 1.821 mmol, 3.00 equiv) in DCM (20 mL) was added phosgene (71 mg, 0.243 mmol, 0.40 equiv) at room temperature. The mixture was stirred for 10 min, then tert-butyl 4-(7-amino-1,6-naphthyridin-2-yl)piperazine-1-carboxylate (200 mg, 0.607 mmol, 1.00 equiv) was added. The mixture was stirred for 30 min, then the resultant residue was purified by reverse flash chromatography with C18 silica gel to afford B18, tert-butyl 4-(7-[[(2H-pyrazol-3-ylmethyl)carbamoyl]amino]-1,6-naphthyridin-2-yl)piperazine-1-carboxylate (40 mg, 14.56%) as a solid. **LCMS** (ES, *m/z*): 453 $[M+H]^+$

Synthesis of Compound 112

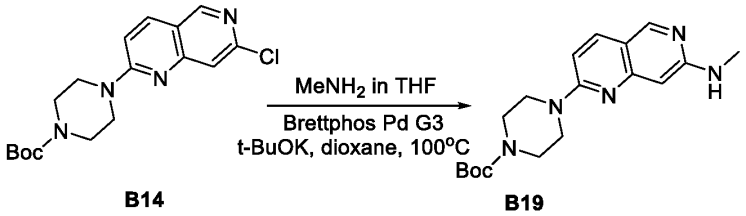


B18 112

To a stirred solution of B18 (40 mg, 0.088 mmol, 1.00 equiv) in MeOH (10 mL) was added HCl(gas)in 1,4-dioxane (0.5 mL) at room temperature. The mixture was stirred 1h at room temperature, then the crude product was purified by prep-HPLC to afford Compound 112, 1-[2-(piperazin-1-yl)-1,6-naphthyridin-7-yl]-3-(2H-pyrazol-3-ylmethyl)urea (14.1 mg, 45.26%) as a solid. **LCMS** (ES, *m/z*): 353 $[M+H]^+$ **1H NMR** (400 MHz, DMSO-d6) δ 12.64 (s, 1H), 9.12 (s, 1H), 8.59 (s, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.62 (s, 1H), 7.46 (s, 1H), 7.08 (d, *J* = 9.3 Hz, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 4.37 (d, *J* = 5.4 Hz, 2H), 3.68 (t, *J* = 5.1 Hz, 4H), 2.78 (t, *J* = 5.1 Hz, 4H).

Example 4: Synthesis of Compound 110

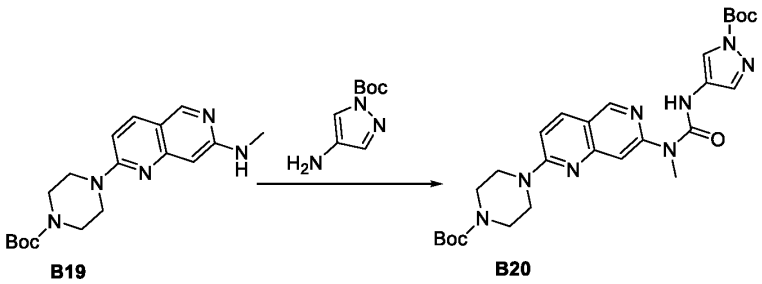
Synthesis of Intermediate B19



B14 B19

To a solution of B14 (600 mg, 1.720 mmol, 1.00 equiv) and methylamine (2M in THF) (1.19 mL, 38.351 mmol, 20.00 equiv) in dioxane (15 mL, 177.061 mmol, 102.94 equiv) and were added BrettPhos Pd G3 (311 mg, 0.344 mmol, 0.20 equiv) and t-BuOK (579 mg, 5.160 mmol, 3.00 equiv). The mixture was stirred for 2h at 100°C under a nitrogen atmosphere, then the residue was purified by silica gel column chromatography, eluting with DCM:MeOH (1:1) to afford B19, tert-butyl 4-[7-(methylamino)-1,6-naphthyridin-2-yl]piperazine-1-carboxylate (300 mg, 50.79%) as a solid. **LCMS** (ES, *m/z*): 344 [M+H] $^+$

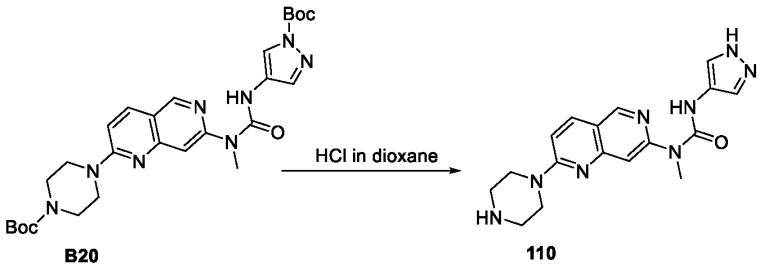
Synthesis of Intermediate B20



B19 B20

To a stirred solution of B19 (160 mg, 0.874 mmol, 1.00 equiv) and TEA (265 mg, 2.621 mmol, 3.00 equiv) in DCM (20 mL) was added phosgene (103 mg, 0.349 mmol, 0.40 equiv) at room temperature. The mixture was stirred for 10min, then tert-butyl 4-[7-(methylamino)-1,6-naphthyridin-2-yl]piperazine-1-carboxylate (300 mg, 0.874 mmol, 1.00 equiv) was added. The mixture was stirred for 30 min at room temperature, then the residue was purified by reverse flash chromatography to afford B20, tert-butyl 4-[7-([[1-(tert-butoxycarbonyl)pyrazol-4-yl]carbamoyl](methyl)amino)-1,6-naphthyridin-2-yl]piperazine-1-carboxylate (100 mg, 20.71%) as a solid. **LCMS** (ES, *m/z*): 553 [M+H] $^+$

Synthesis of Compound 110

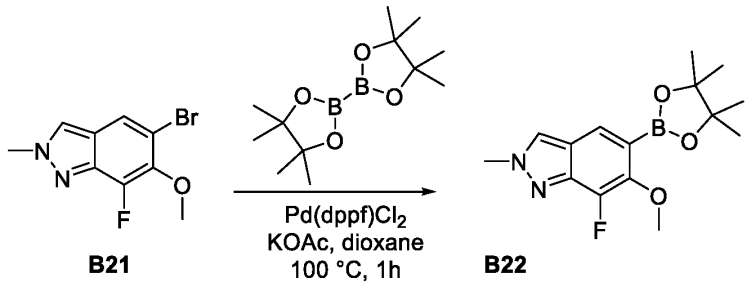


B20 110

To a stirred solution of B20 (100 mg, 0.181 mmol, 1.00 equiv) in MeOH (10 mL) was added HCl(gas)in 1,4-dioxane (2 mL) at room temperature. The mixture was stirred 1h at room temperature, then the crude product was purified by prep-HPLC to afford Compound 110, 1-methyl-1-[2-(piperazin-1-yl)-1,6-naphthyridin-7-yl]-3-(1H-pyrazol-4-yl)urea (24.8 mg, 38.89%) as a solid. **LCMS** (ES, *m/z*): 353 $[M+H]^+$ **1H NMR** (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.80 (s, 1H), 8.10 (d, *J* = 9.3 Hz, 1H), 7.70 (s, 2H), 7.22 (d, *J* = 9.3 Hz, 1H), 7.08 (s, 1H), 3.74 (t, *J* = 5.1 Hz, 4H), 3.42 (s, 4H), 2.78 (d, *J* = 4.9 Hz, 3H).

Example 5: Synthesis of Compound 102

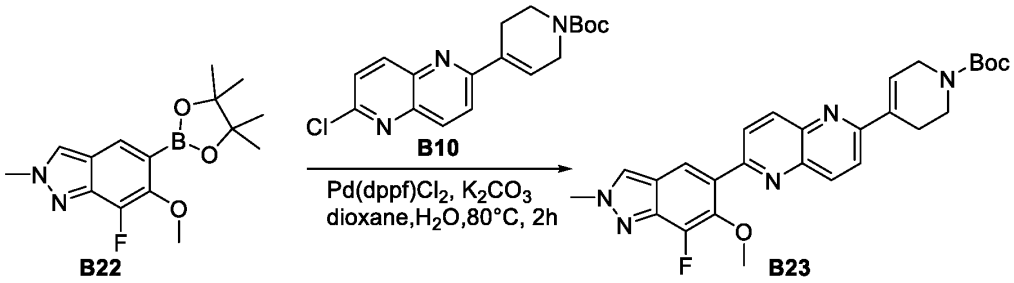
Synthesis of Intermediate B22



B21 B22

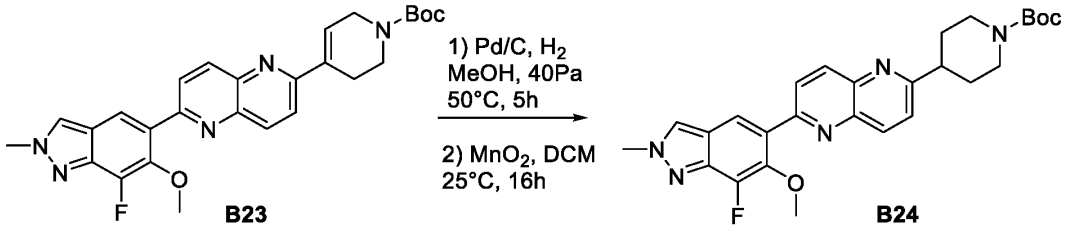
A mixture of 5-bromo-7-fluoro-6-methoxy-2-methylindazole (B21; 300 mg, 1.2 mmol), bis(pinacolato)diboron (441 mg, 1.7 mmol), $Pd(dppf)Cl_2$ (85 mg, 0.1 mmol), and potassium acetate (341 mg, 3.5 mmol) in 1,4-dioxane (5 mL) was stirred for 1 h at 100 °C under an atmosphere of nitrogen, and then filtered and concentrated, to afford crude 7-fluoro-6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (B22; 400 mg) as an oil. **LCMS** (ES, *m/z*): 307 $[M+H]^+$.

Synthesis of Intermediate B23



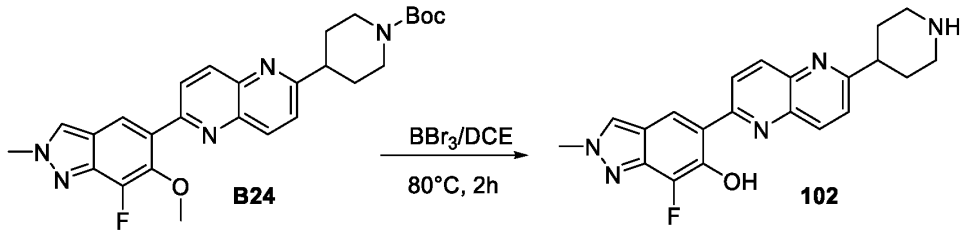
A mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B10 from Example 1; 300 mg, 0.9 mmol), 7-fluoro-6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (B22; 266 mg, 0.9 mmol), $Pd(dppf)Cl_2$ (64 mg, 0.09 mmol), and potassium carbonate (360 mg, 2.6 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was stirred for 2 h at 80 °C, then concentrated. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (7:3), to afford tert-butyl 4-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] -3,6-dihydro-2H-pyridine-1-carboxylate (B23; 165 mg) as a solid. **LCMS** (ES, *m/z*): 490 $[M+H]^+$.

Synthesis of Intermediate B24



A mixture of tert-butyl 4-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] -3,6-dihydro-2H-pyridine-1-carboxylate (B23; 165 mg) and palladium on carbon (60 mg) in methanol (3 mL) was stirred at 50 °C under an atmosphere of hydrogen (40 atm) for 5 h. The mixture was then filtered and concentrated, and the residue was dissolved in dichloromethane (2 mL) and treated with manganese dioxide (736 mg, 8.46 mmol). The resulting mixture was stirred at 25 °C for 16 h, then filtered and concentrated, to afford tert-butyl 4-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (B24; 100 mg). **LCMS** (ES, *m/z*): 492 $[M+H]^+$.

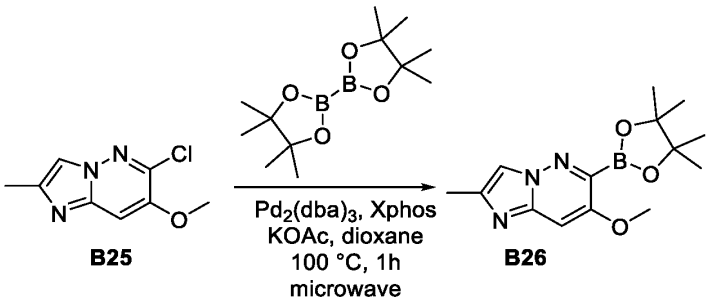
Synthesis of Compound 102



A mixture of tert-butyl 4-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (B24; 100 mg, 0.2 mmol) and boron tribromide (510 mg, 2 mmol) in dichloroethane (2 mL) was stirred for 2 h at 80 °C under an atmosphere of nitrogen. The reaction mixture was then cooled to 25 °C and quenched with 10 mL of methanol. The resulting mixture was concentrated and purified by preparative HPLC (Condition 1, Gradient 1) to afford 7-fluoro-2-methyl-5-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (Compound 102; 2.6 mg) as a solid. **LCMS** (ES, *m/z*): 492 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6, *ppm*) δ 8.64 (d, *J* = 9.3 Hz, 1H), 8.54 - 8.64 (m, 2H), 8.49 (dd, *J* = 17.7, 8.9 Hz, 2H), 7.80 (d, *J* = 8.7 Hz, 1H), 4.19 (s, 3H), 2.99 - 3.22 (m, 3H), 2.69 (td, *J* = 12.0, 2.6 Hz, 2H), 1.89 (t, *J* = 6.7 Hz, 2H), 1.77 (qd, *J* = 12.2, 3.9 Hz, 2H).

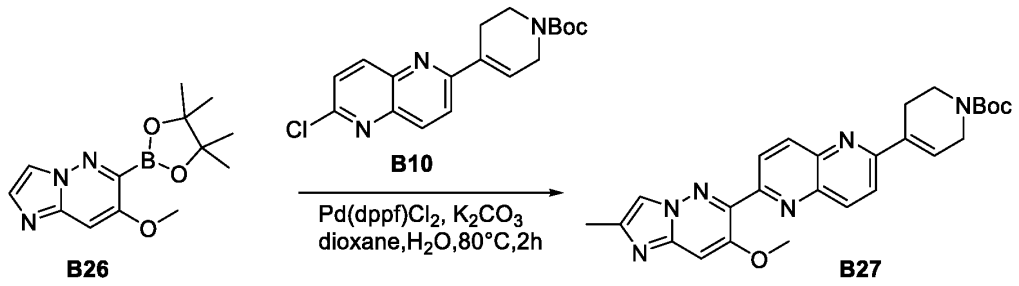
Example 6: Synthesis of Compound 103

Synthesis of Intermediate B26



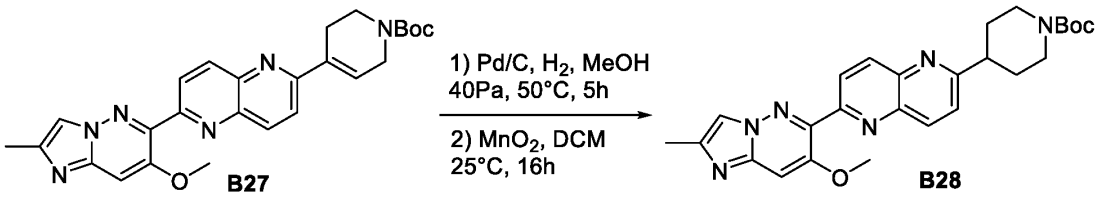
A mixture of 6-chloro-7-methoxy-2-methylimidazo[1,2-b]pyridazine (B25; 500 mg, 2.5 mmol), bis(pinacolato)diboron (964 mg, 3.8 mmol), $Pd_2(dba)_3$ (116 mg, 0.12 mmol), XPhos (121 mg, 0.25 mmol), and potassium acetate (2.47 g, 7.6 mmol) in 1,4-dioxane (12 mL) was irradiated with a microwave for 1 h at 100 °C under an atmosphere of nitrogen. The resulting mixture was then filtered and concentrated, to afford crude 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (B26; 800 mg) as a solid. **LCMS** (ES, m/z): 290 $[M+H]^+$.

Synthesis of Intermediate B27



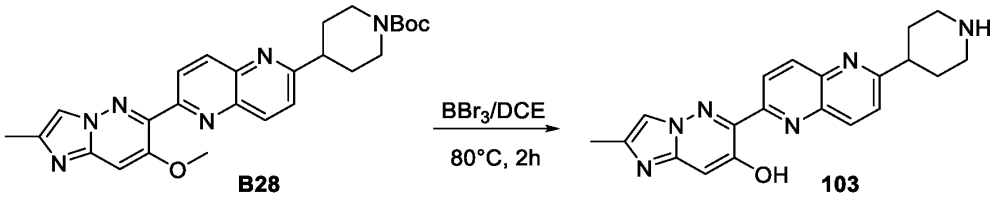
A mixture of 7-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-b]pyridazine (B26; 300 mg, 1 mmol), tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine -1-carboxylate (B10 from Example 1; 359 mg, 1 mmol), $Pd(dppf)Cl_2$ (767 mg, 0.11 mmol), and potassium carbonate (430 mg, 3.1 mmol) in 1,4-dioxane (4 mL) and H_2O (1 mL) was stirred for 2 h at 80 °C. The resulting mixture was then concentrated and purified by silica gel column chromatography, eluting with ethyl acetate/petroleum ether (7:3), to afford tert-butyl 4-(6-[7-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl]-1,5-naphthyridin-2-yl)-3,6-dihydro- 2H-pyridine-1-carboxylate (B27; 240 mg) as a solid. **LCMS** (ES, *m/z*): 473 $[M+H]^+$.

Synthesis of Intermediate B28



A mixture of tert-butyl 4-(6-[7-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl]-1,5-naphthyridin -2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (B27; 200 mg) and palladium on carbon (60 mg) in methanol (3 mL) was stirred at 50 °C under an atmosphere of hydrogen (40 atm) for 5 h. The mixture was then filtered and concentrated, then dissolved in dichloromethane (2 mL). Manganese dioxide (736 mg, 8.5 mmol) was then added, and the reaction was stirred at 25 °C for 16 h. The mixture was then filtered and concentrated, to afford tert-butyl 4-(6-[7-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl] -1,5-naphthyridin-2-yl)piperidine-1-carboxylate (B28; 100 mg) as a solid. **LCMS** (ES, *m/z*): 475 $[M+H]^+$.

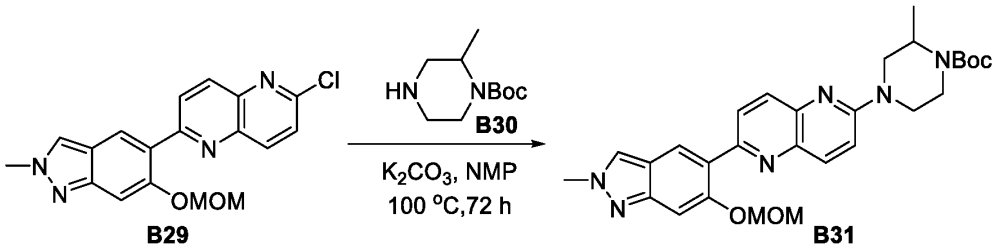
Synthesis of Compound 103



A mixture of tert-butyl 4-(6-[7-methoxy-2-methylimidazo[1,2-b]pyridazin-6-yl]-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (B28; 100 mg, 0.21 mmol) and boron tribromide (528 mg, 2.1 mmol) in dichloroethane (2 mL) was stirred for 2 h at 80 °C, then cooled to 25 °C and quenched with 10 mL of methanol. The resulting mixture was concentrated, and purified by preparative HPLC (Condition 1, Gradient 1) to afford 2-methyl-6-[6-(piperidin-4-yl)-1,5-naphthyridin -2-yl]imidazo [1,2-b]pyridazin-7-ol (Compound 103; 1.8 mg) as a solid. **LCMS** (ES, *m/z*): 361 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-*d*$_6$, *ppm*) δ 8.55 (d, *J* = 8.9 Hz, 1H), 8.39 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.06 (s, 1H), 3.29 - 3.33 (m, 3H), 2.62 - 2.72 (m, 2H), 2.28 - 2.36 (m, 3H), 1.94 (d, *J* = 12.6 Hz, 2H), 1.79 (td, *J* = 12.2, 4.0 Hz, 2H).

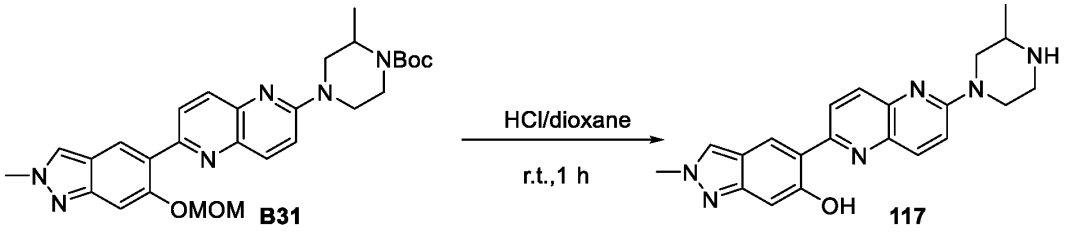
Example 7: Synthesis of Compound 117

Synthesis of Intermediate B31



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl 2-methylpiperazine-1-carboxylate (B30; 67.7 mg, 0.33 mmol) and potassium carbonate (93.4 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was stirred for 72 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% NaCl solution (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford tert-butyl-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2-methylpiperazine-1-carboxylate (B31; 240mg) as an oil. **LCMS** (ES, *m/z*): 519 $[M+H]^+$.

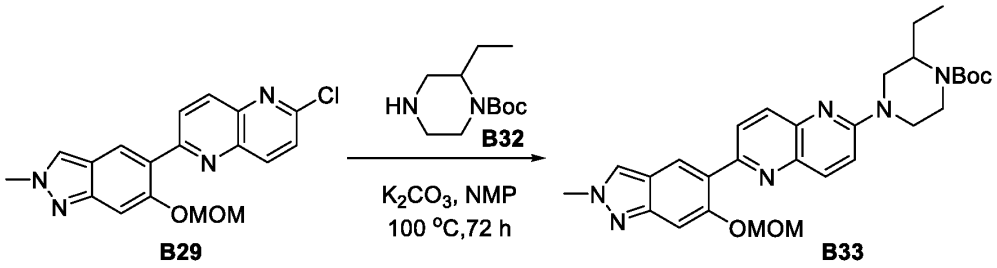
Synthesis of Compound 117



A solution of tert-butyl-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2-methyl-piperazine-1-carboxylate (B31; 20 mg, 0.03 mmol) and HCl in 1,4-dioxane (0.5 mL, 4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 1, Gradient 2) to afford 2-methyl-5-[6-(3-methylpiperazin-1-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (Compound 117; 6.8 mg) as a solid. **LCMS** (ES, *m/z*): 375 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.90 (s, 1H), 8.56 (s, 1H), 8.42 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.10 (dd, *J* = 20.0, 9.2 Hz, 2H), 7.53 (d, *J* = 9.5 Hz, 1H), 6.88 (s, 1H), 4.47 – 4.39 (m, 2H), 4.12 (s, 3H), 3.01 (d, *J* = 11.8 Hz, 1H), 2.91 (td, *J* = 12.2, 3.0 Hz, 1H), 2.73 (td, *J* = 11.8, 11.2, 4.4 Hz, 2H), 2.60 – 2.53 (m, 1H), 1.08 (d, *J* = 6.3 Hz, 3H).

Example 8: Synthesis of Compound 119

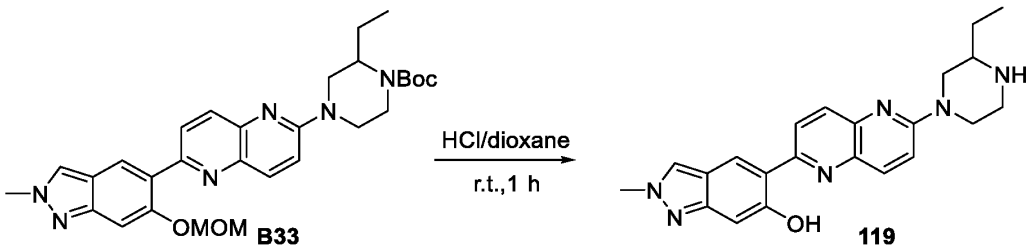
Synthesis of Intermediate B33



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl 2-ethylpiperazine-1-carboxylate (B32; 87 mg, 0.4 mmol) and potassium carbonate (93 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was stirred for 72 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse flash chromatograph, eluting with methanol in dichloromethane (2.9% gradient in 10 min), to afford tert-butyl 2-ethyl-4-[6-[6-

(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] piperazine-1-carboxylate (B33; 40 mg) as a solid. **LCMS** (ES, *m/z*): 533 $[M+H]^+$.

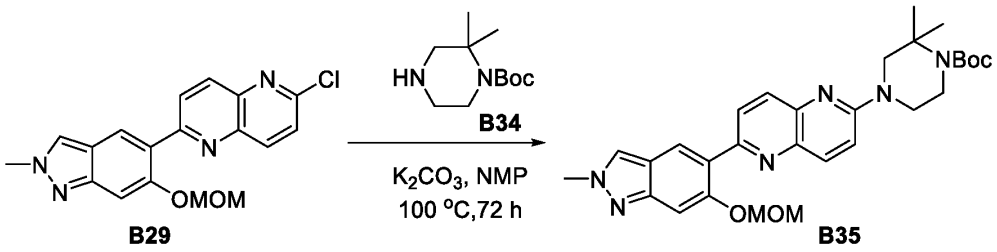
Synthesis of Compound 119



A solution of tert-butyl 2-ethyl-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] piperazine-1-carboxylate (B33; 35 mg, 0.06 mmol) and HCl in 1,4-dioxane (1 mL,4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 1, Gradient 2) to afford 5-[6-(3-ethylpiperazin-1-yl)-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (Compound 119; 13.1 mg) as a solid. **LCMS** (ES, *m/z*): 389 $[M+H]^+$. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 13.90 (s, 1H), 8.56 (s, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.36 (s, 1H), 8.10 (dd, J = 20.4, 9.2 Hz, 2H), 7.54 (d, J = 9.5 Hz, 1H), 6.88 (s, 1H), 4.43 (t, J = 12.7 Hz, 2H), 4.12 (s, 3H), 3.06 – 2.99 (m, 1H), 2.98 – 2.90 (m, 1H), 2.75 – 2.66 (m, 1H), 2.64 – 2.54 (m, 2H), 1.42 (ddq, J = 20.5, 13.6, 7.0 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H).

Example 9: Synthesis of Compound 120

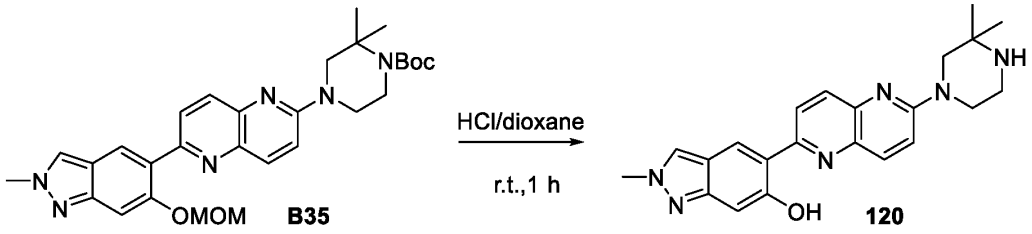
Synthesis of Intermediate B35



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl 2,2-dimethylpiperazine-1-carboxylate (B34; 87 mg, 0.4 mmol) and potassium carbonate (93 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was stirred for 72 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x

30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography eluting with methanol in dichloromethane (3% gradient in 10 min) afford tert-butyl 4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,2-dimethylpiperazine-1-carboxylate (B35; 40 mg) as a solid. **LCMS** (ES, *m/z*): 533 $[M+H]^+$.

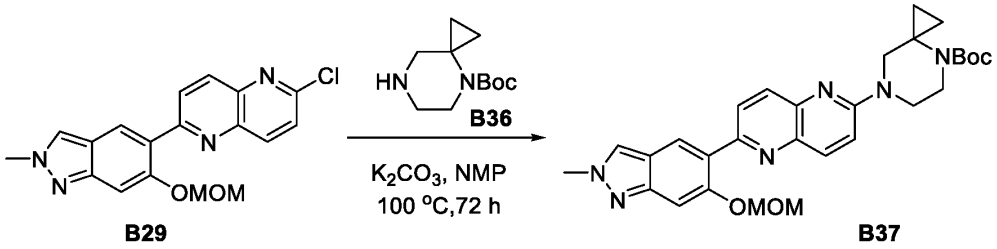
Synthesis of Compound 120



A solution of tert-butyl 4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,2-di-methylpiperazine-1-carboxylate (B35; 35 mg, 0.06 mmol) and HCl in 1,4-dioxane (1 mL,4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 1, Gradient 2) to afford 5-[6-(3,3-dimethylpiperazin-1-yl)-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (Compound 120; 14.7 mg) as a solid. **LCMS** (ES, *m/z*): 389 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.91 (s, 1H), 8.55 (s, 1H), 8.43 – 8.33 (m, 2H), 8.10 (d, J = 9.4 Hz, 1H), 8.05 (d, J = 9.1 Hz, 1H), 7.52 (d, J = 9.5 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.71 (dd, J = 6.2, 4.2 Hz, 2H), 3.51 (s, 2H), 2.90 – 2.83 (m, 2H), 1.08 (s, 6H).

Example 10: Synthesis of Compound 121

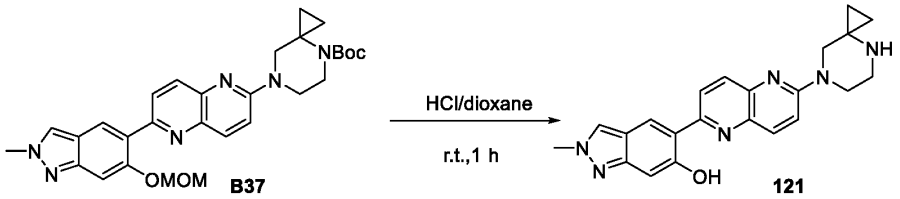
Synthesis of Intermediate B37



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl 4,7-diazaspiro [2.5] octane-4-carboxylate (B36; 72 mg, 0.33 mmol) and potassium carbonate (93 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was

stirred for 72 h at 100 ℃. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, to afford tert-butyl-7-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-y l]-4,7-diazaspiro [2.5]octane-4-carboxylate (B37; 250 mg) as an oil. **LCMS** (ES, *m/z*): 531 $[M+H]^+$.

Synthesis of Compound 121

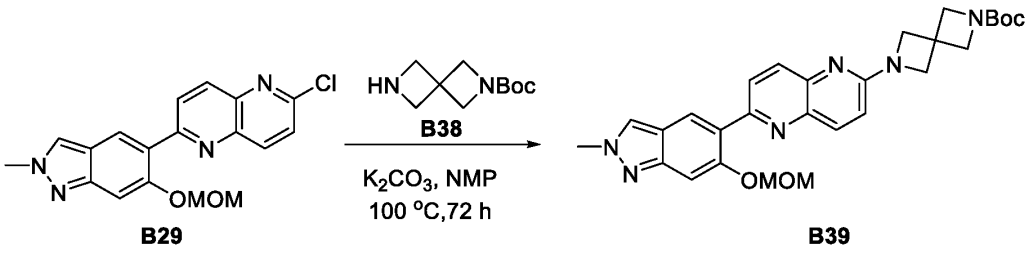


B37 121

A solution of tert-butyl 7-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-4,7-diazaspiro[2.5]octane-4-carboxylate (B37; 230 mg, 0.43 mmol) and HCl in 1,4-dioxane (5 mL,4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and washed with methanol (5 x 10 mL). The residue was then concentrated under reduced pressure to afford 5-(6-[4,7-diazaspiro[2.5]octan-7-yl]-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (Compound 121; 6.1 mg) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.89 (s, 1H), 8.56 (s, 1H), 8.42 – 8.32 (m, 2H), 8.08 (dd, J = 22.5, 9.2 Hz, 2H), 7.50 (d, J = 9.4 Hz, 1H), 6.88 (s, 1H), 4.12 (s, 3H), 3.75 (t, J = 4.7 Hz, 2H), 3.62 (s, 2H), 2.90 (d, J = 5.0 Hz, 2H), 0.62 – 0.44 (m, 4H).

Example 11: Synthesis of Compound 124

Synthesis of Intermediate B39

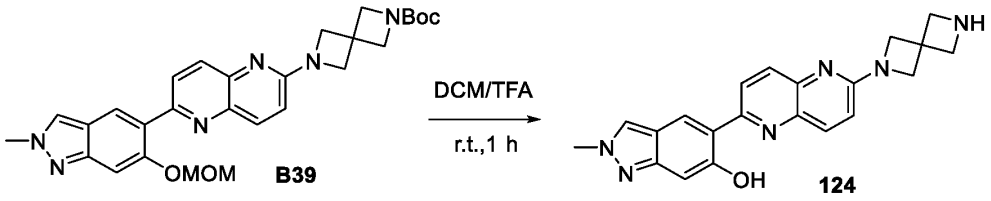


B29 B39

A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl 2,6-diazaspiro [3.3]heptane-2-carboxylate (B38; 80.4 mg, 0.4 mmol) and potassium carbonate (93.4 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was

stirred for 48 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography eluting with methanol in dichloromethane (3% gradient in 10 min), to afford tert-butyl 6-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,6-diazaspiro [3.3] heptane-2-carboxylate (B39; 70 mg) as a solid. **LCMS** (ES, *m/z*): 517 $[M+H]^+$.

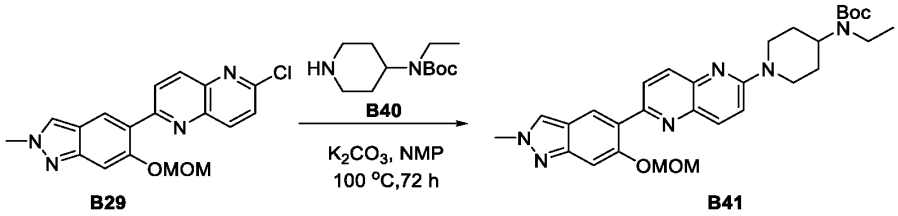
Synthesis of Compound 124



A solution of tert-butyl 6-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,6-diazaspiro [3.3] heptane-2-carboxylate (B39; 60 mg, 0.11 mmol) in dichloromethane (1 mL) and trifluoracetic acid (0.2 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 2, Gradient 1) to afford 5-(6-[2,6-diazaspiro[3.3]heptan-2-yl]-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (Compound 124; 12.2 mg) as a solid. **LCMS** (ES, *m/z*): 373 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.84 (s, 1H), 8.55 (s, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.36 (s, 1H), 8.11 (dd, J = 13.1, 9.1 Hz, 2H), 7.00 (d, J = 9.1 Hz, 1H), 6.88 (s, 1H), 4.23 (s, 4H), 4.12 (s, 4H), 3.68 (s, 3H).

Example 12: Synthesis of Compound 131

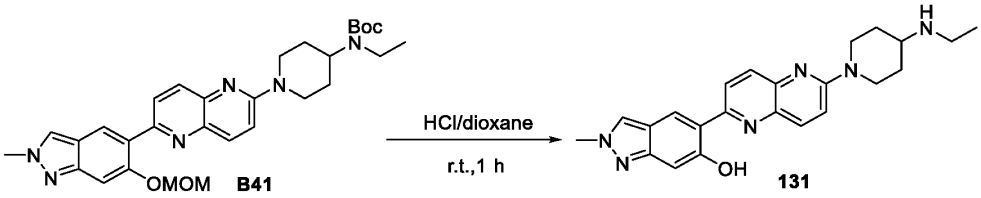
Synthesis of Intermediate B41



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl N-ethyl -N-(piperidin-4-yl) carbamate (B40; 93 mg, 0.4 mmol) and potassium carbonate (93 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was stirred for

72 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography eluting with methanol in dichloromethane (3.3% gradient in 10 min), to afford tert-butyl N-ethyl-N-(1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] piperidin-4-yl) carbamate (B41; 70 mg) as a solid. **LCMS** (ES, *m/z*): 547 $[M+H]^+$.

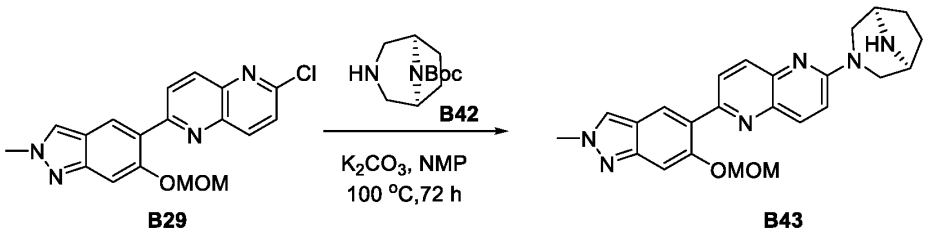
Synthesis of Compound 131



A solution of tert-butyl N-ethyl-N-(1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] piperidin-4-yl) carbamate (B41; 60 mg, 0.11 mmol) and HCl in 1,4-dioxane (1 mL, 4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 1, Gradient 3) to afford 5-[6-[4-(ethylamino)piperidin-1-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (Compound 131; 34.1 mg) as a solid. **LCMS** (ES, *m/z*): 403 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.89 (s, 1H), 8.55 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.12 (d, *J* = 9.4 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 6.88 (s, 1H), 4.48 (dd, *J* = 10.7, 6.5 Hz, 2H), 4.12 (s, 3H), 3.19 – 3.07 (m, 2H), 2.81 (s, 1H), 2.66 (q, *J* = 7.0 Hz, 2H), 1.95 (dd, *J* = 13.1, 3.9 Hz, 2H), 1.37 – 1.22 (m, 2H), 1.05 (t, *J* = 7.1 Hz, 3H).

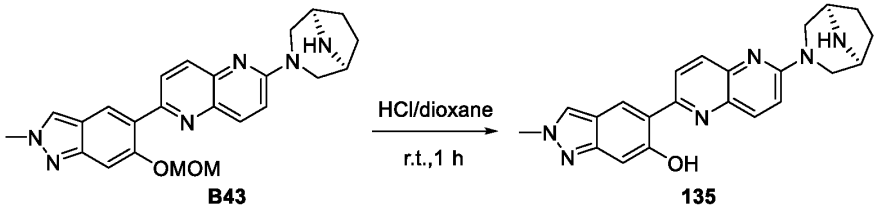
Example 13: Synthesis of Compound 135

Synthesis of Intermediate B43



A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B29; 80 mg, 0.22 mmol), tert-butyl (1R,5S)-3,8-diazabicyclo [3.2.1] octane-8-carboxylate (B42; 86.1 mg, 0.4 mmol) and potassium carbonate (93.4 mg, 0.67 mmol) in N-methyl-2-pyrrolidone (1.6 mL) was stirred for 72 h at 100 °C. The resulting mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with a 50% solution of NaCl (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by reverse phase flash chromatography eluting with methanol in dichloromethane (2.7% gradient in 10 min) to afford 2-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B43; 60 mg) as a solid. **LCMS** (ES, *m/z*): 531 $[M+H]^+$.

Synthesis of Compound 135

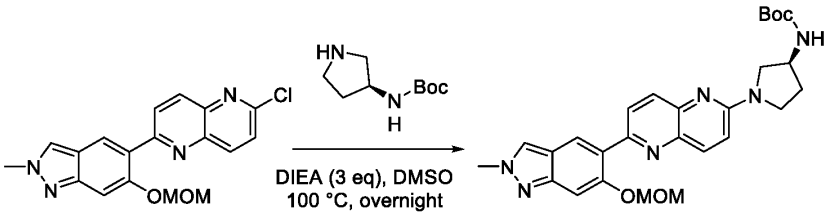


B43 135

A solution of 2-[(1R,5S)-3,8-diazabicyclo [3.2.1] octan-3-yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (B43; 50 mg, 0.11 mmol) and HCl in 1,4-dioxane (1.5 mL,4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure and purified by preparative HPLC (Condition 1, Gradient 2) to afford 5-[6-[(1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (Compound 135; 5.3 mg) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 13.91 (s, 1H), 8.56 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 8.36 (s, 1H), 8.13 (d, J = 9.4 Hz, 1H), 8.07 (d, J = 9.1 Hz, 1H), 7.41 (d, J = 9.5 Hz, 1H), 6.88 (s, 1H), 4.12 (s, 5H), 3.61 (d, J = 3.4 Hz, 2H), 3.08 (dd, J = 12.0, 2.3 Hz, 2H), 1.75 – 1.63 (m, 4H).

Example 14: Synthesis of Compounds 156-160 and 162-165

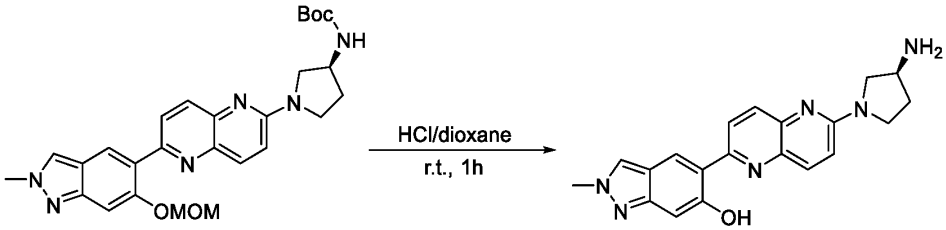
Synthesis of Intermediate B44



B29 B44

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (400 mg, 1.127 mmol, 1.00 equiv), tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (230.99 mg, 1.240 mmol, 1.1 equiv), DMSO (20 mL, 281.571 mmol, 249.75 equiv) and DIEA (437.14 mg, 3.381 mmol, 3 equiv) was stirred overnight at 100 °C. The reaction mixture was cooled to room temperature, then quenched with water (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 30mL). The combined organic layers were washed with half-saturation brine (3x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:5) to afford tert-butyl N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl]carbamate (380 mg, 66.80%) as a solid. **LCMS** (ES, *m/z*): 505 $[M+H]^+$.

Synthesis of Intermediate B45

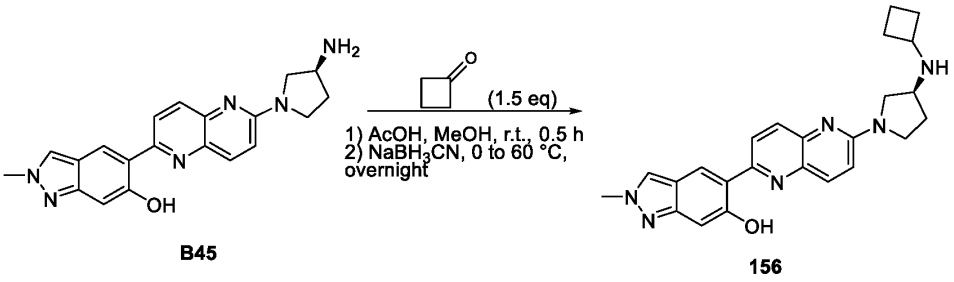


B44 B45

A mixture of tert-butyl N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol -5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl]carbamate (300 mg, 0.595 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (5 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a solid. The solid was dissolved in methanol (2 mL), then basified to pH 8 with NH_3·MeOH. The resulting mixture was stirred for 1 h at room temperature, then filtered, and the filter cake was washed with water and acetonitrile (3x1 mL).

The filter cake was concentrated under reduced pressure to afford 5-{6-[(3S)-3-aminopyrrolidin-1-yl]-1,5-naphthyridin -2-yl}-2-methylindazol-6-ol (150 mg, 70.00%) as a solid. **LCMS** (ES, *m/z*): 361 $[M+H]^+$.

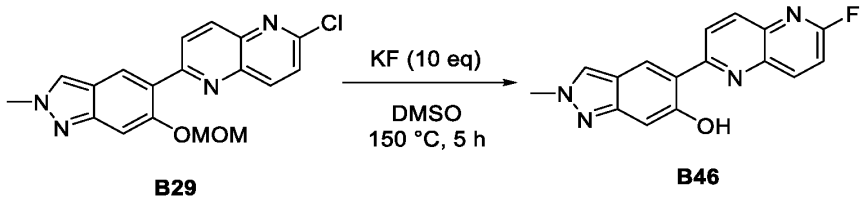
Synthesis of Compound 156



B45 **156**

A mixture of tert-butyl N-cyclobutyl-N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl]carbamate (70 mg, 0.125 mmol, 1.00 equiv), cyclobutanone (20.42 mg, 0.291 mmol, 1.5 equiv), and methanol (5 mL, 156.045 mmol, 803.46 equiv) was stirred for 0.5 h at room temperature. To the reaction mixture was added $NaBH_3CN$ (61.03 mg, 0.970 mmol, 5 equiv) at room temperature. The resulting mixture was stirred overnight at 60 °C. The reaction mixture was cooled to room temperature, then quenched with water (5 mL) at room temperature. A precipitate formed that was collected by filtration. The filter cake was washed with CH_3CN (3x1 mL). The solid was purified by Prep-HPLC (Condition 1, Gradient 4) to afford 5-{6-[(3S)-3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol -6-ol (18.0 mg, 22.32%) as a solid.

Synthesis of Intermediate B46

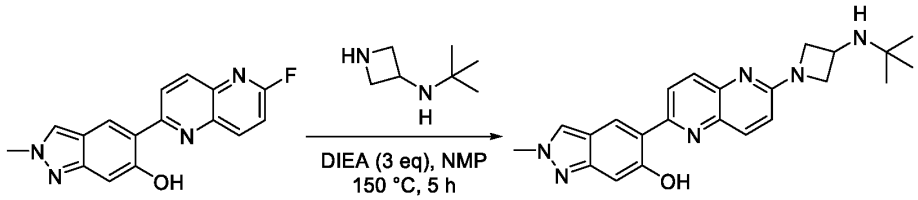


B29 **B46**

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (500 mg, 1.409 mmol, 1.00 equiv), KF (818.75 mg, 14.090 mmol, 10 equiv) and DMSO (10 mL) was stirred for 5 h at 150 °C. The reaction mixture was cooled to room temperature, then quenched

with water (30 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with half-saturation brine (3x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford crude 5-(6-fluoro-1,5-naphthyridin-2-yl) -2-methylindazol-6-ol (405 mg, 97.65%) as a solid. **LCMS** (ES, *m/z*): 339 $[M+H]^+$.

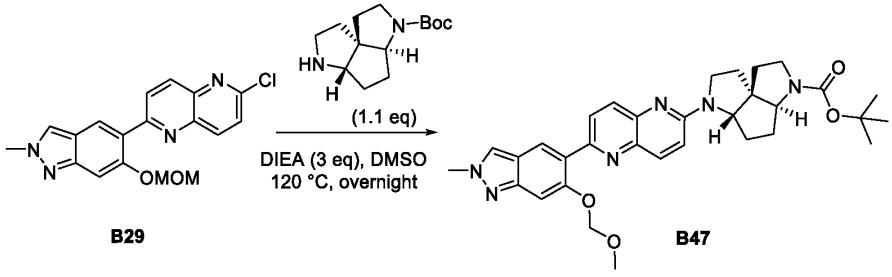
Synthesis of Compound 165



B46 **165**

A mixture of 2-fluoro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (80 mg, 0.236 mmol, 1.00 equiv), N-tert-butylazetidin-3-amine (33.35 mg, 0.260 mmol, 1.1 equiv), NMP (4 mL) and DIEA (91.68 mg, 0.708 mmol, 3 equiv) was stirred for 5 h at 150 °C. The reaction mixture was cooled to room temperature, then quenched with water (20 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with half-saturation brine (3x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, CH_3CN in water; gradient, 40% to 75% in 15 min) to afford N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}azetidin -3-amine (75 mg, 71.03%) as a solid. **LCMS** (ES, *m/z*): 447 $[M+H]^+$.

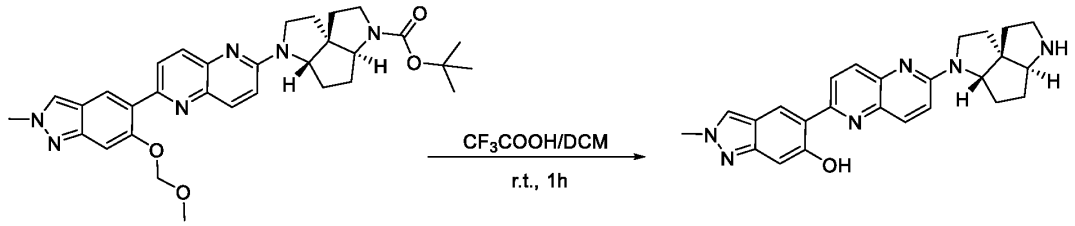
Synthesis of Intermediate B47



B29 **B47**

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (70 mg, 0.197 mmol, 1.00 equiv), tert-butyl (1R,5S,8S)-4,9-diazatricyclo[6.3.0.0^{1,5}]undecane-4-carboxylate (54.77 mg, 0.217 mmol, 1.1 equiv), DMSO (3 mL, 42.236 mmol, 214.07 equiv) and DIEA (76.50 mg, 0.591 mmol, 3 equiv) was stirred overnight at 120 °C. The reaction mixture was cooled to room temperature, then quenched with water (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with half-saturation brine (3x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl (1R,5S,8S)-9-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}-4,9-diazatricyclo[6.3.0.0^{1,5}]undecane-4-carboxylate (50 mg, 44.41%) as a solid. **LCMS** (ES, *m/z*): 571 $[M+H]^+$.

Synthesis of Compound 160

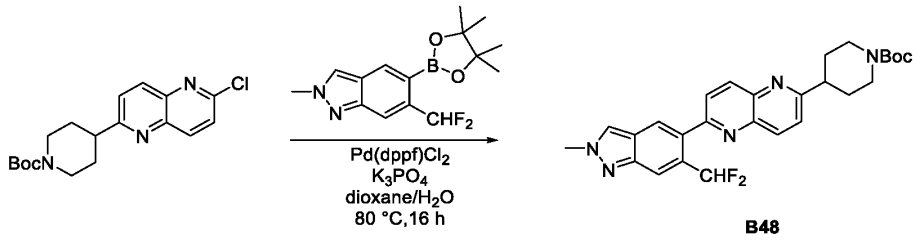


B47 160

A mixture of tert-butyl (1R,5S,8S)-9-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl] -1,5-naphthyridin-2-yl}-4,9-diazatricyclo[6.3.0.0^{1,5}]undecane-4-carboxylate (50 mg, 0.088 mmol, 1.00 equiv), CF_3COOH (0.3 mL, 4.039 mmol, 46.10 equiv) and DCM (3 mL, 47.19 mmol, 538.62 equiv) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 2) to afford 5-{6-[(1R,5S,8S)-4,9-diazatricyclo[6.3.0.0^{1,5}] undecan-4-yl]-1,5-naphthyridin-2-yl} -2-methylindazol-6-ol (12.6 mg, 33.47%) as a solid.

Example 15: Synthesis of Compound 196

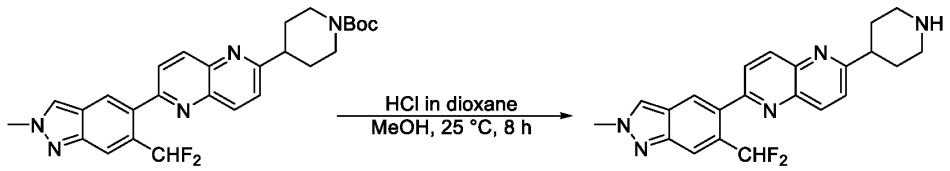
Synthesis of Intermediate B48



B48

To a stirred mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (100 mg, 0.287 mmol, 1.00 equiv) and 6-(difluoromethyl)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazole (132.88 mg, 0.430 mmol, 1.5 equiv) in dioxane (10 mL) and water (0.25 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (46.84 mg, 0.057 mmol, 0.2 equiv) and K_3PO_4 (183.07 mg, 0.861 mmol, 3 equiv) dropwise. The reaction mixture was stirred for 16 h at 80 °C under N_2 atmosphere, then cooled to 25°C. The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with water (3 x 10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (15:1) to afford tert-butyl 4-{6-[6-(difluoromethyl)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}piperidine -1-carboxylate (70 mg, 49.33%) as a solid. **LCMS** (ES, *m/z*): 494 $[M+H]^+$.

Synthesis of Compound 196



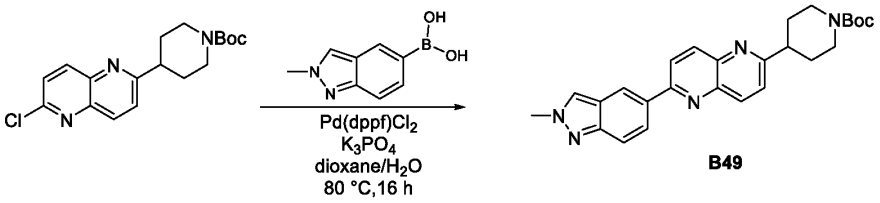
B48 196

A mixture of tert-butyl 4-{6-[6-(difluoromethyl) -2-methylindazol-5-yl]-1,5-naphthyridin-2-yl} piperidine-1-carboxylate (100 mg, 0.203 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (10 mL) in MeOH (10 mL) was stirred for 8 h at 25 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 3) to afford 2-[6-(difluoromethyl)-2-methylindazol -5-yl]-6-(piperidin-4-yl)-1,5-naphthyridine (53.3 mg, 66.86%) as a solid. **LCMS** (ES, *m/z*): 394 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.44 (dd, J = 8.7, 0.9 Hz, 1H), 8.38 (dd, J = 8.7, 0.9 Hz, 1H),

8.17 (d, J = 1.0 Hz, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 7.82 – 7.73 (m, 2H), 4.27 (s, 3H), 3.12 – 2.98 (m, 3H), 2.67 (td, J = 11.8, 2.6 Hz, 2H), 1.88 (d, J = 10.6 Hz, 2H), 1.77 (qd, J = 12.2, 3.9 Hz, 2H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -111.33.

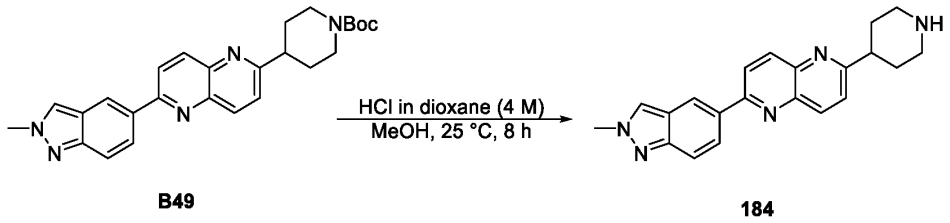
Example 16: Synthesis of Compound 184

Synthesis of Intermediate B49



To a stirred mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (50 mg, 0.144 mmol, 1 equiv) and 2-methylindazol-5-ylboronic acid (37.94 mg, 0.216 mmol, 1.5 equiv) in dioxane (5 mL) and water (1.25 mL) was added Pd(dppf)Cl_2.CH_2Cl_2 (11.71 mg, 0.014 mmol, 0.1 equiv) and K_3PO_4 (91.54 mg, 0.432 mmol, 3 equiv). The reaction mixture was stirred for 16 h at 80°C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (2 x 20mL). The combined organic layers were washed with water (3 x 20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl 4-[6-(2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (40 mg, 62.74%) as a solid. **LCMS** (ES, m/z): 444 $[M+H]^+$.

Synthesis of Compound 184

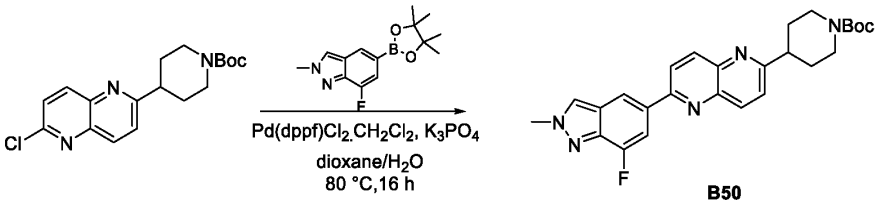


A mixture of tert-butyl 4-[6-(2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (60 mg, 0.135 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (0.6 mL) in methanol (0.6 mL) was stirred for 6 h at 25 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 4) to afford 2-(2-methylindazol-5-yl)-6-(piperidin-4-yl)-1,5-naphthyridine (7.4 mg, 15.93%) as a solid. **LCMS** (ES, m/z): 344 $[M+H]^+$. **^{1}H**

NMR (400 MHz, DMSO-d_6) δ 8.66 (t, J = 1.2 Hz, 1H), 8.53 (s, 1H), 8.42 (d, J = 8.9 Hz, 1H), 8.41 – 8.34 (m, 2H), 8.27 (dd, J = 9.1, 1.7 Hz, 1H), 7.73 (dd, J = 8.9, 5.3 Hz, 2H), 4.22 (s, 3H), 3.11-3.08 (m, 2H), 3.01 (ddt, J = 11.7, 7.3, 3.7 Hz, 1H), 2.71 – 2.60 (m, 2H), 1.87 (d, J = 12.4 Hz, 2H), 1.75 (qd, J = 12.3, 4.0 Hz, 2H).

Example 17: Synthesis of Compound 185

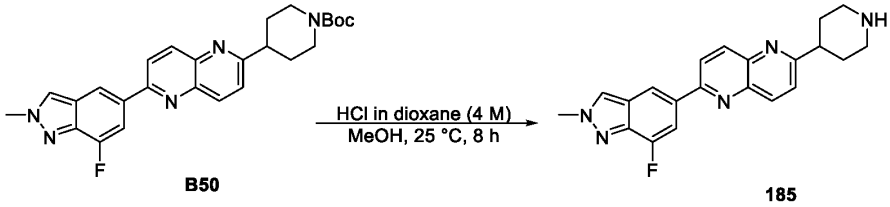
Synthesis of Intermediate B50



B50

To a stirred mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (100 mg, 0.287 mmol, 1 equiv) and 7-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (119.07 mg, 0.430 mmol, 1.5 equiv) in dioxane (10 mL) and water (2.5 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (46.84 mg, 0.057 mmol, 0.2 equiv) and K_3PO_4 (183.07 mg, 0.861 mmol, 3 equiv) dropwise. The reaction mixture was stirred for 16 h at 80 °C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford tert-butyl 4-[6-(7-fluoro-2-methylindazol-5-yl) -1,5-naphthyridin-2-yl]piperidine-1-carboxylate (90 mg, 67.83%) as a solid. **LCMS** (ES, *m/z*): 462 $[M+H]^+$.

Synthesis of Compound 185



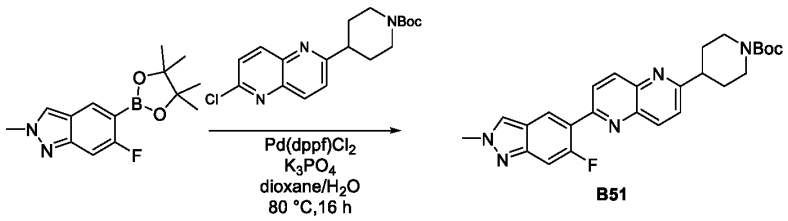
B50 185

A mixture of tert-butyl 4-[6-(7-fluoro-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (70 mg, 0.152 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (5 mL) in methanol (5 mL) was stirred for 8 h at 25°C. The resulting mixture was concentrated under reduced pressure to give a

residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 5) to afford 2-(7-fluoro-2-methylindazol-5-yl)-6-(piperidin-4-yl)-1,5-naphthyridine (35.8 mg, 65.31%) as a solid. **LCMS** (ES, *m/z*): 362 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.52 (d, J = 9.0 Hz, 1H), 8.41 (d, J = 7.4 Hz, 3H), 7.84 (dd, J = 12.4, 1.1 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 4.25 (s, 3H), 3.14 – 2.96 (m, 3H), 2.71 – 2.60 (m, 2H), 1.92 – 1.83 (m, 2H), 1.75 (qd, J = 12.3, 4.0 Hz, 2H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -116.75, -182.13.

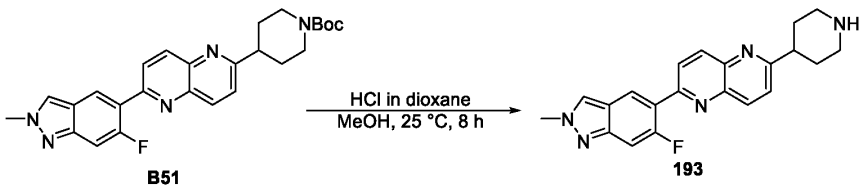
Example 18: Synthesis of Compound 193

Synthesis of Intermediate B51



To a stirred mixture of 6-fluoro-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (100 mg, 0.362 mmol, 1.00 equiv) and tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (151.17 mg, 0.434 mmol, 1.2 equiv) in dioxane (8 mL) and water (2 mL) was added Pd(dppf)Cl_2.CH_2Cl_2 (59 mg, 0.072 mmol, 0.2 equiv) and K_3PO_4 (230.62 mg, 1.086 mmol, 3 equiv) dropwise. The reaction mixture was stirred for 16 h at 80 °C under N_2 atmosphere, then cooled to 25°C. The resulting mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic layers were washed with water (3 x 15 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl 4-[6-(6-fluoro -2-methylindazol -5-yl)-1,5-naphthyridin -2-yl]piperidine-1-carboxylate (70 mg, 41.88%) as a solid. **LCMS** (ES, *m/z*): 462 $[M+H]^+$.

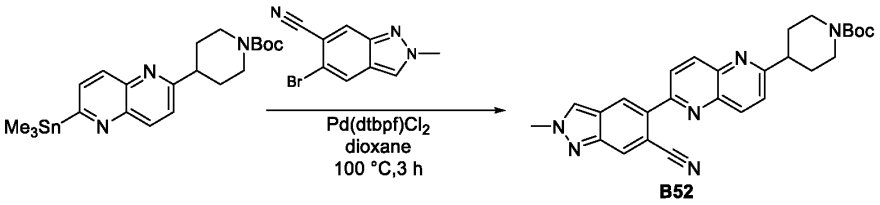
Synthesis of Compound 193



A mixture of tert-butyl 4-[6-(6-fluoro-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine -1-carboxylate (60 mg, 0.130 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (6 mL) in methanol (6 mL) was stirred for 8 h at 25 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 6) to afford 2-(6-fluoro-2-methylindazol-5-yl)-6-(piperidin-4-yl)-1,5-naphthyridine (37.3 mg, 79.39%) as a solid. **LCMS** (ES, *m/z*): 362 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.45 – 8.34 (m, 3H), 8.08 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 12.6 Hz, 1H), 4.21 (s, 3H), 3.11 – 2.97 (m, 3H), 2.66 (td, *J* = 12.1, 2.6 Hz, 2H), 1.88 (d, *J* = 12.1 Hz, 2H), 1.75 (qd, *J* = 12.2, 4.0 Hz, 2H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -119.05.

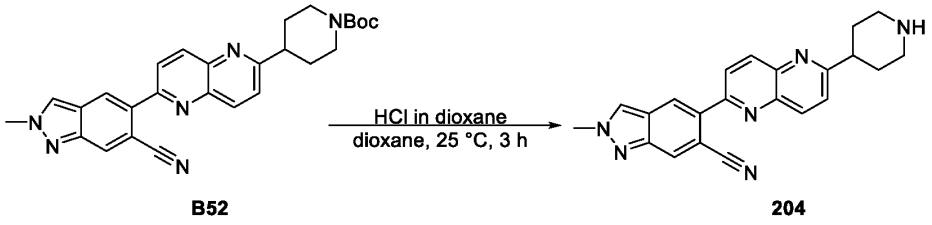
Example 19: Synthesis of Compound 204

Synthesis of Intermediate B52



To a stirred mixture of 5-bromo-2-methylindazole-6-carbonitrile (111.54 mg, 0.472 mmol, 1.50 equiv) and $Pd(DtBPF)Cl_2$ (41.06 mg, 0.063 mmol, 0.2 equiv) in dioxane (15 mL) was added tert-butyl 4-[6-(trimethylstannyl) -1,5-naphthyridin-2-yl]piperidine-1-carboxylate (150 mg, 0.315 mmol, 1 equiv) portionwise. The reaction mixture was stirred for 3 h at 100 °C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford tert-butyl 4-[6-(6-cyano-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (120 mg, 81.31%) as a solid. **LCMS** (ES, *m/z*): 469 $[M+H]^+$.

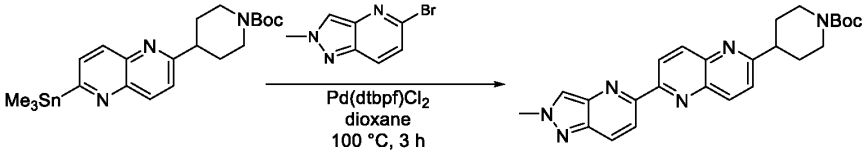
Synthesis of Compound 204



To a stirred solution of tert-butyl 4-[6-(6-cyano-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] piperidine-1-carboxylate (100 mg, 0.213 mmol, 1.00 equiv) in dioxane (3 mL) was added HCl (gas) in 1,4-dioxane (3 mL) portionwise. The reaction mixture was stirred for 3 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 7) to afford 2-methyl-5-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazole-6-carbonitrile (23.6 mg, 30.01%) as a solid. **LCMS** (ES, *m/z*): 369 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.51 – 8.44 (m, 2H), 8.43 – 8.36 (m, 2H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 4.30 (s, 3H), 3.18 – 3.03 (m, 3H), 2.72 (t, *J* = 11.9 Hz, 2H), 1.92 (d, *J* = 12.8 Hz, 2H), 1.87 – 1.73 (m, 2H)

Example 20: Synthesis of Compound 199

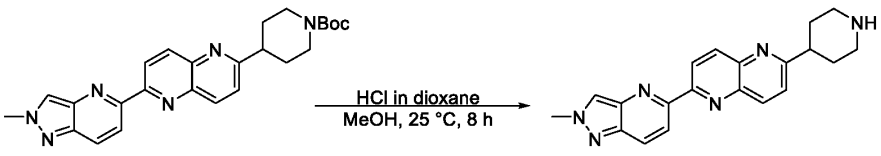
Synthesis of Intermediate B53



B53

To a stirred mixture of 5-bromo-2-methylpyrazolo[4,3-b]pyridine (120.23 mg, 0.567 mmol, 1.5 equiv) and Pd(DtBPF)Cl_2 (49.27 mg, 0.076 mmol, 0.2 equiv) in dioxane (20 mL) was added tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (180 mg, 0.378 mmol, 1 equiv) portionwise. The reaction mixture was stirred for 3 h at 100 °C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:1) to afford tert-butyl 4-(6-{2-methylpyrazolo[4,3-b]pyridin-5-yl}-1,5-naphthyridin-2-yl)piperidine -1-carboxylate (90 mg, 53.56%) as a solid. **LCMS** (ES, *m/z*): 445 $[M+H]^+$.

Synthesis of Compound 199

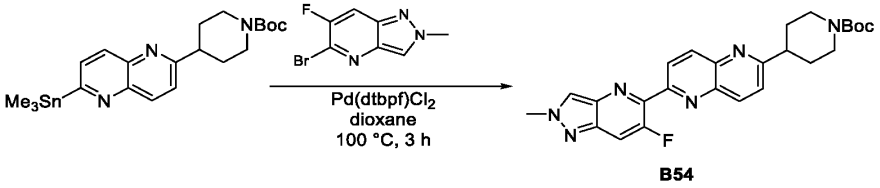


B53 199

A solution of tert-butyl 4-(6-{2-methylpyrazolo[4,3-b] pyridin-5-yl}-1,5-naphthyridin-2-yl) piperidine-1-carboxylate (80 mg, 0.180 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (8 mL) in methanol (8 mL) was stirred for 8 h at 25 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 5) to afford 2-{2-methylpyrazolo[4,3-b]pyridin-5-yl}-6-(piperidin-4-yl)-1,5-naphthyridine (12.1 mg, 19.52%) as a solid. **LCMS** (ES, *m/z*): 345 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.85 – 8.79 (m, 2H), 8.58 (d, J = 9.1 Hz, 1H), 8.45 (dd, J = 8.7, 5.2 Hz, 2H), 8.26 (dd, J = 9.1, 1.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 4.27 (s, 3H), 3.06 (t, J = 13.7 Hz, 3H), 2.68 – 2.60 (m, 2H), 1.89 (s, 2H), 1.75 (qd, J = 12.3, 4.0 Hz, 2H).

Example 21: Synthesis of Compound 205

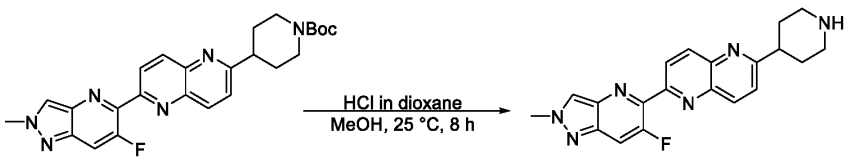
Synthesis of Intermediate B54



B54

To a stirred solution of 5-bromo-6-fluoro-2-methylpyrazolo[4,3-b]pyridine (144.92 mg, 0.630 mmol, 1.5 equiv) and Pd(DtBPF)Cl_2 (54.74 mg, 0.084 mmol, 0.2 equiv) in dioxane (20 mL) were added tert-butyl 4-[6-(trimethy lstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (200 mg, 0.420 mmol, 1 equiv) in portions for 3 h at 100 °C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (3 x 40 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl 4-(6-{6-fluoro-2-methylpyrazolo [4,3-b]pyridin-5-yl}-1,5-naphthyridin-2-yl) piperidine -1-carboxylate (100 mg, 51.48%) as a solid. **LCMS** (ES, *m/z*): 463 $[M+H]^+$.

Synthesis of Compound 205

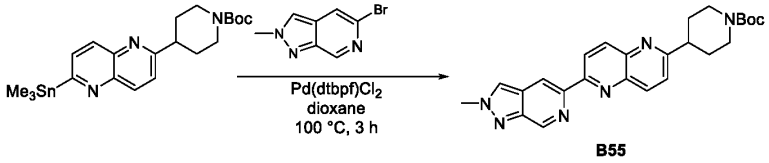


B54 **205**

To a stirred solution of tert-butyl 4-(6-{6-fluoro-2-methylpyrazolo [4,3-b]pyridin-5-yl}-1,5-naphthyridin-2-yl) piperidine-1-carboxylate (90 mg, 0.195 mmol, 1.00 equiv) in dioxane (5 mL) was added HCl (gas) in 1,4-dioxane (5 mL, 164.559 mmol, 845.71 equiv) in portions. The reaction mixture was stirred for 8 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 6) to afford 2-{6-fluoro-2-methylpyrazolo[4,3-b]pyridin-5-yl}-6-(piperidin-4-yl)-1,5-naphthyridine (12.4 mg, 17.58%) as a solid. **LCMS** (ES, *m/z*): 363 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.49 (dd, *J* = 8.8, 0.8 Hz, 1H), 8.41 (dd, *J* = 8.7, 0.8 Hz, 1H), 8.30 (dd, *J* = 8.8, 1.0 Hz, 1H), 8.13 (dd, *J* = 11.8, 1.0 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 4.26 (s, 3H), 3.13 – 2.99 (m, 3H), 2.66 (td, *J* = 12.3, 2.5 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.76 (qd, *J* = 12.2, 4.0 Hz, 2H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -123.77.

Example 22: Synthesis of Compound 200

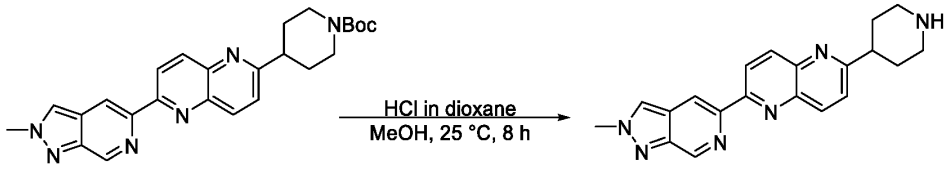
Synthesis of Intermediate B55



B55

To a stirred mixture of tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (180 mg, 0.378 mmol, 1 equiv) and 5-bromo-2-methylpyrazolo[3,4-c]pyridine (120.23 mg, 0.567 mmol, 1.5 equiv) in dioxane (15 mL) was added Pd(DtBPF)Cl_2 (49.27 mg, 0.076 mmol, 0.2 equiv) in portions. The reaction mixture was stirred for 3 h at 100 °C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (3x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl 4-(6-{2-methylpyrazolo[3,4-c]pyridin-5-yl} -1,5-naphthyridin-2-yl)piperidine-1-carboxylate (95 mg, 56.54%) as a solid. **LCMS** (ES, *m/z*): 445 $[M+H]^+$.

Synthesis of Compound 200

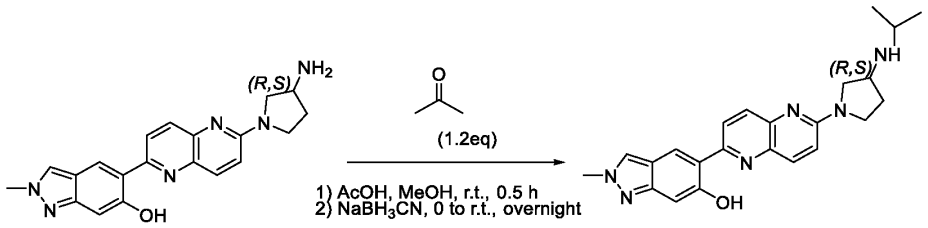


B55 200

A mixture of tert-butyl 4-(6-{6-fluoro-2-methylpyrazolo[4,3-b]pyridin-5-yl}-1,5-naphthyridin-2-yl) piperidine-1-carboxylate (90 mg, 0.195 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (8 mL) in methanol (8 mL) was stirred for 8 h at 25 °C. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 6) to afford 2-{6-fluoro-2-methylpyrazolo[4,3-b]pyridin-5-yl}-6-(piperidin-4-yl)-1,5-naphthyridine (10.3 mg, 14.61%) as a solid. **LCMS** (ES, *m/z*): 345 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.31 (t, *J* = 1.1 Hz, 1H), 8.92 (d, *J* = 1.4 Hz, 1H), 8.80 (d, *J* = 8.9 Hz, 1H), 8.67 (s, 1H), 8.42 (ddd, *J* = 17.6, 8.8, 0.8 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 1H), 4.31 (s, 4H), 3.12 – 2.98 (m, 3H), 2.77 (s, 1H), 2.69 – 2.61 (m, 2H), 1.89 (d, *J* = 12.2 Hz, 2H), 1.77 (qd, *J* = 12.2, 3.9 Hz, 2H).

Example 23: Synthesis of Compounds 169-173, 179, 180, 182, 188, 189, 192, 194, 195

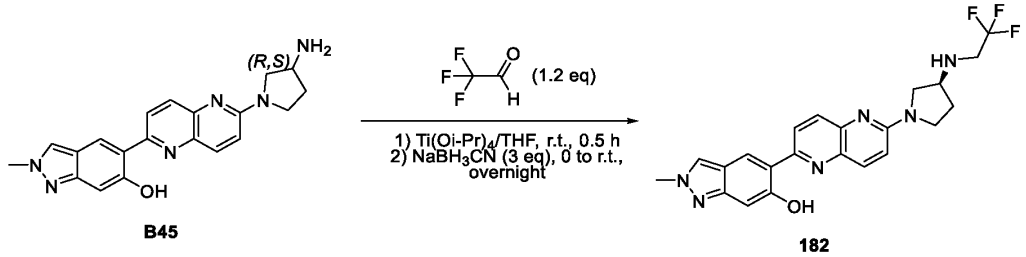
Synthesis of Compound 171



B45 171

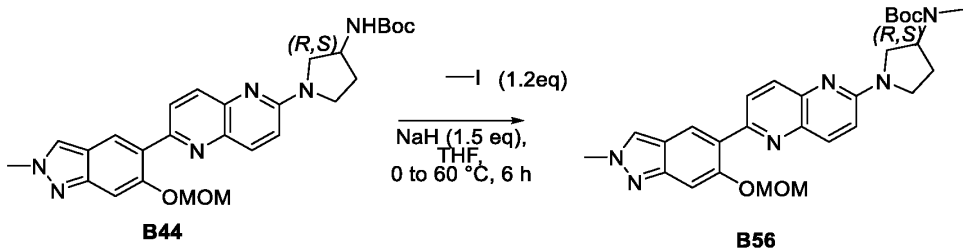
5-{6-[(3S)-3-aminopyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (70 mg, 0.194 mmol, 1.00 equiv), acetone (16.92 mg, 0.291 mmol, 1.5 equiv), methanol (2 mL), and CH_3COOH (11.66 mg, 0.194 mmol, 1 equiv) were combined at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. To the reaction mixture was added a solution of $NaBH_3CN$ (36.62 mg, 0.582 mmol, 3 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with water (3 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 4) to afford 5-{6-[(3S)-3-(cyclobutylamino)pyrrolidin-1-yl] -1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (24.1 mg, 29.91%) as a solid.

Synthesis of Compound 182



5-{6-[(3S)-3-aminopyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (100 mg, 0.277 mmol, 1.00 equiv), 2,2,2-trifluoroethane-1,1-diol (64.39 mg, 0.554 mmol, 2 equiv), THF (1.6 mL) and $Ti(Oi\text{-}Pr)_4$ (0.4 mL, 1.337 mmol, 4.82 equiv) were combined at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. To the reaction mixture was added $NaBH_3CN$ (52.31 mg, 0.831 mmol, 3 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with water (10 mL) at room temperature. The resulting mixture was filtered, and the filter cake was washed with methanol (3 x 10 mL). The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 2, Gradient 2) to afford 2-methyl-5-{6-[(3S)-3-[(2,2,2-trifluoroethyl) amino]pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (3.3 mg) as a solid.

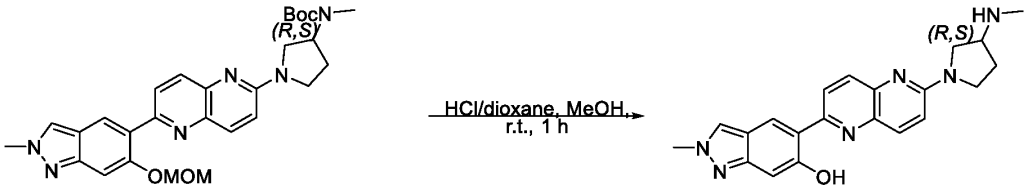
Synthesis of Intermediate B56



Tert-butyl N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl]carbamate (70 mg, 0.139 mmol, 1 equiv), THF (2 mL), and NaH (4.99 mg, 0.209 mmol, 1.5 equiv) were combined at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. To the reaction mixture was added MeI (39.38 mg, 0.278 mmol, 2 equiv) at 0 °C. The resulting mixture was stirred overnight at 60 °C, then quenched with water/ice (5 mL) at room temperature. The resulting mixture was concentrated under reduced pressure to afford tert-butyl N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-

yl]-N-methylcarbamate (50 mg, 69.50%), which was used in the next step without further purification.

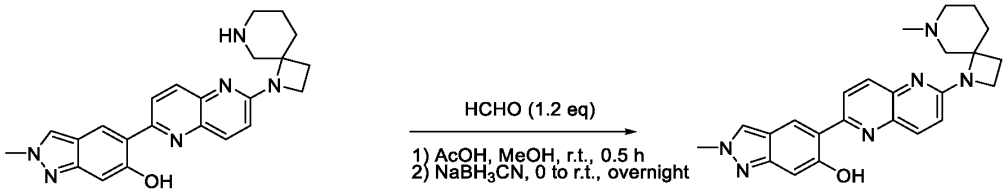
Synthesis of Compounds 170 and 172



B56 **170, 172**

Tert-butyl N-[(3S)-1-{6-[6-(methoxymethoxy)-2-methylindazol -5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl]-N-methylcarbamate (50 mg, 0.096 mmol, 1.00 equiv), methanol (3 mL), and HCl (gas) in 1,4-dioxane (3 mL, 98.736 mmol, 1024.12 equiv) were combined at room temperature. The resulting mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 8) to afford 2-methyl-5-{6-[(3S)-3-(methylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (11.5 mg, 31.70%) as a solid.

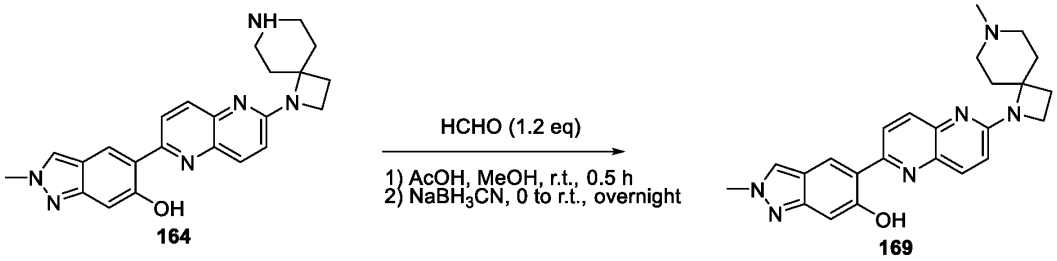
Synthesis of Compound 192



163 **192**

5-(6-{1,6-diazaspiro[3.5]nonan-1-yl}-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (30 mg, 0.075 mmol, 1.00 equiv), HCHO (3.37 mg, 0.112 mmol, 1.5 equiv), methanol (2 mL), and AcOH (4.50 mg, 0.075 mmol, 1 equiv) were combined at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. To the reaction mixture was added $NaBH_3CN$ (14.12 mg, 0.225 mmol, 3 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with water (5 mL) at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-chiral-HPLC (Condition 1, Gradient 1, Retention time (min): 5.9) to afford 2-methyl-5-(6-{6-methyl-1,6-diazaspiro[3.5]nonan-1-yl}-1,5-naphthyridin-2-yl)indazol-6-ol (1.8 mg) as a solid.

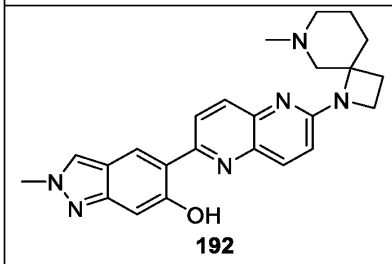
Synthesis of Compound 169

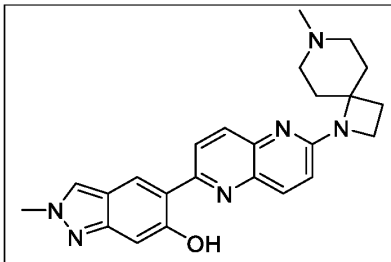
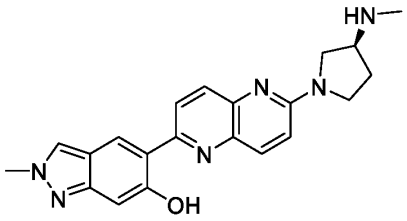
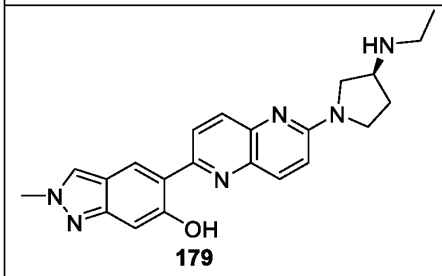


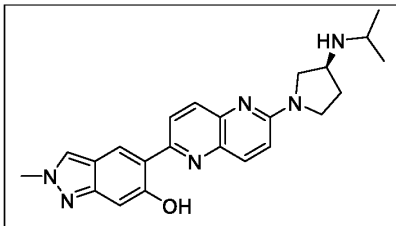
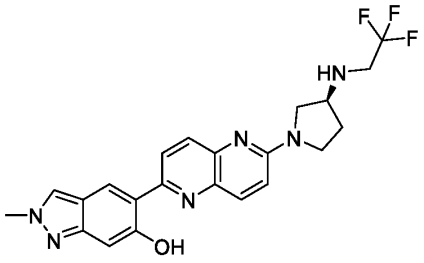
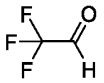
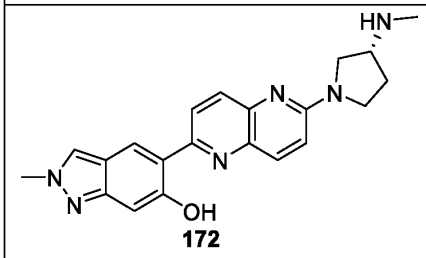
164 169

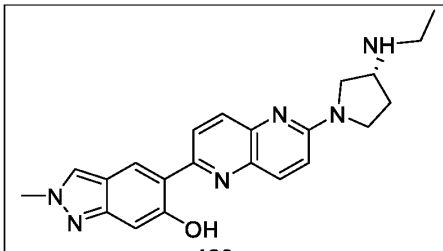
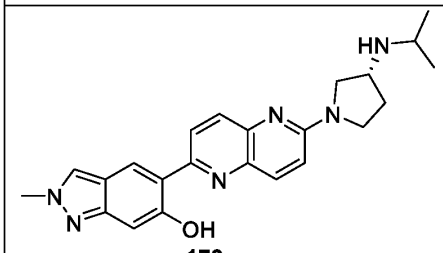
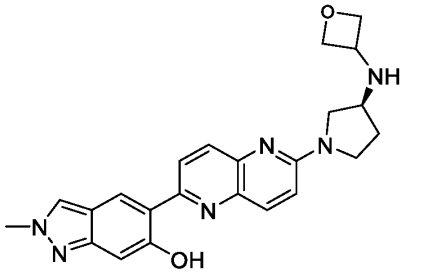
5-(6-{1,6-diazaspiro[3.5]nonan-1-yl}-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (30 mg, 0.075 mmol, 1.00 equiv), HCHO (3.37 mg, 0.112 mmol, 1.5 equiv), methanol (2 mL), and AcOH (4.50 mg, 0.075 mmol, 1 equiv) were combined at room temperature. The resulting mixture was stirred for 0.5 h at room temperature. To the reaction mixture was added $NaBH_3CN$ (14.12 mg, 0.225 mmol, 3 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with water (5 mL) at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 2) to afford 2-methyl-5-(6-{6-methyl-1,6-diazaspiro[3.5]nonan-1-yl}-1,5-naphthyridin-2-yl)indazol-6-ol (3.7 mg, 11.06%) as a solid.

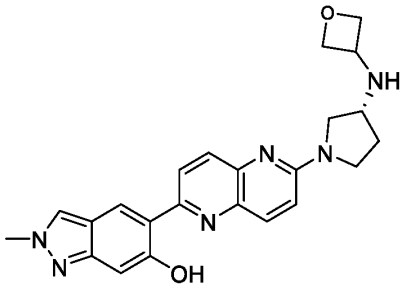
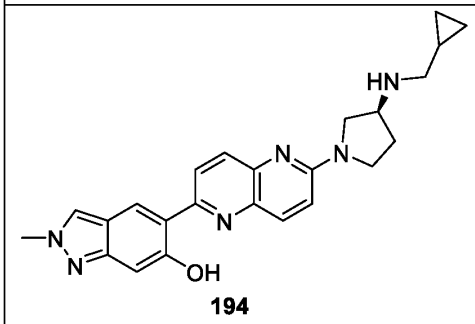
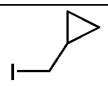
Compounds 169-173, 179, 180, 182, 188, 189, 192, 194, and 195 were prepared according to the procedures outlined herein, outlined in this Example 23. The table below provides intermediates used in these procedures and final compound characterization data.

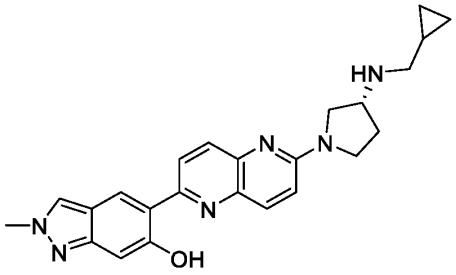
Compound No. and Structure	**Coupling Reagent**	**LCMS (ESI, *m/z*) $[M+H]^+$**	**^{1}H NMR δ**
 **192**	—I	415	(400 MHz, DMSO-d_6) δ 13.90 (s, 1H), 8.55 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.05 (t, J = 8.5 Hz, 2H), 6.99 (s, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 4.01 (t, J = 7.6 Hz, 2H), 3.31 – 3.29 (m, 2H), 2.89 (s, 1H), 2.71 (s, 1H), 2.29 (d, J = 4.5 Hz, 1H), 2.23 (s, 3H), 2.18 (t, J = 8.0 Hz, 1H), 1.86 (s, 2H), 1.65 (s, 1H), 1.56 (s, 1H)

 **169**	—I	415	(400 MHz, DMSO-d_6) δ 13.61 (s, 1H), 8.46 (s, 1H), 8.32 (d, J = 9.1 Hz, 1H), 8.28 (s, 1H), 8.02 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.1 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 4.06 – 3.97 (m, 2H), 2.77 (t, J = 12.1 Hz, 2H), 2.63 (s, 2H), 2.21 (d, J = 6.8 Hz, 5H), 1.98 (t, J = 12.1 Hz, 2H), 1.77 (d, J = 12.3 Hz, 2H)
 **170**	—I	375	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 13.6, 9.2 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.75 – 3.54 (m, 3H), 3.38 (s, 1H), 3.33 – 3.26 (m, 1H), 2.33 (s, 3H), 2.11 (dt, J = 12.9, 6.3 Hz, 1H), 1.95 – 1.79 (m, 2H)
 **179**		389	(400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.09 (dd, J = 14.6, 9.2 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.74 (dd, J = 10.6, 5.8 Hz, 1H), 3.67 (s, 1H), 3.57 (s, 1H), 3.45 – 3.34 (m, 2H), 2.61 (tt, J = 7.3, 3.6 Hz, 2H), 2.14 (dq, J = 12.2, 6.3 Hz, 1H), 1.86 (d, J = 6.3 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H)

 **171**		403	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 14.1, 9.1 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.80 (dd, J = 10.3, 6.2 Hz, 1H), 3.71 (s, 1H), 3.55 (dd, J = 16.4, 7.7 Hz, 2H), 3.28 (s, 1H), 2.86 (p, J = 6.2 Hz, 1H), 2.16 (dq, J = 12.2, 5.9 Hz, 1H), 1.82 (dt, J = 12.4, 7.1 Hz, 1H), 1.72 (s, 1H), 1.03 (dd, J = 6.2, 4.5 Hz, 6H)
 **182**		443	(400 MHz, DMSO-d_6) δ 8.45 – 8.37 (m, 2H), 8.33 (d, J = 7.1 Hz, 2H), 8.27 (d, J = 9.4 Hz, 1H), 7.31 (d, J = 9.5 Hz, 1H), 6.93 (s, 1H), 4.12 (s, 3H), 3.96 – 3.78 (m, 2H), 3.76 – 3.71 (m, 1H), 3.70 – 3.58 (m, 2H), 3.49 (q, J = 10.1 Hz, 2H), 2.26 (dt, J = 13.4, 6.4 Hz, 1H), 2.06 (dq, J = 13.0, 6.5 Hz, 1H)
 **172**	—I	375	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.1 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 13.6, 9.2 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.75 – 3.62 (m, 3H), 3.40 (s, 1H), 3.30 (d, J = 4.9 Hz, 1H), 2.33 (s, 3H), 2.12 (dq, J = 12.9, 6.9 Hz, 1H), 1.87 (dd, J = 12.8, 6.9 Hz, 2H)

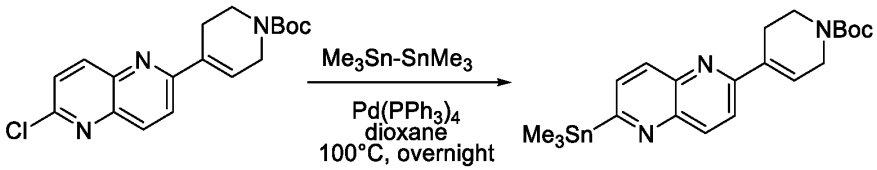
 **180**		389	(400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (ddd, J = 14.3, 9.2, 0.8 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (d, J = 1.0 Hz, 1H), 4.12 (s, 3H), 3.73 (dd, J = 10.5, 5.7 Hz, 1H), 3.67 (s, 1H), 3.57 (d, J = 8.3 Hz, 1H), 3.40 (dd, J = 10.5, 5.2 Hz, 2 H), 2.61 (qt, J = 7.0, 3.6 Hz, 2H), 2.19 – 2.08 (m, 1H), 1.85 (q, J = 6.4 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H)
 **173**		403	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.54 (s, 1H), 8.43 – 8.33 (m, 2H), 8.13 – 8.03 (m, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (d, J = 1.0 Hz, 1H), 4.12 (s, 3H), 3.79 (t, J = 8.4 Hz, 1H), 3.70 (s, 1H), 3.60 – 3.48 (m, 2H), 3.31 – 3.24 (m, 1H), 2.86 (hept, J = 6.1 Hz, 1H), 2.16 (ddd, J = 12.3, 7.2, 3.7 Hz, 1H), 1.80 (ddd, J = 24.2, 15.9, 8.7 Hz, 2H), 1.03 (dd, J = 6.2, 4.6 Hz, 6H)
 **189**		417	(400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.09 (ddd, J = 16.9, 9.2, 0.8 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.88 (s, 1H), 4.68 (ddd, J = 7.0, 5.7, 3.0 Hz, 2H), 4.36 (dt, J = 9.0, 6.2 Hz, 2H), 4.12 (s, 3H), 4.01 (q, J = 7.3 Hz, 1H), 3.74 – 3.66 (m, 2H), 3.55 (d, J = 9.0 Hz, 1H),

			3.37 (s, 1H), 2.81 (d, J = 7.3 Hz, 1H), 2.08 (dq, J = 12.8, 6.5 Hz, 1H), 1.81 (dd, J = 12.3, 6.5 Hz, 1H)
 **188**		417	(400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 9.3 Hz, 1H), 8.35 (s, 1H), 8.09 (dd, J = 16.9, 9.2 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.68 (td, J = 6.5, 2.9 Hz, 2H), 4.36 (dt, J = 9.1, 6.2 Hz, 2H), 4.12 (s, 3H), 4.01 (q, J = 7.2 Hz, 1H), 3.73 – 3.66 (m, 2H), 3.55 (d, J = 9.4 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.84 – 2.76 (m, 1H), 2.08 (dd, J = 12.1, 6.2 Hz, 1H), 1.81 (dd, J = 12.1, 6.4 Hz, 1H)
 **194**		415	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.54 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.35 (t, J = 0.8 Hz, 1H), 8.09 (ddd, J = 15.3, 9.1, 0.8 Hz, 2H), 7.16 (d, J = 9.3 Hz, 1H), 6.87 (t, J = 0.7 Hz, 1H), 4.12 (s, 3H), 3.75 (dd, J = 11.0, 6.0 Hz, 1H), 3.68 (s, 1H), 3.58 (s, 1H), 3.46 (t, J = 5.4 Hz, 1H), 2.47 (d, J = 6.6 Hz, 2H), 2.14 (dd, J = 12.4, 6.2 Hz, 1H), 1.88 (s, 2H), 0.94 – 0.85 (m, 1H), 0.46 – 0.37 (m, 2H), 0.18 – 0.05 (m, 2H)

 195		415	(400 MHz, DMSO-d_6) δ 13.98 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 9.3 Hz, 1H), 8.36 (s, 1H), 8.09 (dd, J = 15.9, 9.2 Hz, 2H), 7.16 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.75 (dd, J = 10.8, 5.9 Hz, 1H), 3.68 (s, 1H), 3.58 (s, 1H), 3.46 (s, 1H), 3.37 (s, 1H), 2.47 (d, J = 6.3 Hz, 2H), 2.14 (dd, J = 12.5, 6.4 Hz, 1H), 1.87 (s, 2H), 0.96 – 0.84 (m, 1H), 0.47 – 0.38 (m, 2H), 0.14 (dt, J = 5.7, 2.8 Hz, 2H)

Example 24: Synthesis of Compound 101

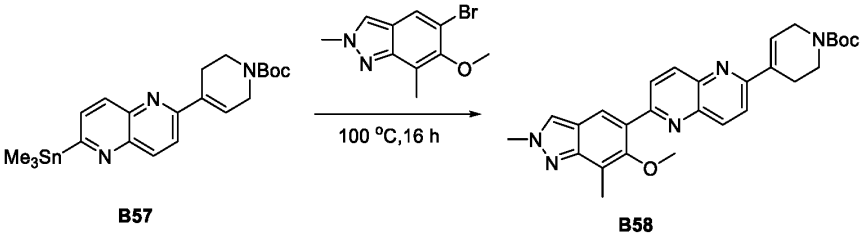
Synthesis of Intermediate B57



B57

Tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (200.0 mg, 0.57 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (66.83 mg, 0.058 mmol, 0.1 equiv), 1,4-dioxane (3.0 mL, 35.41 mmol, 61.23 equiv), and Sn_2Me_6 (670.98 mg, 1.156 mmol, 2.0 equiv) were combined. The reaction mixture was irradiated with microwave radiation for 16 h at 100 °C, then cooled to 25 °C. The reaction mixture was then quenched with KF. The resulting solution was extracted with ethyl acetate (3x10 mL), and the organic layers combined. The combined organic layers were concentrated *in vacuo* to afford tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200 mg, 72.9%) as a solid. **LCMS** (ES, *m/z*): 476 $[M+H]^+$.

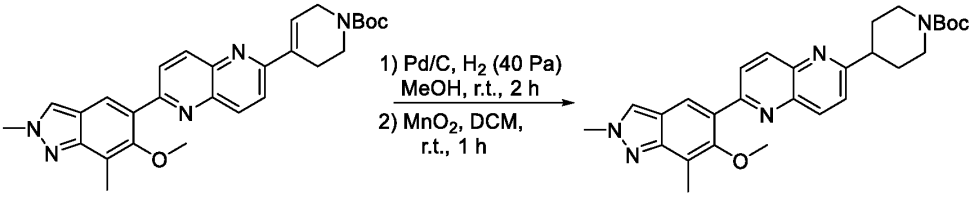
Synthesis of Intermediate B58



B57 B58

Tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (180.0 mg, 0.38 mmol, 1.0 equiv), 5-bromo-6-methoxy-2,7-dimethylindazole (96.84 mg, 0.38 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (43.86 mg, 0.038 mmol, 0.10 equiv), and toluene (3.0 mL, 28.19 mmol, 74.28 equiv) were combined. The reaction mixture was stirred for 16 h at 100 °C, then cooled to 25 °C. The reaction was then quenched with KF. The resulting solution was extracted with ethyl acetate (3x10 mL), and the organic layers were combined and concentrated to give a residue. The residue was purified by silica gel column with ethyl acetate/petroleum ether (9;1) to afford tert-butyl 4-[6-(6-methoxy-2,7-dimethylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (110 mg, 59.6%) as an oil. **LCMS** (ES, *m/z*): 486 $[M+H]^+$.

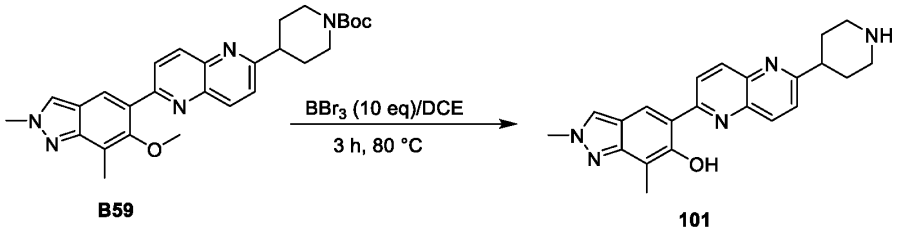
Synthesis of Intermediate B59



B58 B59

A mixture of tert-butyl 4-[6-(6-methoxy-2,7-dimethylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro -2H-pyridine-1-carboxylate (100 mg), Pd/C (20 mg), and methanol (3 ml) was stirred at 25 °C under a H_2 atmosphere (40 Pa) for 5 h. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to yield a solid. The solid was dissolved in DCM (3 mL), and combined with MnO_2 (179.03 mg, 2.06 mmol, 10 eq). The reaction mixture was stirred at 25 °C for 16 h, filtered, and the filtrate was concentrated *in vacuo* to afford tert-butyl 4-[6-(6-methoxy-2,7-dimethylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (90 mg, 89.6%) as a solid. **LCMS** (ES, *m/z*): 488 $[M+H]^+$.

Synthesis of Compound 101

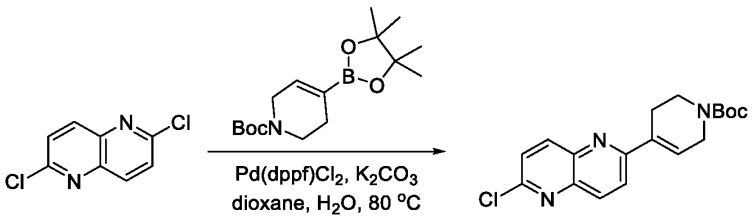


B59 101

Tert-butyl 4-[6-(6-methoxy-2,7-dimethylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (90.0 mg, 0.185 mmol, 1.0 equiv), DCE (1.0 mL, 12.63 mmol, 68.44 equiv), and BBr_3 (462.41 mg, 1.85 mmol, 10.0 equiv) were combined. The reaction mixture was stirred for 3 h at 80 °C, then quenched with methanol. The resulting mixture was concentrated *in vacuo* to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30 - 150mm 5μm; Mobile Phase A: water (10mmol/L NH_4HCO_3), and ACN (5% Phase B up to 45% in 8 min)) to afford 2,7-dimethyl-5-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (9.4 mg, 13.6%) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.17 (s, 1H), 8.57 - 8.67 (m, 2H), 8.40 - 8.48 (m, 3H), 7.78 (d, *J* = 8.7 Hz, 1H), 4.16 (s, 3H), 3.09 (s, 2H), 3.03 (s, 1H), 2.54 - 2.77 (m, 2H), 2.40 (s, 3H), 1.88 (d, *J* = 12.4 Hz, 2H), 1.75 (d, *J* = 11.9 Hz, 2H).

Example 25: Synthesis of Compound 105

Synthesis of Intermediate B60

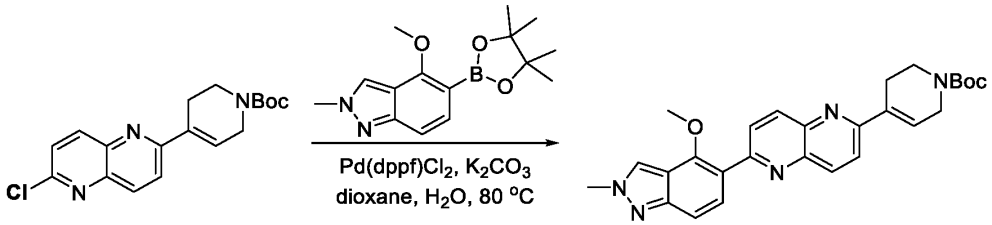


B60

To 2,6-dichloro-1,5-naphthyridine (2 g, 10.04 mmol, 1.00 equiv) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.73 g, 12.06 mmol, 1.2 equiv) in a mixture of dioxane (16 mL) and water (4 mL) was added K_2CO_3 (4.2 g, 36.18 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (394.8 mg, 1.81mmol, 0.05 equiv) under N_2 atmosphere. The reaction mixture was stirred at 80 °C for 2 h, then diluted with ethyl acetate (100 mL) and water (100 mL). The aqueous layer was extracted with ethyl acetate (2x100 mL). The organic layers were combined, washed with brine (250 mL), dried with Na_2SO_4, filtered, and evaporated

under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (70% EA in PE) to afford tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.2 g, 63.31%) as an oil. **LCMS** (ESI, *m/z*): 346.00 $[M+H]^+$.

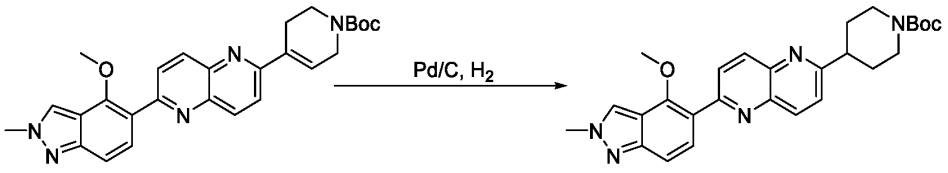
Synthesis of Intermediate B61



B60 **B61**

To a mixture of tert-butyl 4-(6-chloro-1,5-naphthyridin-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (200.00 mg, 0.578 mmol, 1.00 equiv), 4-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (166.64 mg, 0.578 mmol, 1.00 equiv), and K_2CO_3 (239.78 mg, 1.734 mmol, 3.00 equiv) in dioxane (1.60 mL) and water (0.40 mL) was added $Pd(dppf)Cl_2$ (21.16 mg, 0.029 mmol, 0.05 equiv). The reaction mixture was stirred at 80 °C for 16 h, then diluted with ethyl acetate (10 mL) and water (15 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The organic layers were combined, washed with saturated brine (40 mL), dried over anhydrous sodium, and concentrated to give a residue. The residue was purified by flash column chromatography to afford tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (260 mg, 95.34%) as an oil. **LCMS** (ESI, *m/z*): 472.05 $[M+H]^+$.

Synthesis of Intermediate B62



B61 **B62**

To a solution of tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (260.00 mg) in methanol (10.00 mL) was added Pd/C (200.00 mg). The reaction mixture was stirred at room temperature for 2 h under H_2 atmosphere (15 psi), then filtered, and the filter cake washed with methanol. The filtrate was concentrated

under reduced pressure to afford tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl) -1,5-naphthyridin-2-yl]piperidine-1-carboxylate (200 mg, 70% purity). **LCMS** (ESI, *m/z*): 474.10 $[M+H]^+$.

Synthesis of Compound 105

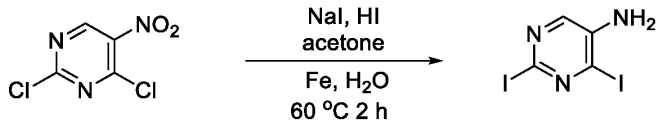


B62 **105**

To a solution of tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] piperidine-1-carboxylate (100 mg, 0.211 mmol, 1.00 equiv) in DCM (5.00 mL) was added BBr_3 (6.33 mL, 6.330 mmol, 30.00 equiv). The reaction mixture was stirred at 80°C for 16 h, then concentrated *in vacuo* to give a residue. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 min) to afford 2-methyl-5-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-4-ol (1.3 mg, 1.61%) as a solid. **LCMS** (ESI, *m/z*): 360.15 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.46 – 8.40 (m, 3H), 8.37 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 9.2 Hz, 1H), 4.22 (s, 3H), 3.40 (m, 2H), 3.28 – 3.19 (m, 1H), 3.02 (t, *J* = 12.3 Hz, 2H), 2.22 – 1.95 (m, 4H).

Example 26: Synthesis of Compound 107

Synthesis of Intermediate B63

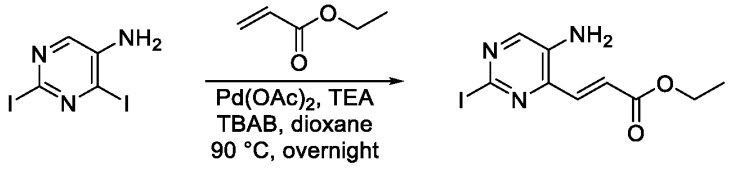


B63

A mixture of 2,4-dichloro-5-nitropyrimidine (10.0 g, 51.554 mmol, 1.00 equiv), NaI (30.9 g, 206.212 mmol, 4.00 equiv), and HI (3.0 mL, 39.894 mmol, 0.77 equiv) in acetone (100.0 mL) was stirred for 3 h at room temperature under nitrogen atmosphere. To the reaction mixture was added Fe (14.4 g, 257.857 mmol, 5.00 equiv) and water (5.00 mL). The resulting mixture was stirred for an additional 2 h at 60 °C. The resulting mixture was filtered, the filter cake washed with ethyl acetate (2 x 20 mL), and the filtrate concentrated under reduced pressure to give a

residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford 2,4-diiodopyrimidin-5-amine (5 g, 27.96%) as a solid. **LCMS** (ES, *m/z*): 348 $[M+H]^+$.

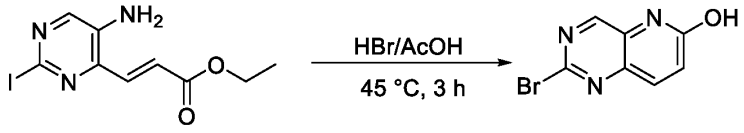
Synthesis of Intermediate B64



B63 **B64**

A mixture of 2,4-diiodopyrimidin-5-amine (5.00 g, 14.413 mmol, 1.00 equiv), ethyl acrylate (7.22 g, 72.116 mmol, 5.00 equiv), TBAB (6.97 g, 21.620 mmol, 1.50 equiv), $Pd(AcO)_2$(0.16 g, 0.721 mmol, 0.05 equiv), and TEA (5.83 g, 57.654 mmol, 4.00 equiv) in dioxane (50.00 mL) was stirred overnight at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford ethyl (2E)-3-(5-amino-2-iodopyrimidin-4-yl) prop-2-enoate (2g,43.48%) as a solid. **LCMS** (ES, *m/z*): 320 $[M+H]^+$.

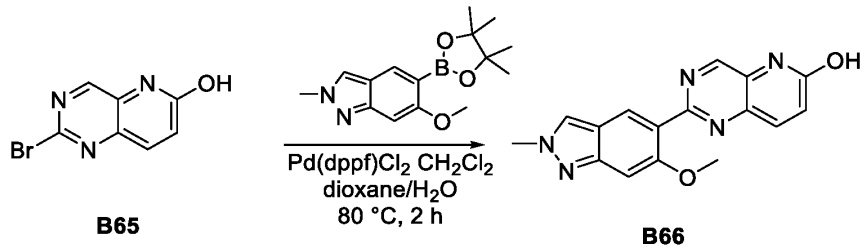
Synthesis of Intermediate B65



B64 **B65**

A mixture of ethyl (2E)-3-(5-amino-2-iodopyrimidin-4-yl) prop-2-enoate (2.00 g, 6.268 mmol, 1.00 equiv) in HBr in acetic acid (40%) (20.00 mL) was stirred for 3 h at 45 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in methanol (5 mL), neutralized to pH 7 with saturated $NaHCO_3$ (aq.), and a precipitate formed. The precipitated solid was collected by filtration and washed with methanol (1x2 mL) to afford 2-bromopyrido[3,2-d] pyrimidin-6-ol (1.2g,84.70%) as a solid. **LCMS** (ES, *m/z*): 226 $[M+H]^+$.

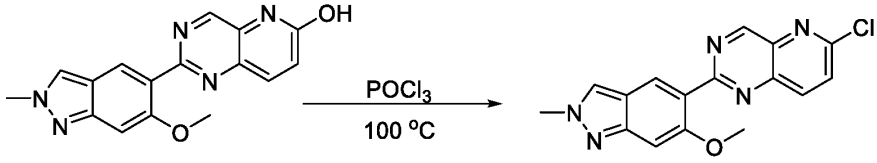
Synthesis of Intermediate B66



B65 **B66**

To a mixture of 2-bromopyrido[3,2-d] pyrimidin-6-ol (400.00 mg, 1.770 mmol, 1.00 equiv) and 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazole (611.91 mg, 2.124 mmol, 1.20 equiv) in dioxane (4.00 mL) and water (1.00 mL) was added K_3PO_4 (1126.91 mg, 5.309 mmol, 3.00 equiv) and $Pd(dppf)Cl_2$ CH_2Cl_2(72.08 mg, 0.088 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h at 80 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(6-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-ol (300mg, 55.16%) as a solid. **LCMS** (ES, *m/z*): 308[M+H]$^+$.

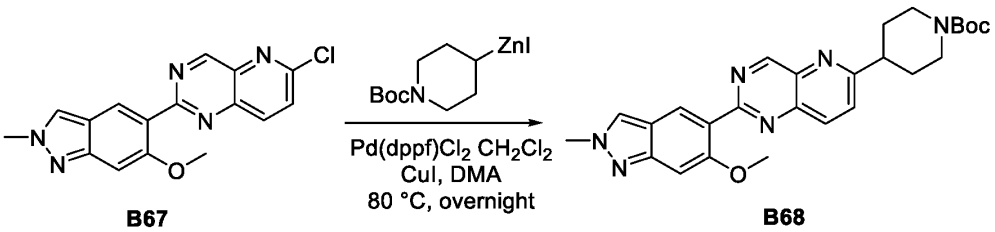
Synthesis of Intermediate B67



B66 **B67**

A solution of 2-(6-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-ol (130.00 mg, 0.423 mmol, 1.00 equiv) in $POCl_3$(3.00 mL) was stirred for 1 h at 100 °C under nitrogen atmosphere. The reaction mixture was quenched with water/ice (20mL) at room temperature, then basified to pH 8 with saturated Na_2CO_3 (aq.). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (1x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 5-[6-chloropyrido[3,2-d] pyrimidin-2-yl]-6-methoxy-2-methylindazole (100mg, 72.57%) as a solid. **LCMS** (ES, *m/z*): 326 [M+H]$^+$.

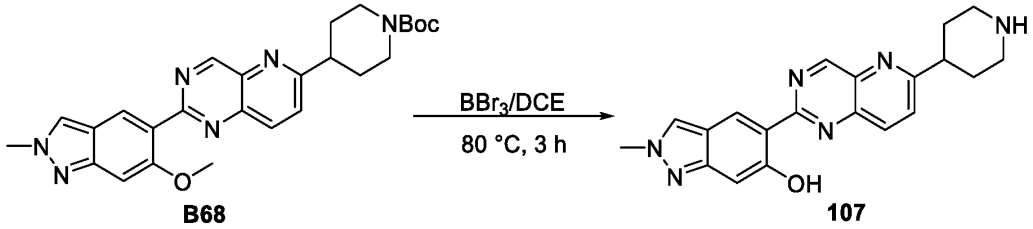
Synthesis of Intermediate B68



B67 B68

A mixture of 5-[6-chloropyrido[3,2-d] pyrimidin-2-yl]-6-methoxy-2-methylindazole (100 mg, 0.307 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ CH_2Cl_2(25.01 mg, 0.031 mmol, 0.10 equiv), CuI (11.69 mg, 0.061 mmol, 0.20 equiv), and [1-(tert-butoxycarbonyl) piperidin-4-yl] (iodo)zinc (0.77 mL, 0.614 mmol, 2.00 equiv) in DMA (5.00 mL) was stirred for 1 h at 80 °C under nitrogen atmosphere. The reaction mixture was quenched with water at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (1x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-yl] piperidine-1-carboxylate (60 mg, 41.19%) as a solid. **LCMS** (ES, *m/z*): 475 $[M+H]^+$.

Synthesis of Compound 107



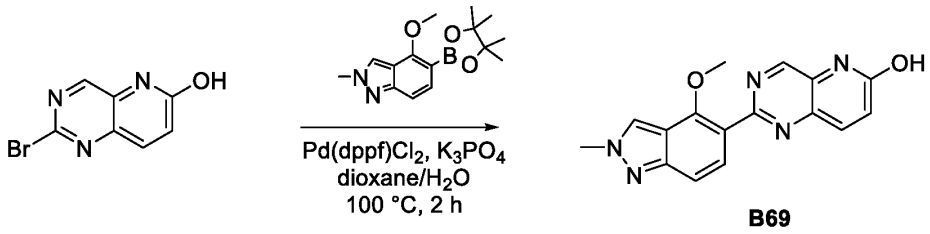
B68 107

A mixture of tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-yl] piperidine-1-carboxylate (60.00 mg, 0.126 mmol, 1.00 equiv) and BBr_3 (316.74 mg, 1.264 mmol, 10.00 equiv) in DCE (2.00 mL) was stirred for 3 h at 80 °C under nitrogen atmosphere. The reaction mixture was quenched with methanol (1mL) at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column, YMC-Actus Triart C18, 30 mm x 150 mm, 5um; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% PhaseB up to 37% in 8 min); Detector, uv220nm) to afford 2-methyl-5-[6-(piperidin-4-yl) pyrido[3,2-d] pyrimidin-2-yl] indazol-6-ol (14.8 mg, 32.48%) as a solid.

LCMS (ES, *m/z*): 361 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.73 (d, *J* = 0.8 Hz, 1H), 9.15 (s, 1H), 8.52 – 8.46 (m, 2H), 8.03 (d, *J* = 8.8 Hz, 1H), 6.94 (s, 1H), 4.14 (s, 3H), 3.14 – 3.03 (m, 3H), 2.71 – 2.60 (m, 2H), 1.89 (d, *J* = 13.0 Hz, 2H), 1.75 (qd, *J* = 12.2, 3.9 Hz, 2H).

Example 27: Synthesis of Compound 108

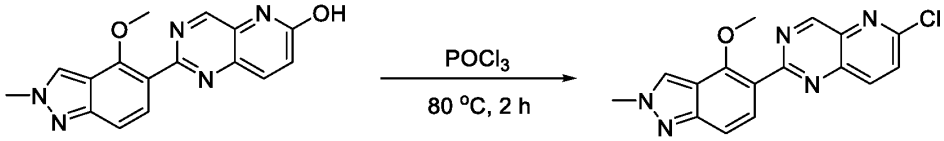
Synthesis of Intermediate B69



B69

To a mixture of 2-bromopyrido[3,2-d] pyrimidin-6-ol (500.00 mg, 2.212 mmol, 1.00 equiv) and 4-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazole (764.89 mg, 2.654 mmol, 1.20 equiv) in dioxane (8.00 mL) and water (2.00 mL) was added K_3PO_4(1408.64 mg, 6.636 mmol, 3.00 equiv) and Pd(dppf)Cl_2 CH_2Cl_2(90.10 mg, 0.111 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h at 100 °C under a nitrogen atmosphere, then concentrated *in vacuo* to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford 2-(4-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-ol (300 mg, 44.13%) as a solid. **LCMS** (ES, *m/z*): 308 $[M+H]^+$.

Synthesis of Intermediate B70

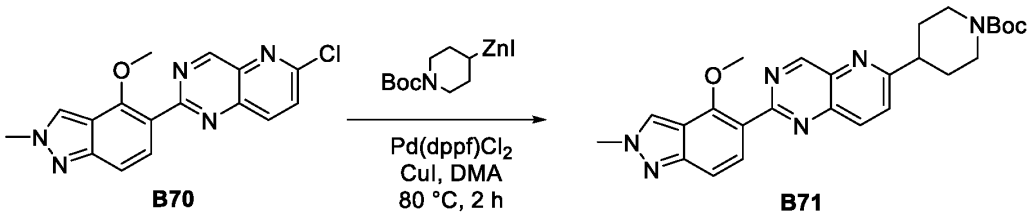


B69 B70

A solution of 2-(4-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-ol (150.00 mg, 0.488 mmol, 1.00 equiv) in $POCl_3$ (7.50 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The reaction mixture was quenched with water/ice (20 mL) at room temperature, then basified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (1x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under

reduced pressure to afford 5-[6-chloropyrido[3,2-d] pyrimidin-2-yl]-4-methoxy-2-methylindazole (90 mg, 56.60%) as a solid. **LCMS** (ES, *m/z*): 326 [M+H] $^{+}$.

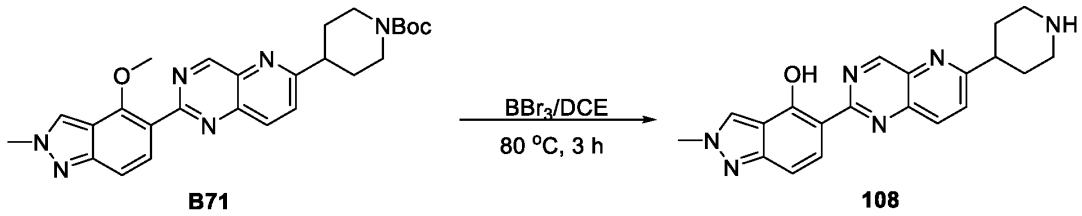
Synthesis of Intermediate B71



B70 B71

To a solution of 5-[6-chloropyrido[3,2-d] pyrimidin-2-yl]-4-methoxy-2-methylindazole (15.00 mg, 0.046 mmol, 1.00 equiv) and [1-(tert-butoxycarbonyl) piperidin-4-yl] (iodo)zinc (0.12 mL, 0.096 mmol, 2.08 equiv) in DMA (9.00 mL) was added CuI (1.75 mg, 0.009 mmol, 0.20 equiv) and Pd(dppf)Cl_2 CH_2Cl_2 (3.75 mg, 0.005 mmol, 0.10 equiv). The reaction mixture was stirred for 2 h at 80 °C under a nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) at room temperature, then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[2-(4-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-yl] piperidine-1-carboxylate (50 mg, 38.14%) as a solid. **LCMS** (ES, *m/z*): 493 [M+H]$^{+}$.

Synthesis of Compound 108



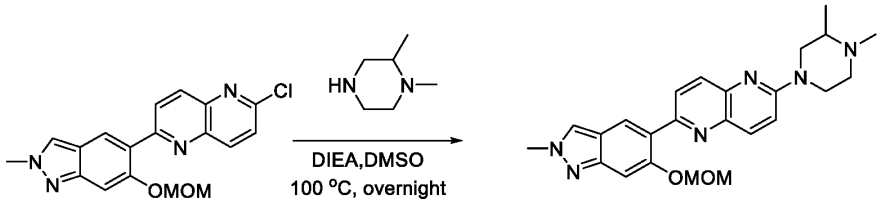
B71 108

A mixture of tert-butyl 4-[2-(4-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-yl] piperidine-1-carboxylate (50.00 mg, 0.105 mmol, 1.00 equiv) and BBr_3 (263.95 mg, 1.054 mmol, 10 equiv) in DCE (2.00 mL) was stirred for 3 h at 80 °C under nitrogen atmosphere. The reaction mixture was quenched with methanol (2 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC

(Column, YMC-Actus Triart C18, 30 x 150 mm, 5um; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% PhaseB up to 50% in 8 min); Detector, uv220nm) to afford 2-methyl-5-[6-(piperidin-4-yl) pyrido[3,2-d] pyrimidin-2-yl] indazol-4-ol (2.8 mg, 7.37%) as a solid. **LCMS** (ES, *m/z*): 361 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 14.62 (s, 1H), 9.68 (d, *J* = 0.7 Hz, 1H), 8.61 (s, 1H), 8.48 – 8.41 (m, 1H), 8.35 (d, *J* = 9.2 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.17 (dd, *J* = 9.2, 0.9 Hz, 1H), 4.17 (s, 3H), 3.15 – 2.99 (m, 3H), 2.66 (t, *J* = 11.4 Hz, 2H), 1.89 (d, *J* = 12.6 Hz, 2H), 1.75 (qd, *J* = 11.9, 3.6 Hz, 2H).

Example 28: Synthesis of Compound 118

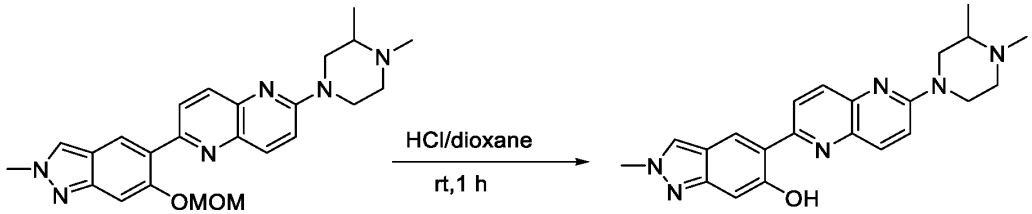
Synthesis of Intermediate B72



B72

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (60.00 mg, 0.169 mmol, 1.00 equiv), 1,2-dimethylpiperazine (23.17 mg, 0.203 mmol, 1.20 equiv), and DIEA (65.57 mg, 0.507 mmol, 3.00 equiv) in DMSO (4 mL). The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (DCM/MeOH=5:1) to afford 2-(3,4-dimethylpiperazin-1-yl)-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (65 mg, 88.86%) as a solid. **LCMS** (ES, *m/z*): 433 $[M+H]^+$.

Synthesis of Compound 118

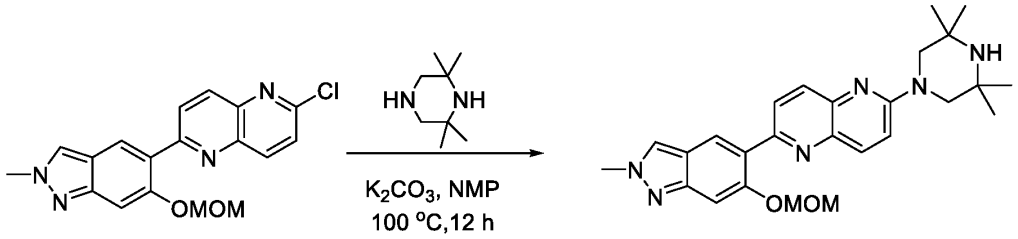


B72 **118**

To a stirred mixture of 2-(3,4-dimethylpiperazin-1-yl)-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (100.0 mg) in 1,4-dioxane (4 mL) was added HCl (gas) in 1,4-dioxane (4M, 4.00 mL) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was adjusted to pH 8 with NH_3/MeOH, and recrystallized with MeOH to afford 5-[6-(3,4-dimethylpiperazin-1-yl)-1,5-naphthyridin-2-yl] -2-methylindazol-6-ol (14.6 mg, 16.26%) as a solid. **LCMS** (ES, *m/z*): 389 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.86 (s, 1H), 8.56 (s, 1H), 8.42 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H),8.21(s,1H), 8.12 (dd, *J* = 22.6, 9.3 Hz, 1H), 7.56 (d, *J* = 9.5 Hz, 1H), 6.88 (s, 1H), 4.35 (m,2H), 4.12 (s, 3H), 3.21 – 3.08 (m, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.76 (dd, *J* = 12.8, 10.1 Hz, 1H), 2.24 (s, 3H), 2.22 – 2.05 (m, 1H), 2.10 (s, 1H), 1.10 (d, *J* = 6.2 Hz, 3H).

Example 29: Synthesis of Compound 122

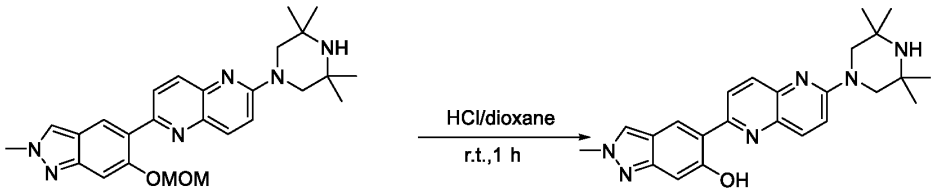
Synthesis of Intermediate B73



B73

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (80.0 mg, 0.22 mmol, 1.00 equiv), 2,2,6,6-tetramethylpiperazine (57.7 mg, 0.40 mmol, 1.80 equiv), and K_2CO_3 (93.4 mg, 0.67 mmol, 3.00 equiv) in NMP (1.50 mL) was stirred for 12 at 100 °C. The resulting mixture was diluted with water (20.0 mL), and extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were washed with 50% of NaCl (3 x 30.0 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography with DCM/MeOH=10:1 to afford 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-(3,3,5,5-tetramethylpiperazin-1-yl)-1,5-naphthy- ridine (18.0 mg, 11.0%) as a solid. **LCMS** (ES, *m/z*): 461 $[M+H]^+$.

Synthesis of Compound 122

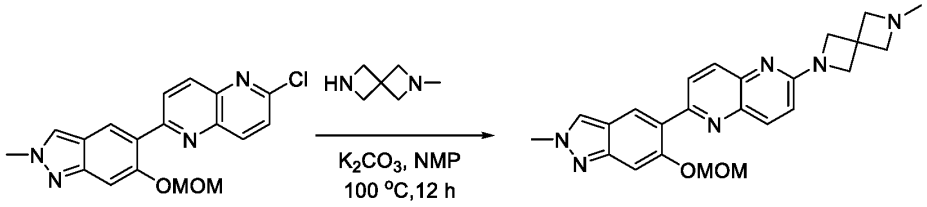


B73 122

A solution of 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-(3,3,5,5-tetramethylpiperazin-1-yl)-1,5-naphthyridine (14.0 mg, 0.03 mmol, 1.00 equiv) in DCM (1.00 mL) and TFA (0.10 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:10% B to 55% B in 8 min; 220 nm; RT1:7.37;) to afford 2-methyl-5-[6-(3,3,5,5-tetramethylpiperazin-1-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (1.6 mg, 12.5%) as a solid. **LCMS** (ES, *m/z*): 417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.89 (s, 1H), 8.54 (s, 1H), 8.42 – 8.33 (m, 2H), 8.10 (dd, *J* = 9.4, 0.8 Hz, 1H), 8.03 (dd, *J* = 9.1, 0.8 Hz, 1H), 7.54 (d, *J* = 9.5 Hz, 1H), 6.89 – 6.84 (m, 1H), 4.12 (s, 3H), 3.59 (s, 4H), 1.12 (s, 12H).

Example 30: Synthesis of Compound 123

Synthesis of Intermediate B74

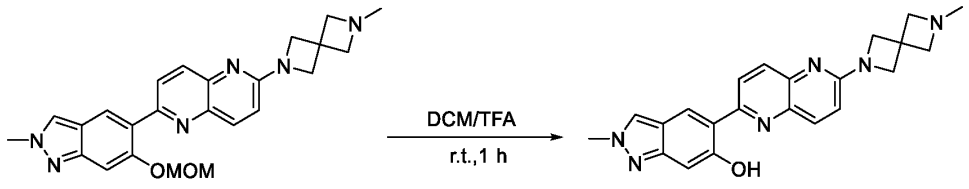


B74

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (60.0 mg, 0.16 mmol, 1.00 equiv), 2-methyl-2,6-diazaspiro[3.3]heptane (34.1 mg, 0.30 mmol, 1.80 equiv), and K_2CO_3 (70.1 mg, 0.50 mmol, 3.00 equiv) in NMP (1.50 mL) was stirred for 12 h at 100 °C. The resulting mixture was diluted with water (20.0 mL), then extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were washed with NaCl (3 x 30.0 mL, 50%), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography with

9% MeOH in DCM to afford 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]-1,5-naphthyridine (27.0 mg, 29.6%) as a solid. **LCMS** (ES, *m/z*): 431 $[M+H]^+$.

Synthesis of Compound 123

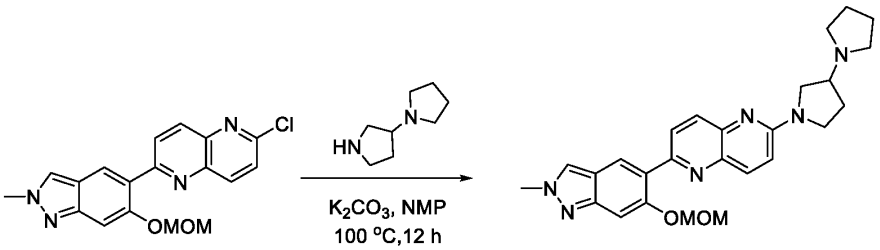


B74 **123**

A solution of 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]-1,5-naphthyridine (24.0 mg, 0.05 mmol, 1.00 equiv) in DCM (1.00 mL) and TFA (0.10 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:5% B to 40% B in 8 min; 220 nm; RT1:7.17;) to afford 2-methyl-5-(6-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]-1,5-naphthyridin-2-yl)indazol-6-ol (1.8 mg, 7.8%) as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.83 (s, 1H), 8.55 (s, 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.36 (s, 1H), 8.12 (dd, J = 13.3, 9.1 Hz, 2H), 7.00 (d, J = 9.1 Hz, 1H), 6.88 (s, 1H), 4.22 (s, 4H), 4.12 (s, 3H), 3.33 (s, 4H), 2.25 (s, 3H).

Example 31: Synthesis of Compound 125

Synthesis of Intermediate B75

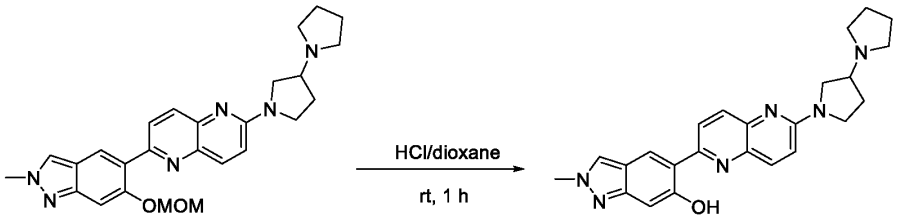


B75

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (60.0 mg, 0.16 mmol, 1.00 equiv), 1,3'-bipyrrolidine (42.6 mg, 0.30 mmol, 1.80 equiv), and K_2CO_3

(93.4 mg, 0.67 mmol, 4.00 equiv) in NMP (1.50 mL) was stirred for 12 h at 120 °C. The resulting mixture was diluted with water (20.0 mL), and extracted with ethyl acetate (3 x 20.0 mL). The combined organic layers were washed with NaCl (3 x 30.0 mL, 50%), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography with 6.8% MeOH in DCM to afford 2-[[1,3□bipyrrolidin]-1□yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (24.0 mg, 24.7%) as a solid. **LCMS** (ES, *m/z*): 459 $[M+H]^+$.

Synthesis of Compound 125

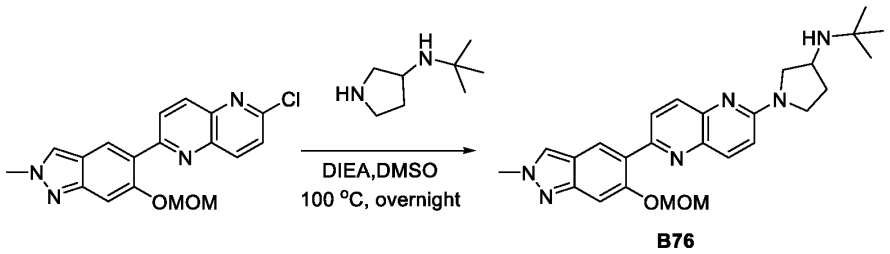


B75 **125**

A solution of 2-[[1,3□bipyrrolidin]-1□yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (20.0 mg, 0.04 mmol, 1.00 equiv) in DCM (1.00 mL) and TFA (0.10 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:10% B to 50% B in 8 min; 220 nm; RT1:7.62) to afford 5-(6-[[1,3□bipyrrolidin]-1□yl]-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (5.8 mg, 32.0%) as a solid. **LCMS** (ES, *m/z*): 415 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.55 (s, 1H), 8.40 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.16 – 8.04 (m, 2H), 7.18 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 0.8 Hz, 1H), 4.12 (s, 4H), 3.85 (s, 1H), 3.76 (s, 1H), 3.60 – 3.38 (m, 2H), 3.17 (d, *J* = 5.2 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.62 – 2.53 (m, 2H), 2.20 (s, 1H), 1.95 (dd, *J* = 19.5, 9.3 Hz, 1H), 1.73 (s, 4H).

Example 32: Synthesis of Compound 127

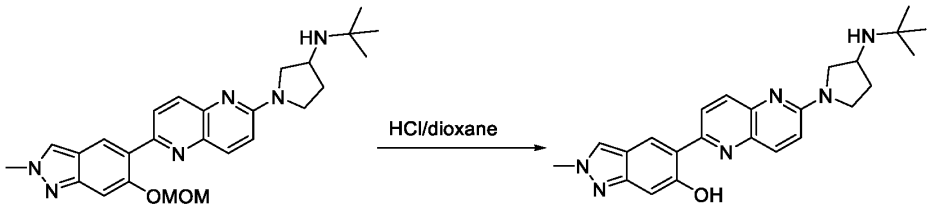
Synthesis of Intermediate B76



B76

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (100.00 mg, 0.282 mmol, 1.00 equiv) and DIEA (109.28 mg, 0.846 mmol, 3 equiv) in DMSO (4 mL) was stirred at 100 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford N-tert-butyl-1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl] -1,5-naphthyridin-2-yl] pyrrolidin-3-amine (55 mg, 42.37%) as a solid. **LCMS** (ES, *m/z*): 461 $[M+H]^+$.

Synthesis of Compound 127



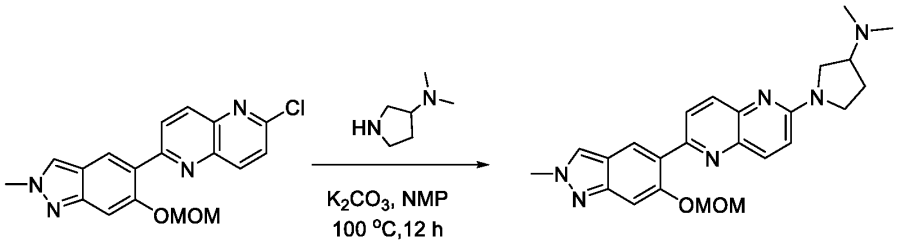
B76 127

To a stirred mixture of N-tert-butyl-1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] pyrrolidin-3-amine (55.00 mg, 0.119 mmol, 1.00 equiv) in 1,4-dioxane (4M, 4 mL) was added HCl (gas) in 1,4-dioxane (4 mL) at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:5% B to 55% B in 8 min; 220 nm; RT1:5.07) to afford 5-[6-[3-(tert-butylamino) pyrrolidin-1-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (25.3 mg, 50.87%) as a solid. **LCMS** (ES, *m/z*): 417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.97 (s, 1H), 8.54 (s, 1H), 8.43 – 8.33 (m, 2H), 8.09 (dd, *J* = 13.0, 9.2 Hz, 2H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.88 (s, 1H), 4.12

(s, 3H), 3.87 (s, 1H), 3.72 (s, 1H), 3.56 (s, 1H), 3.54 – 3.46 (m, 1H), 3.15 (s, 1H), 2.20 (s, 1H), 1.83 – 1.74 (m, 1H), 1.11 (s, 9H).

Example 33: Synthesis of Compound 129

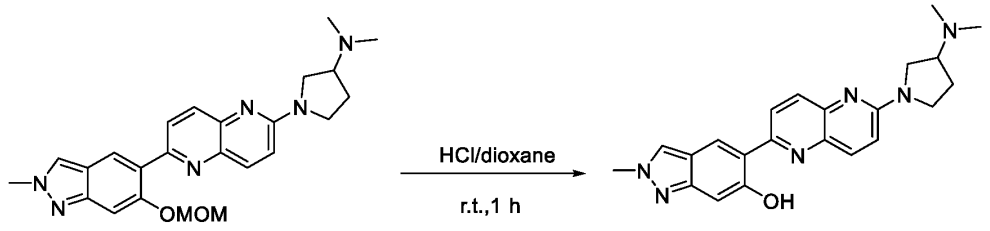
Synthesis of Intermediate B77



B77

A solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (60.0 mg, 0.16 mmol, 1.00 equiv), N,N-dimethylpyrrolidin-3-amine (34.7 mg, 0.30 mmol, 1.80 equiv), and K_2CO_3 (70.1 mg, 0.50 mmol, 3.00 equiv) in NMP (1.50 mL) was stirred for 12 h at 100 °C.The resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with NaCl (3 x 30 mL, 50%), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography with 6.2% MeOH in DCM to afford 1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-N,N-dimethylpyrrolidin-3-amine (38.0 mg, 49.3%) as a solid. **LCMS** (ES, *m/z*): 433 $[M+H]^+$.

Synthesis of Compound 129



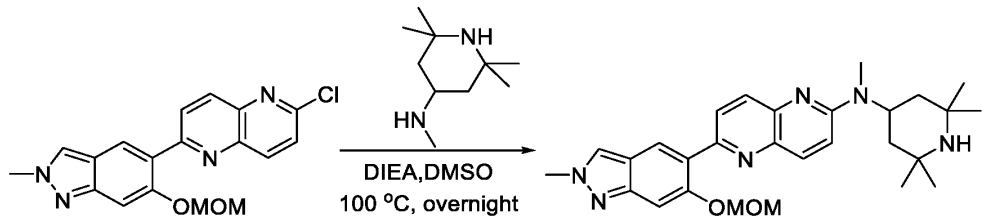
B77 129

A solution of 1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-N,N-dimethylpyrrolidin-3-amine (34.0 mg, 0.07 mmol, 1.00 equiv) in HCl (gas) in 1,4-dioxane (1.00 mL, 4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3),

Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:10 B to 50 B in 8 min; 220 nm; RT1:7.62;) to afford 5-[6-[3-(dimethylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (13.3 mg, 43.29%) as a solid. **LCMS** (ES, *m/z*): 389 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.95 (s, 1H), 8.55 (s, 1H), 8.40 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.11 (dd, J = 14.0, 9.2 Hz, 2H), 7.19 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.89 (s, 1H), 3.80 (s, 1H), 3.70 – 3.36 (m, 2H), 2.83 (p, J = 7.6 Hz, 1H), 2.24 (s, 7H), 1.85 (q, J = 10.1 Hz, 1H).

Example 34: Synthesis of Compound 130

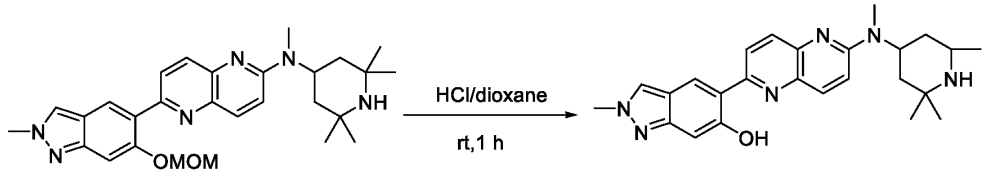
Synthesis of Intermediate B78



B78

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (90.00 mg, 0.254 mmol, 1.00 equiv), N,2,2,6,6-pentamethylpiperidin-4-amine (51.84 mg, 0.305 mmol, 1.20 equiv), and DIEA (98.36 mg, 0.762 mmol, 3.00 equiv) in DMSO (4 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) at room temperature and extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (DCM/MeOH=5:1) to afford 6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-N-Methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-1,5-naphthyridin-2-amine (30 mg, 24.20%) as a solid. **LCMS** (ES, *m/z*): 489 $[M+H]^+$.

Synthesis of Compound 130



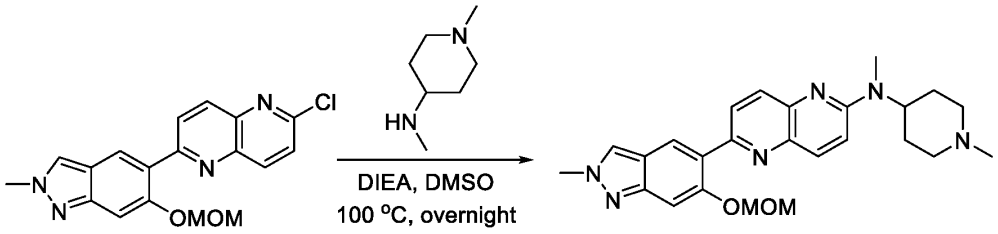
B78 **130**

To a stirred solution of 6-[6-(methoxymethoxy)-2-methyl-octahydroindazol-5-yl]-N-methyl-N-(2,2,6,6-tetramethylpiperidin-4-yl)-decahydro-1,5-naphthyridin-2-amine (30.00 mg, 0.059 mmol,

1.00 equiv) in 1,4-dioxane (3 mL) was added HCl (gas) in 1,4-dioxane (3.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere, then quenched with water (10 mL) at room temperature and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered.. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water(10MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:20% B to 50% B in 8 min) to afford 2-methyl-5-[6-[methyl(2,2,6,6-tetramethylpiperidin-4-yl)amino]-decahydro-1,5-naphthyridin-2-yl]-octahydroindazol-6-ol (3.2 mg, 11.68%) as a solid. **LCMS** (ES, *m/z*): 431[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.55 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 1H),8.38(s,1H), 8.36 (s, 1H), 8.14 (d, *J* = 9.4 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.38 (d, *J* = 9.4 Hz, 1H), 6.88 (s, 1H), 4.12 (s, 3H), 3.03 (s, 3H),2.96(s,1H), 1.59 (s, 2H), 1.51 (s, 2H), 1.36 (s, 6H), 1.16 (s, 6H).

Example 35: Synthesis of Compound 126

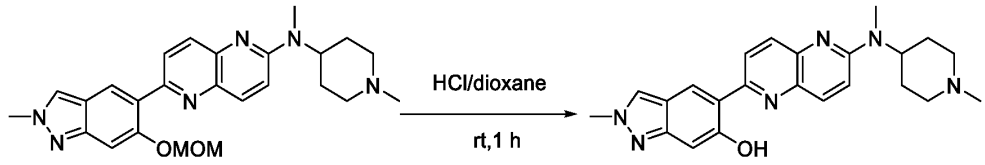
Synthesis of Intermediate B79



B79

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (90.00 mg, 0.254 mmol, 1.00 equiv), N,1-dimethylpiperidin-4-amine (48.79 mg, 0.381 mmol, 1.50 equiv), and DIEA (98.36 mg, 0.762 mmol, 3.00 equiv) in DMSO (4 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC(DCM/MeOH=5:1) to afford 6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-N-Methyl-N-(1-methylpiperidin-4-yl)-1,5-naphthyridin-2-amine (40 mg, 35.31%) as a solid. **LCMS** (ES, *m/z*): 447 [M+H]$^+$.

Synthesis of Compound 126

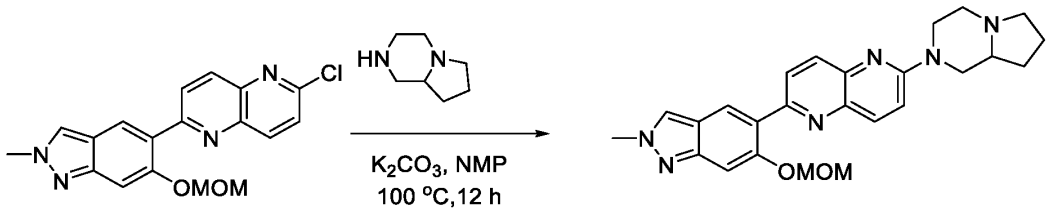


B79 **126**

A mixture of 6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-N-Methyl-N-(1-methylpiperidin-4-yl)-1,5-naphthyridin-2-amine (40.00 mg, 0.090 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (4.00 mL) in 1,4-dioxane (4 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) at room temperature and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water(10MMOL/L NH4HCO3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:5% B to 45% B in 8 min; 220 nm; RT1:5.33) to afford 2-methyl-5-[6-[methyl(1-methylpiperidin-4-yl)amino]-1,5-naphthyridin-2-yl]indazol-6-ol (0.6 mg, 1.66%) as a solid. **LCMS** (ES, *m/z*): 402 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.96 (s, 1H), 8.56 (s, 1H), 8.40 (d, J = 9.3 Hz, 1H), 8.35 (s, 1H), 8.10 (dd, J = 20.9, 9.3 Hz, 2H), 7.40 (d, J = 9.4 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.05 (s, 3H), 2.97 (s, 1H), 2.89 (d, J = 11.3 Hz, 2H), 2.22 (s, 3H), 2.09 (t, J = 11.6 Hz, 2H), 1.94 – 1.80 (m, 2H), 1.63 (d, J = 12.2 Hz, 2H).

Example 36: Synthesis of Compound 134

Synthesis of Intermediate B80

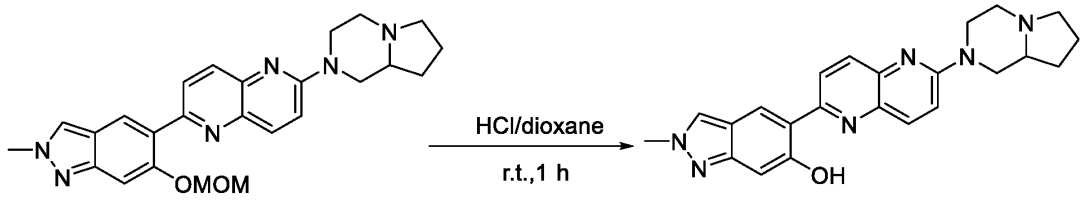


B80

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (60.0 mg, 0.16 mmol, 1.00 equiv), octahydropyrrolo[1,2-a]pyrazine (38.4 mg, 0.30 mmol, 1.80 equiv),

and K_2CO_3 (70.1 mg, 0.50 mmol, 3.00 equiv) in NMP (1.50 mL) was stirred for 12 h at 100 °C. The resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with NaCl (3 x 30 mL, 50%), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography with 5% MeOH in DCM to afford 2-[hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (40.0 mg, 52.1%) as a solid. **LCMS** (ES, *m/z*): 445 $[M+H]^+$.

Synthesis of Compound 134

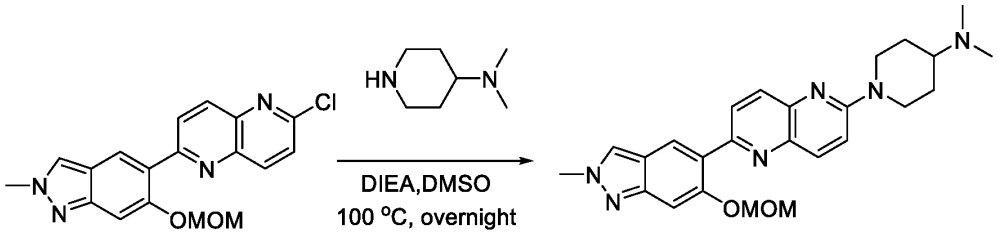


B80 **134**

A solution of 2-[hexahydro-1H-pyrrolo[1,2-a] pyrazin-2-yl]-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (36.0 mg, 0.08 mmol, 1.00 equiv) in HCl (gas) in 1,4-dioxane (1.00 mL, 4M) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:25% B to 65% B in 8 min; 220 nm; RT1:6.12) to afford 5-(6-[hexahydro-1H-pyrrolo[1,2-a]pyrazin-2-yl]-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (12.5 mg, 38.08%) as a solid. **LCMS** (ES, *m/z*): 401 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.87 (s, 1H), 8.56 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 8.36 (s, 1H), 8.11 (dd, J = 22.0, 9.2 Hz, 2H), 7.57 (d, J = 9.5 Hz, 1H), 6.88 (s, 1H), 4.72 (d, J = 12.3 Hz, 1H), 4.55 (d, J = 12.7 Hz, 1H), 4.12 (s, 3H), 3.16 – 2.99 (m, 3H), 2.75 – 2.68 (m, 1H), 2.19 (dd, J = 11.1, 3.3 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.09 – 1.98 (m, 1H), 1.98 – 1.83 (m, 1H), 1.73 (dddd, J = 15.7, 11.9, 8.8, 3.2 Hz, 2H), 1.41 (tt, J = 11.1, 5.7 Hz, 1H).

Example 37: Synthesis of Compound 133

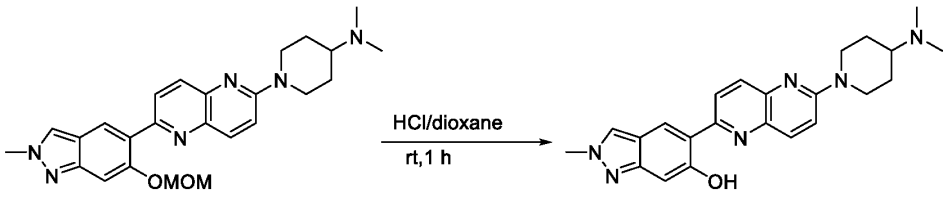
Synthesis of Intermediate B81



B81

To a mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (100.00 mg, 0.282 mmol, 1.00 equiv) and N,N-dimethylpiperidin-4-amine (54.21 mg, 0.423 mmol, 1.50 equiv) in DMSO (4 mL) was added DIEA (109.28 mg, 0.846 mmol, 3.00 equiv) at room temperature. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-N,N-dimethylpiperidin-4-amine (70 mg, 55.62%) as a solid. **LCMS** (ES, *m/z*): 447 $[M+H]^+$.

Synthesis of Compound 133



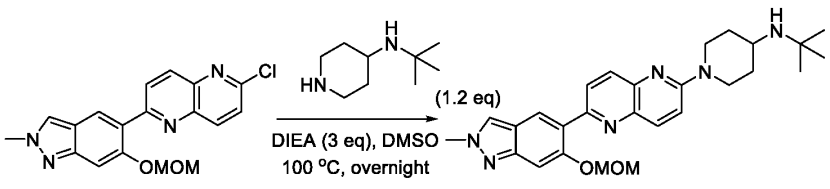
B81 **133**

To a stirred mixture of 1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-N, N-dimethylpiperidin-4-amine (70.00 mg, 0.157 mmol, 1.00 equiv) in 1,4-dioxane (4 mL) was added HCl (gas) in 1,4-dioxane (4M, 4.00 mL) dropwise under nitrogen atmosphere. The resulting mixture was stirred for 30 min at room temperature, then concentrated under reduced pressure to give a residue. The residue was adjusted to pH 8 with NH_3/MeOH, and recrystallized with methanol to afford 5-[6-[4-(dimethylamino) piperidin-1-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (10.1 mg, 16.01%) as a solid. **LCMS** (ES, *m/z*): 403$[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.82 (s, 1H), 8.57 (s, 1H), 8.43 (d, J = 9.2 Hz, 1H), 8.37 (s, 1H), 8.18 (d, J =

9.3 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 9.5 Hz, 1H), 6.89 (s, 1H), 4.74 (d, *J* = 13.6 Hz, 2H), 4.12 (s, 3H), 3.3 (m, 6H), 3.02 (t, *J* = 12.9 Hz, 2H), 2.6 (m, 1H), 2.08 (s, 2H), 1.58 (s, 2H).

Example 38: Synthesis of Compound 132

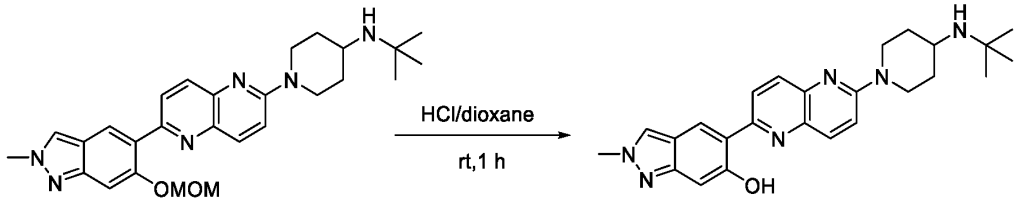
Synthesis of Intermediate B82



B82

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (80.00 mg, 0.225 mmol, 1.00 equiv), N-tert-butylpiperidin-4-amine (42.28 mg, 0.271 mmol, 1.2 equiv), and DIEA (87.43 mg, 0.675 mmol, 3.00 equiv) in DMSO (4 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The reaction was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC(DCM/MeOH=5:1) to afford N-tert-butyl-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl] cyclohexan-1-amine (40 mg, 37.46%) as a solid. **LCMS** (ES, *m/z*): 475 $[M+H]^+$.

Synthesis of Compound 132



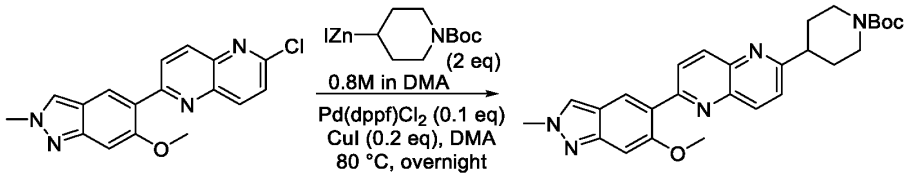
B82 **132**

To a stirred solution of N-tert-butyl-1-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]piperidin-4-amine (40.00 mg, 0.084 mmol, 1.00 equiv) in 1,4-dioxane (4 mL) was added HCl (gas) in 1,4-dioxane (4 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water

(10MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:5% B to 85% B in 8 min; 220 nm; RT1:5.83) to afford 5-[6-[4-(tert-butylamino)piperidin-1-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (3.3 mg, 9.09%) as a solid. **LCMS** (ES, *m/z*):431 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.88 (s, 1H), 8.56 (s, 1H), 8.41 (d, *J* = 9.1 Hz, 1H), 8.36 (s, 1H), 8.07 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 9.5 Hz, 1H), 6.88 (s, 1H),4.51(m,2H), 4.12 (s, 3H), 3.15(m,3H),1.92(m,2H), 1.36 (s, 2H), 1.14 (s, 9H).

Example 39: Synthesis of Compound 142

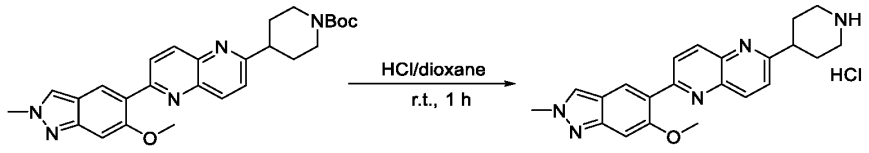
Synthesis of Intermediate B83



B83

To a stirred mixture of 2-chloro-6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridine (200 mg, 0.62 mmol, 1.00 equiv), Pd(dppf)Cl_2 CH_2Cl_2 (50.17 mg, 0.06 mmol, 0.10 equiv), and CuI (23.46 mg, 0.12 mmol, 0.20 equiv) in DMA (10 mL) was added [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (463.76 mg, 1.23 mmol, 2.00 equiv) in portions. The reaction mixture was stirred overnight at 80 °C under N_2 atmosphere, then cooled to room temperature. The reaction was quenched with water at 0 °C and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with NaCl (3x30, semi-saturated), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a resiude. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1/10) to afford tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (260 mg, 89.15%) as a solid. **LCMS** (ES, *m/z*): 474 $[M+H]^+$.

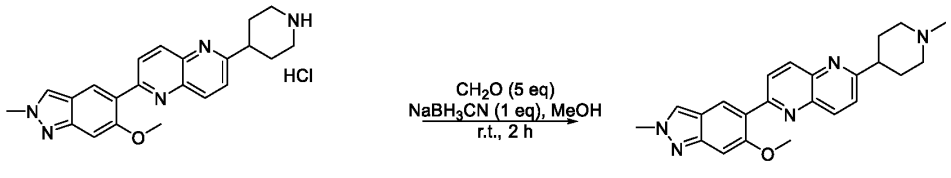
Synthesis of Intermediate B84



B83 **B84**

A solution of tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (260 mg, 0.55 mmol, 1.00 equiv) in HCl (gas) in 1,4-dioxane (2 mL, 35.04 mmol, 63.81 equiv) was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to afford 2-(6-methoxy-2-methylindazol-5-yl) -6-(piperidin-4-yl)-1,5-naphthyridine hydrochloride (290 mg, 128.86%) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$.

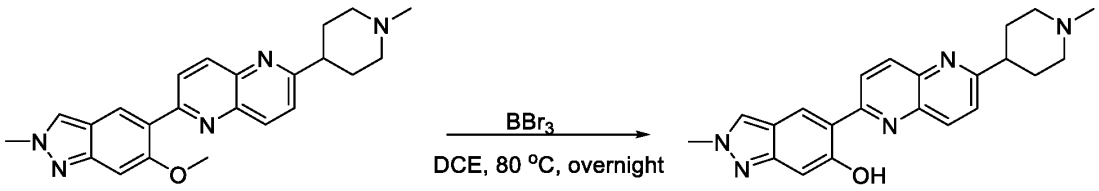
Synthesis of Intermediate B85



B84 **B85**

To a stirred mixture of 2-(6-methoxy-2-methylindazol-5-yl)-6-(piperidin-4-yl)-1,5-naphthyridine hydrochloride (290 mg, 0.71 mmol, 1.00 equiv) and TEA (214.76 mg, 2.12 mmol, 3.00 equiv) in methanol (3 mL, 74.10 mmol, 104.74 equiv) was added formaldehyde (106.21 mg, 3.54 mmol, 5.00 equiv) and $NaBH_3CN$ (44.46 mg, 0.71 mmol, 1.00 equiv) in portions. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, washed with saturated NaCl (10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(6-methoxy-2-methylindazol-5-yl)-6-(1-methylpiperidin-4-yl)-1,5-naphthyridine (250 mg) as a solid. **LCMS** (ES, *m/z*): 388 $[M+H]^+$.

Synthesis of Compound 142



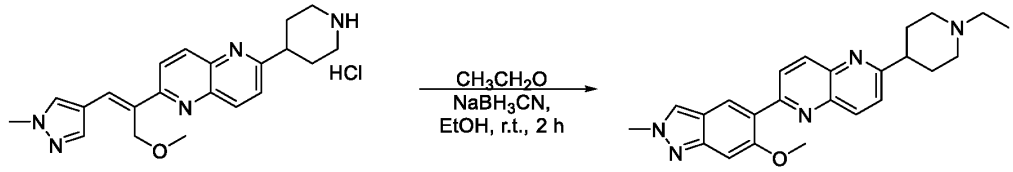
B85 **142**

A mxiture of 2-(6-methoxy-2-methylindazol-5-yl)-6-(1-methylpiperidin-4-yl)-1,5-naphthyridine (210 mg, 0.54 mmol, 1.00 equiv) and BBr_3 (0.5 mL, 5.29 mmol, 9.76 equiv) in DCE (3 mL, 37.90 mmol, 69.92 equiv) was stirred for overnight at 80 °C, then cooled to room temperature. The reaction mixture was quenched with methanol at 0 °C, then concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18

Column, 30 x 150mm 5um; Mobile Phase A:Water(10MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:10% B to 40% B in 8 min, 220 nm; RT1:6.7;) to afford 2-methyl-5-[6-(1-methylpiperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (37.7 mg, 18.63%) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.62 (s, 1H), 8.70 (s, 1H), 8.61 (d, *J* = 9.3 Hz, 1H), 8.48 (d, *J* = 9.1 Hz, 1H), 8.45 – 8.39 (m, 2H), 7.80 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 4.14 (s, 3H), 2.99 – 2.85 (m, 3H), 2.25 (s, 3H), 2.08 (td, *J* = 11.2, 3.3 Hz, 2H), 1.92 (tdd, *J* = 11.7, 6.9, 3.1 Hz, 4H).

Example 40: Synthesis of Compound 138

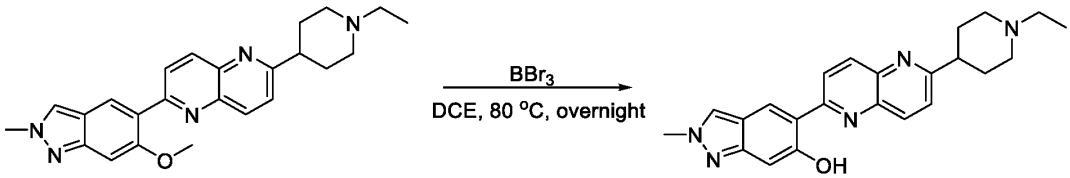
Synthesis of Intermediate B86



B86

To a stirred mixture of 2-(6-methoxy-2-methylindazol-5-yl)-6-(piperidin-4-yl)-1,5-naphthyridine hydrochloride (220 mg, 0.54 mmol, 1.00 equiv) and TEA (163 mg, 1.61 mmol, 3.00 equiv) in ethanol (2.2 mL, 47.75 mmol, 70.56 equiv) was added acetaldehyde (118.21 mg, 2.68 mmol, 5.00 equiv) and $NaBH_3CN$ (33.73 mg, 0.54 mmol, 1.00 equiv) in portions. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated NaCl (10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 2-(1-ethylpiperidin-4-yl)-6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridine (480 mg) as a solid. **LCMS** (ES, m/z): 402 $[M+H]^+$.

Synthesis of Intermediate 138



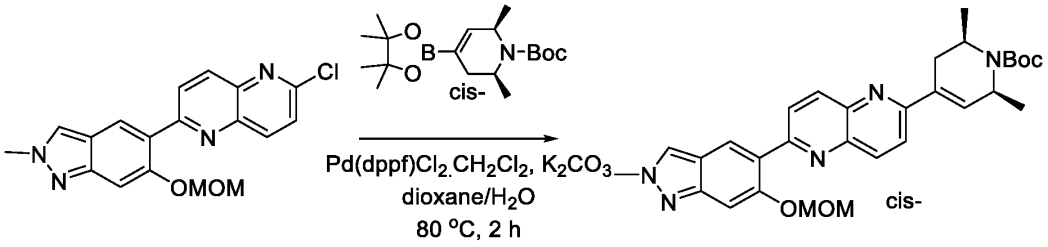
B86 **138**

A mixture of 2-(1-ethylpiperidin-4-yl)-6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridine (480 mg, 1.20 mmol, 1.00 equiv) and BBr_3 (1 mL, 10.58 mmol, 8.85 equiv) in DCE (5 mL, 63.16 mmol, 52.83 equiv) was stirred overnight at 80 °C, then cooled to room temperature. The

reaction mixture was quenched with methanol at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30 x 150mm 5um; Mobile Phase A:Water(10MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:5% B to 37% B in 8 min, 37 B to B in min, B to B in min, B to B in min, B to B in min; 220 nm; RT1:7.73; RT2:; Injection Volumn: ml; Number Of Runs:;) to afford 5-[6-(1-ethylpiperidin-4-yl)-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (8.8 mg, 1.90%) as a solid. **LCMS** (ES, m/z): 388 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.61 (s, 1H), 8.70 (s, 1H), 8.61 (d, J = 9.3 Hz, 1H), 8.47 (dd, J = 9.1, 0.8 Hz, 1H), 8.45 – 8.38 (m, 1H), 7.81 (d, J = 8.7 Hz, 1H), 6.93 (s, 1H), 4.14 (s, 3H), 3.03 (d, J = 11.2 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.39 (q, J = 7.2 Hz, 2H), 2.12 – 1.99 (m, 2H), 1.99 – 1.81 (m, 4H), 1.05 (t, J = 7.2 Hz, 3H).

Example 41: Synthesis of Compound 137

Synthesis of Intermediate B87

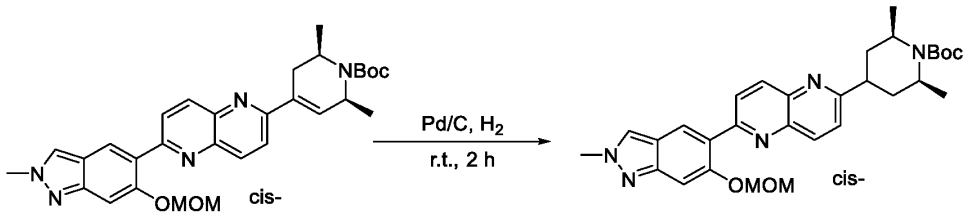


B87

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (100 mg, 0.28 mmol, 1.00 equiv), tert-butyl (cis-)-2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-2H-pyridine-1-carboxylate (114.07 mg, 0.34 mmol, 1.20 equiv), K_2CO_3 (116.86 mg, 0.85 mmol, 3.00 equiv) in water (1.5 mL, 83.26 mmol, 295.41 equiv), and $Pd(dppf)Cl_2.CH_2Cl_2$ (22.96 mg, 0.03 mmol, 0.10 equiv) in dioxane (6 mL, 68.10 mmol, 251 equiv) was stirred for 2 h at 80 °C under N_2 atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated NaCl (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with MeOH/DCM (1/10) to afford tert-butyl (2R,6S)-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-

yl]-1,5-naphthyridin-2-yl]-2,6-dimethyl-3,6-dihydro-2H-pyridine-1-carboxylate (105 mg, 70.3%) as a solid. **LCMS** (ES, m/z): 530[M+H]$^+$.

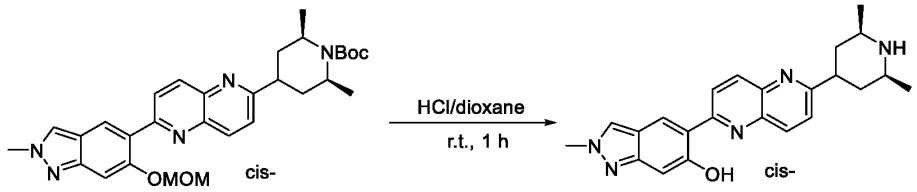
Synthesis of Intermediate B88



B87 **B88**

A mixture of tert-butyl (cis-)-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,6-dimethyl-3,6-dihydro-2H-pyridine-1-carboxylate (95.00 mg, 0.18 mmol, 1.00 equiv) and Pd/C (284.99 mg, 2.68 mmol, 14.93 equiv) in methanol (9.5 mL) was stirred for 2 h at room temperature under H_2 atmosphere. The Pd/C was collected by filtration and washed with methanol (3x20 mL). The resulting filtrate was concentrated under vacuum to afford tert-butyl (2R,6S)-4-[6-[6-(methoxymethoxy)-2-methylindazol -5-yl]-1,5-naphthyridin-2-yl] -2,6-dimethylpiperidine-1-carboxylate (90 mg, 94.4%) as a solid. **LCMS** (ES, m/z): 532 [M+H]$^+$.

Synthesis of Compound 137



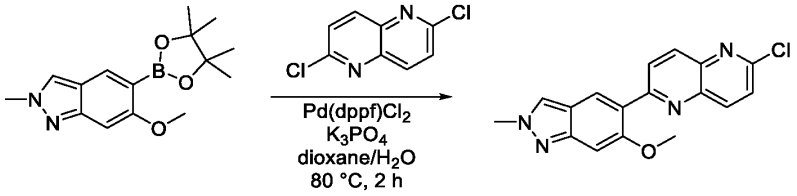
B88 **137**

A solution of tert-butyl (cis-)-4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]-2,6-dimethylpiperidine-1-carboxylate (80.00 mg, 0.15 mmol, 1.00 equiv) in HCl (gas) in 1,4-dioxane (24 mL) was stirred for 1 h at room temperature under N_2 atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Column: Xselect CSH OBD Column 30*150mm 5um, n; Mobile Phase A: Water (0.05% HCl), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:5 B to 30 B in 8 min; 220 nm; RT1:7.52) to afford 5-[6-[(2R,6S)-2,6-dimethylpiperidin-4-yl]-1,5-naphthyridin-2-yl]-2-methylindazol-6-ol (5.1 mg, 8.8%) as a solid. **LCMS** (ES, *m/z*): 388 [M+H]$^+$. **^{1}H NMR**

(400 MHz, DMSO-d_6) δ 13.58 (s, 1H), 8.70 (s, 1H), 8.61 (d, J = 9.2 Hz, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.42 (t, J = 4.4 Hz, 2H), 7.77 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 4.14 (s, 3H), 3.14-3.17 (m, 1H), 2.94 (s, 2H), 1.94 (d, J = 12.5 Hz, 2H), 1.43 (d, J = 12.6 Hz, 2H), 1.13 (d, J = 6.2 Hz, 6H).

Example 42: Synthesis of Compound 139

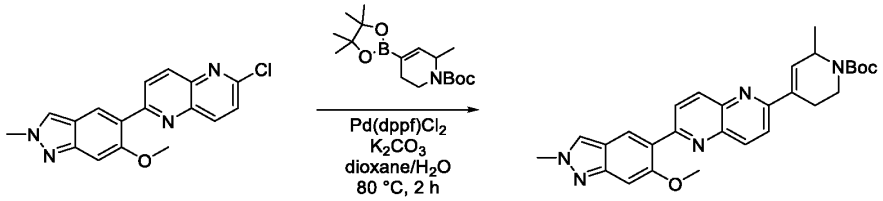
Synthesis of Intermediate B89



B89

A mixture of 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (1.35 g, 4.69 mmol, 1.00 equiv), 2,6-dichloro-1,5-naphthyridine (1.12 g, 5.62 mmol, 1.20 equiv), Pd(dppf)Cl_2 CH_2Cl_2 (0.38 g, 0.47 mmol, 0.10 equiv), and K_3PO_4 (2.98 g, 14.06 mmol, 3.00 equiv) in dioxane (24 mL) and water (6 mL) was stirred for 2 h at 80 °C under N_2 atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with saturated NaCl (50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, DCM in MeOH, 0% to 10% gradient in 10 min; detector, UV 254 nm) to afford 2-chloro-6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridine (1 g, 65.72%) as a solid.

Synthesis of Intermediate B90

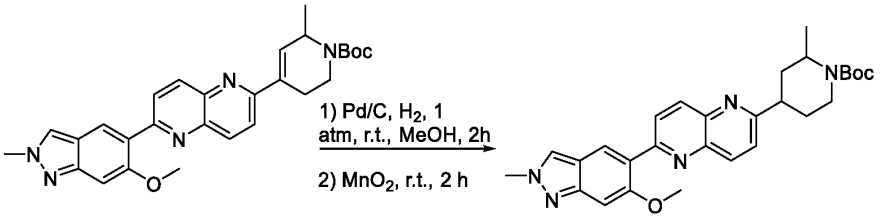


B89 **B90**

A solution of 2-chloro-6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridine (360.00 mg, 1.11 mmol, 1.00 equiv), tert-butyl 2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-

dihydro-2H-pyridine-1-carboxylate (358.30 mg, 1.11 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ CH_2Cl_2 (90.30 mg, 0.11 mmol, 0.10 equiv), and K_2CO_3 (459.59 mg, 3.33 mmol, 3.00 equiv) in dioxane (2.70 mL, 30.64 mmol, 28.75 equiv) and water (0.90 mL, 49.96 mmol, 45.07 equiv) was stirred for 2 h at 80 °C under N_2 atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with saturated NaCl (20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, DCM in MeOH, 0% to 10% gradient in 20 min; detector, UV 254 nm) to afford tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-2-methyl-5,6-dihydro-2H-pyridine-1-carboxylate (520 mg, 96.61%) as a solid. **LCMS** (ES, *m/z*): 486 $[M+H]^+$.

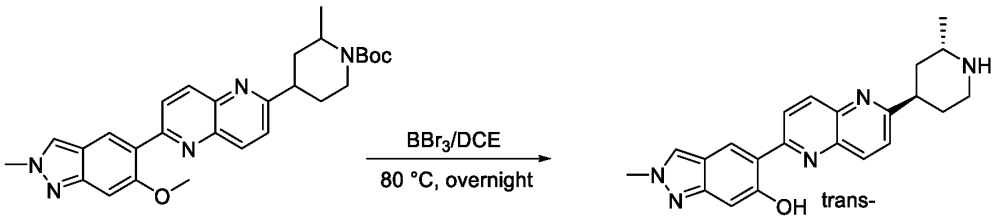
Synthesis of Intermediate B91



B90 **B91**

A mixture of tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-2-methyl-5,6-dihydro-2H-pyridine-1-carboxylate (319.00 mg, 0.66 mmol, 1.00 equiv) and Pd/C (797.69 mg, 7.5 mmol, 11.41 equiv) in methanol (16 mL) was stirred for 2 h at room temperature under H_2 atmosphere. The resulting mixture was filtered, the filter cake was washed with methanol (3x50 mL), and the filtrate was concentrated under reduced pressure to give a residue. To the residue was added MnO_2 (571.12 mg, 6.57 mmol, 10.00 equiv) in DCM (16 mL), and the reaction mixture was stirred for 1 h at room temperature. The resulting mixture was filtered and the filter cake was washed with methanol (3x50 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-2-methylpiperidine-1-carboxylate (190 mg, 59.31%) as a solid. **LCMS** (ES, *m/z*): 488 $[M+H]^+$.

Synthesis of Compound 139



B91 139

A mixture of tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] -2-methylpiperidine-1-carboxylate (190.00 mg, 0.390 mmol, 1.00 equiv) and BBr_3 (0.20 mL, 2.12 mmol, 5.43 equiv) in DCE (2 mL, 25.263 mmol, 64.83 equiv) was stirred for 2 h at 80 °C. The reaction mixture was cooled to room temperature, then quenched with methanol at 0 °C. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-Chiral-HPLC (Column: CHIRALPAK ID, 2*25cm,5Â¦ÃŒm; Mobile Phase A:MTBE (0.1%DEA)-HPLC, Mobile Phase B:EtOH--HPLC; Flow rate:20 mL/min; Gradient:20 B to 20 B in 15 min; 220/254 nm; RT1:9.8; RT2:12.5; Injection Volumn:0.7 ml; Number Of Runs:7;) to afford 2-methyl-5-[6-[(2S,4R)-2-methylpiperidin-4-yl]-1,5-naphthyridin-2-yl]indazol-6-ol (3.8 mg, 2.61%) as a solid. The absolute stereochemistry of the compound as arbitrarily assigned. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.60 (s, 1H), 8.69 (s, 1H), 8.61 (d, J = 9.2 Hz, 1H), 8.48 (dd, J = 9.1, 0.8 Hz, 1H), 8.45 – 8.37 (m, 2H), 7.81 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 0.9 Hz, 1H), 4.14 (s, 3H), 3.41 (dt, J = 7.9, 4.4 Hz, 1H), 3.21 (td, J = 6.6, 4.0 Hz, 1H), 2.93 (ddd, J = 10.7, 7.3, 4.2 Hz, 1H), 2.16 (ddd, J = 12.0, 7.5, 3.9 Hz, 1H), 2.02 (s, 1H), 1.96 – 1.85 (m, 1H), 1.76 – 1.65 (m, 1H), 1.16 (d, J = 6.6 Hz, 3H).

Example 43: Synthesis of Compound 140

Synthesis of Compound 140



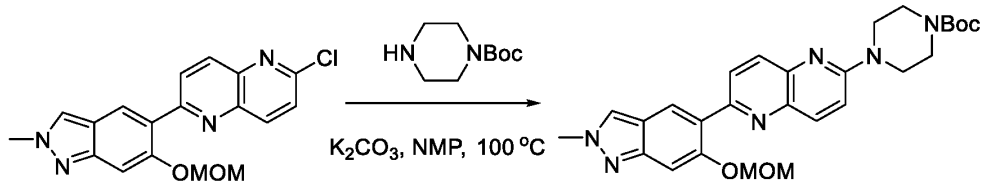
B91 140

A mixture of tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl]-2-methylpiperidine-1-carboxylate (190 mg, 0.39 mmol, 1.00 equiv) and BBr_3 (0.2 mL, 2.12 mmol, 5.43 equiv) in DCE (2 mL, 25.26 mmol, 64.83 equiv) was stirred for 2 h at 80 °C. The reaction mixture was cooled to room temperature, then quenched with methanol at 0 °C. The resulting

mixture was concentrated under vacuum to give residue. The residue was purified by Prep-chiral-HPLC (Column: CHIRALPAK ID, 2*25cm,5Â¦ÃŒm; Mobile Phase A:MTBE (0.1%DEA)-HPLC, Mobile Phase B:EtOH--HPLC; Flow rate:20 mL/min; Gradient:20 B to 20 B in 15 min; 220/254 nm; RT1:9.8; RT2:12.5; Injection Volumn:0.7 ml; Number Of Runs:7) to afford 2-methyl-5-[6-[(2S,4S)-2-methylpiperidin-4-yl]-1,5-naphthyridin-2-yl]indazol-6-ol (12.9 mg) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.62 (s, 1H), 8.68 (s, 1H), 8.59 (d, *J* = 9.2 Hz, 1H), 8.46 (d, *J* = 9.1 Hz, 1H), 8.43 – 8.36 (m, 2H), 7.75 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 4.13 (s, 3H), 3.11 (ddd, *J* = 9.5, 7.6, 5.1 Hz, 1H), 3.04 (tt, *J* = 12.1, 4.0 Hz, 1H), 2.79 – 2.63 (m, 2H), 1.93 – 1.81 (m, 2H), 1.67 (qd, *J* = 12.3, 4.1 Hz, 1H), 1.39 (q, *J* = 11.9 Hz, 1H), 1.06 (d, *J* = 6.2 Hz, 3H). The absolute stereochemistry of the compound was assigned arbitrarily.

Example 44: Synthesis of Compound 136

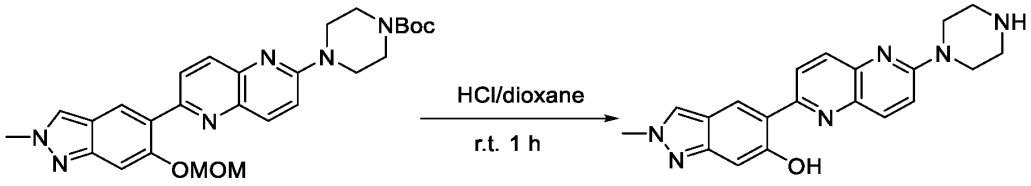
Synthesis of Intermediate B92



B92

To a stirred solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (70.00 mg, 0.197 mmol, 1.00 equiv) and tert-butyl piperazine-1-carboxylate (55.12 mg, 0.296 mmol, 1.5 equiv) in NMP (1.00 mL) was added K_2CO_3 (81.80 mg, 0.592 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere. The reaction mixture was quenched with water (10 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl 4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]piperazine-1-carboxylate (50 mg, 50.22%) as a solid. **LCMS** (ES, *m/z*): 505 $[M+H]^+$.

Synthesis of Compound 136

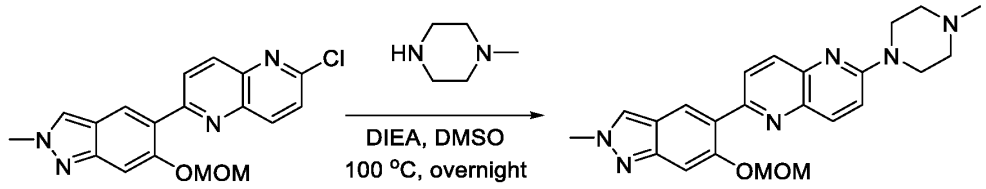


B92 **136**

To a stirred solution of tert-butyl 4-[6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl]piperazine-1-carboxylate (45.00 mg, 0.089 mmol, 1.00 equiv) in 1,4-dioxane (4 mL) was added HCl (gas) in 1,4-dioxane (4.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column, XBridge Prep OBD C18 Column, 30x150mm 5um; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% PhaseB up to 38% in 8 min); Detector, uv.220nm product was obtained) to afford 2-methyl-5-[6-(4-methylpiperazin-1-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (3.3 mg, 9.88%) as a solid. **LCMS** (ES, *m/z*):361 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 7.67 (s, 1H), 7.54 (d, *J* = 9.1 Hz, 1H), 7.43 (s, 1H), 7.31 (dd, *J* = 11.1, 9.4 Hz, 2H), 6.66 (d, *J* = 9.4 Hz, 1H), 6.16 (s, 1H), 3.37 (s, 3H), 3.06 – 2.99 (m, 4H), 2.24 – 2.17 (m, 4H).

Example 45: Synthesis of Compound 116

Synthesis of Intermediate B93

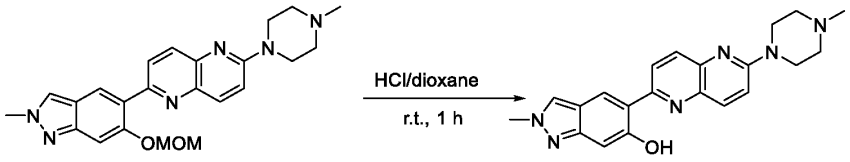


B93

To a stirred solution of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (80.00 mg, 0.225 mmol, 1.00 equiv) and piperazine, 1-methyl- (33.88 mg, 0.338 mmol, 1.5 equiv) in DMSO (5.00 mL) was added DIEA (87.43 mg, 0.676 mmol, 3 equiv) dropwise at room temperature under nitrogen atmosphere. The resulting mixture was stirred for overnight at 100 °C under nitrogen atmosphere. The reaction was quenched by the addition of Water (10mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 10mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. This resulted in 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-(4-

methylpiperazin-1-yl)-1,5-naphthyridine (65 mg, 68.88%) as a solid. **LCMS** (ES, *m/z*): 419 $[M+H]^+$.

Synthesis of Compound 116

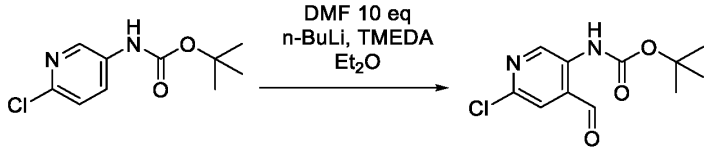


B93 **116**

To a stirred solution of 2-[6-(methoxymethoxy)-2-methylindazol-5-yl]-6-(4-methylpiperazin-1-yl)-1,5-naphthyridine (60.00 mg, 0.143 mmol, 1.00 equiv) in 1,4-dioxane (4 mL) was added HCl (gas) in 1,4-dioxane (4.00 mL) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30x150mm 5um; Mobile Phase A:Water (10MMOL/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:5% B to 38% B in 8 min 220 nm; RT1:7.28) to afford 2-methyl-5-[6-(4-methylpiperazin-1-yl)-1,5-naphthyridin-2-yl]indazol-6-ol (11.2 mg, 20.86%) as a solid. **LCMS** (ES, *m/z*):375 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.86 (s, 1H), 8.56 (s, 1H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.15 (d, *J* = 9.4 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 9.5 Hz, 1H), 6.88 (s, 1H), 4.12 (s, 3H), 3.76 (t, *J* = 5.0 Hz, 4H), 2.45 (t, *J* = 5.1 Hz, 4H), 2.25 (s, 3H).

Example 46: Synthesis of Compound 104

Synthesis of Intermediate B94

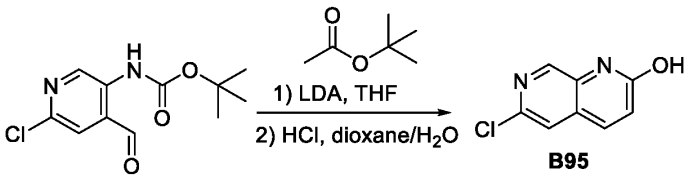


B94

To a stirred mixture of tert-butyl N-(6-chloropyridin-3-yl)carbamate (20 g, 87.458 mmol, 1.00 equiv) and TMEDA (10.16 g, 87.458 mmol, 1 equiv) in diethyl ether (200 mL, 1927.913 mmol, 22.04 equiv) was added butyllithium (11.20 g, 174.916 mmol, 2 equiv) in portions at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 2 h at -78 °C under nitrogen atmosphere. To the reaction mixture was added DMF (63.93 g, 874.580 mmol, 10 equiv). The

resulting mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The resulting mixture was diluted with water (200 mL) and extracted with ethyl acetate (2 x 300 mL). The organic layers were combined, washed with brine (2x300 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford tert-butyl N-(6-chloro-4-formylpyridin-3-yl)carbamate (2 g, 8.91%) as a solid.

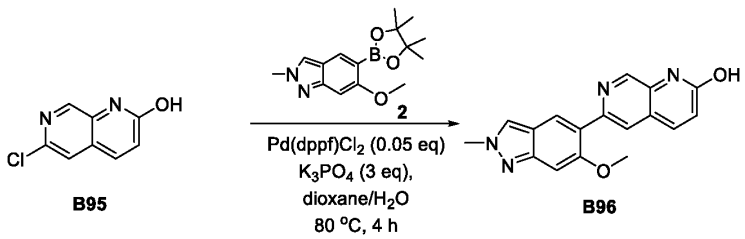
Synthesis of Intermediate B95



B94 B95

To a stirred solution of tert-butyl N-(6-chloro-4-formylpyridin-3-yl)carbamate (2 g, 7.791 mmol, 1.00 equiv) in THF (20 mL) was added LDA (in 2M THF) (2.50 g, 23.373 mmol, 3 equiv) in portions at -78 °C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at -78 °C under nitrogen atmosphere. To the reaction mixture was added tert-butyl acetate (1.36 g, 11.687 mmol, 1.5 equiv), and the reaction mixture was stirred for an additional 30 min at -78 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine (2x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure. The residue was combined with HCl (gas) in 1,4-dioxane (10 mL, 329.119 mmol, 42.24 equiv) and water (10 mL, 555.084 mmol, 71.24 equiv) and stirred for 1 h at 60 °C under nitrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with water (2x10 mL). The filtrate was concentrated under reduced pressure to afford 6-chloro-1,7-naphthyridin-2-ol (585 mg, 41.58%) as a solid.

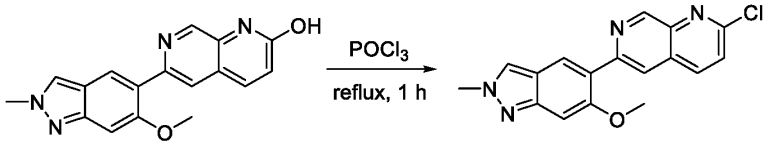
Synthesis of Intermediate B96



B95 B96

To a stirred mixture of 6-chloro-1,7-naphthyridin-2-ol (200 mg, 1.107 mmol, 1.00 equiv) and 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (382.94 mg, 1.328 mmol, 1.2 equiv) in dioxane (4 mL, 47.216 mmol, 24.36 equiv) was added K_3PO_4 (705.24 mg, 3.321 mmol, 3 equiv), $Pd(dppf)Cl_2$ (45.11 mg, 0.055 mmol, 0.05 equiv), and water (1 mL, 55.508 mmol, 50.12 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (2:1) to afford 6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-ol (280 mg, 82.54%) as a solid. **LCMS** (ES, *m/z*): 307 $[M+H]^+$.

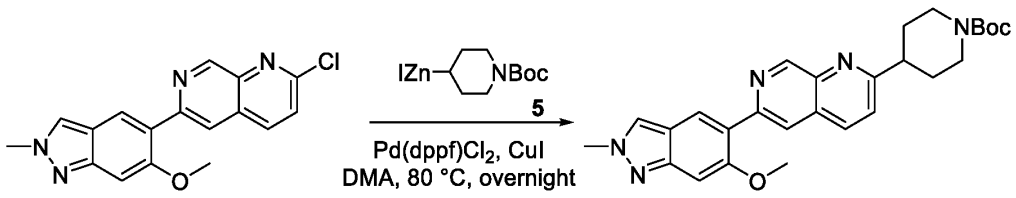
Synthesis of Intermediate B97



B96 **B97**

To a mixture of 6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-ol (250 mg, 0.816 mmol, 1.00 equiv) in phosphorus oxychloride (3.00 mL, 19.568 mmol, 23.98 equiv) was stirred overnight at 80 °C under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure to afford 2-chloro-6-(6-methoxy-2-methylindazol-5-yl) -1,7-naphthyridine (100 mg, 37.73%) as a solid. **LCMS** (ES, *m/z*): 325 $[M+H]^+$.

Synthesis of Intermediate B98

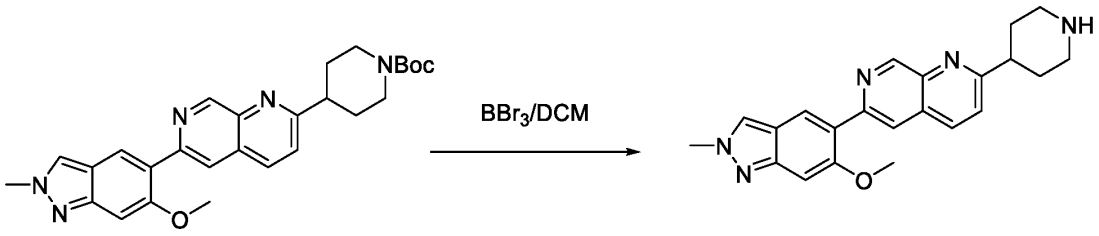


B97 **B98**

To a stirred solution of 2-chloro-6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridine (90 mg, 0.277 mmol, 1.00 equiv) and CuI (5.28 mg, 0.028 mmol, 0.1 equiv) in DMA (1 mL, 10.755 mmol, 38.81 equiv) was added $Pd(dppf)Cl_2$ (11.29 mg, 0.014 mmol, 0.05 equiv) and [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (208.69 mg, 0.554 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under

nitrogen atmosphere. The resulting mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford tert-butyl 4-[6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl]piperidine-1-carboxylate (32 mg, 24.38%) as a solid.

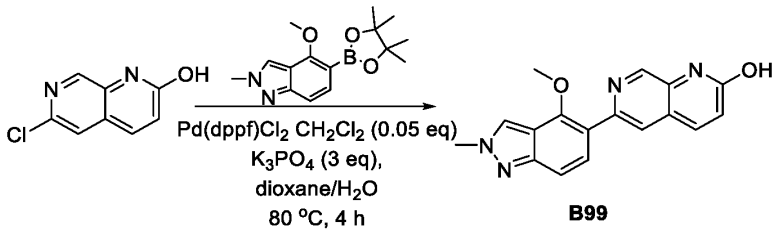
Synthesis of Compound 104



A mixture of tert-butyl 4-[6-(7-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl] piperidine-1-carboxylate (27.00 mg, 0.057 mmol, 1.00 equiv) and BBr_3 (0.10 mL, 0.000 mmol, 0.01 equiv) in DCM (1.00 mL) was stirred overnight at room temperature under nitrogen atmosphere. The reaction mixture was quenched with methanol (3 mL) at 0 °C, then filtered, and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC ((SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30 mm X 150 mm, 5um; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% PhaseB up to 40% in 8 min); Detector, uv.220nm product was obtained) to afford 2-methyl-5-[2-(piperidin-4-yl)-1,7-naphthyridin-6-yl] indazol-7-ol (1 mg, 4.88%) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.55 (s, 1H), 9.39 (s, 1H), 8.68 (d, *J* = 1.0 Hz, 1H), 8.48 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 8.37 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 4.12 (s, 3H), 3.11 (d, *J* = 12.7 Hz, 2H), 3.03 (d, *J* = 11.6 Hz, 1H), 1.89 (d, *J* = 12.0 Hz, 2H), 1.76 (q, *J* = 12.0 Hz, 2H).

Example 47: Synthesis of Compound 106

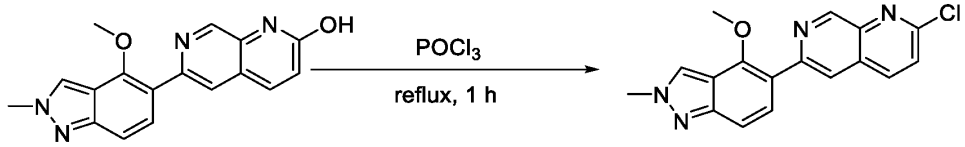
Synthesis of Intermediate B99



B99

To a stirred mixture of 6-chloro-1,7-naphthyridin-2-ol (350 mg, 1.938 mmol, 1.00 equiv) and 4-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazole (670.15 mg, 2.326 mmol, 1.2 equiv) in dioxane (4 mL) was added K_3PO_4 (1234.17 mg, 5.814 mmol, 3 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (78.94 mg, 0.097 mmol, 0.05 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-ol (450 mg, 75.80%) as a solid.

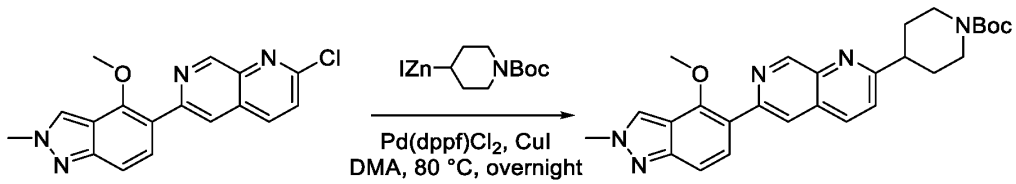
Synthesis of Intermediate B100



B99 B100

A mixture of 6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-ol (400 mg, 1.306 mmol, 1.00 equiv) in phosphorus oxychloride (4 mL, 26.089 mmol, 19.98 equiv) was stirred overnight at 80 °C under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate concentrated under reduced pressure to afford 2-chloro-6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridine (500 mg, 117.90%) as a solid.

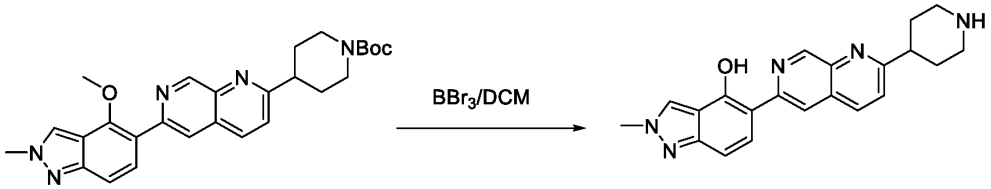
Synthesis of Intermediate B101



B100 B101

To a mixture of 2-chloro-6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridine (380 mg, 1.170 mmol, 1.00 equiv) and CuI (22.28 mg, 0.117 mmol, 0.1 equiv) in DMA (4 mL, 43.021 mmol, 36.77 equiv) was added Pd(dppf)Cl_2 (47.66 mg, 0.058 mmol, 0.05 equiv) and [1-(tert-butoxycarbonyl)piperidin-4-yl](iodo)zinc (881.15 mg, 2.340 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x10 mL). The organic layers were combined, washed with brine (2x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl]piperidine-1-carboxylate (65 mg, 11.73%) as a solid. **LCMS** (ES, *m/z*): 325 $[M+H]^+$.

Synthesis of Compound 106



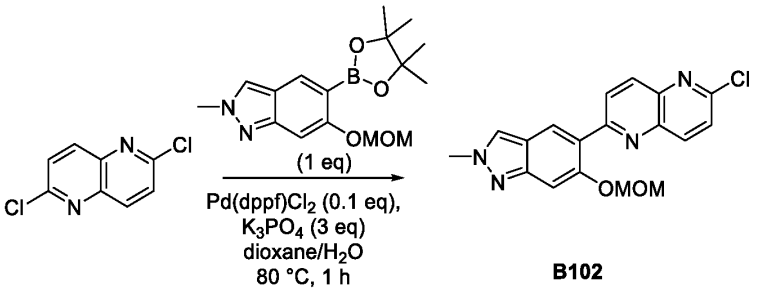
B101 **106**

To a stirred solution of tert-butyl 4-[6-(4-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl] piperidine-1-carboxylate (55 mg, 0.116 mmol, 1.00 equiv) in DCE (1 mL, 12.631 mmol, 108.76 equiv) was added BBr_3 (0.2 mL, 2.116 mmol, 18.22 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with methanol (5mL), then filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% ACN up to 45% in 8 min); Detector, uv 220nm product was obtained which Alpha) to afford 2-methyl-5-[2-(piperidin-4-yl)-1,7-naphthyridin-6-yl]indazol-4-ol (6.7 mg, 16.05%) as a solid. **LCMS** (ES, *m/z*): 374 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ14.96 (s, 1H), 9.39 (s, 1H), 8.52 (d, *J* = 17.4 Hz, 2H), 8.39 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.16

(d, J = 9.1 Hz, 1H), 4.15 (s, 3H), 3.13 (d, J = 12.1 Hz, 2H), 3.05 (s, 1H), 2.75 – 2.67 (m, 2H), 1.91 (d, J = 12.5 Hz, 2H), 1.78 (tt, J = 12.7, 6.4 Hz, 2H).

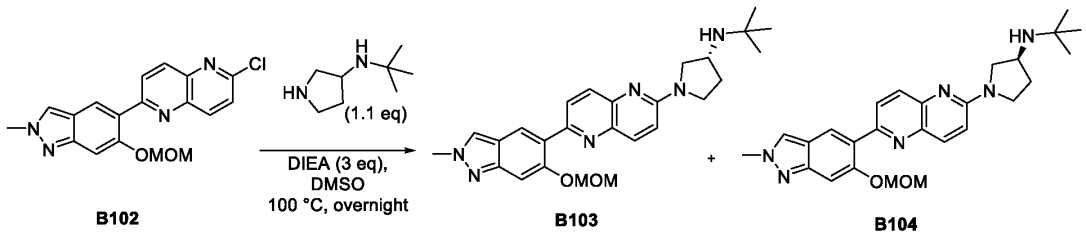
Example 48: Synthesis of Compound 127

Synthesis of Intermediate B102



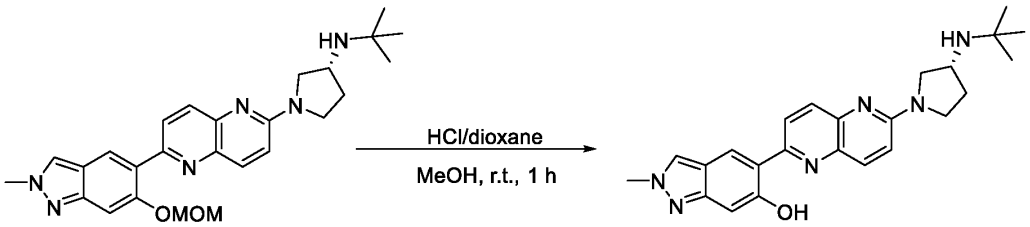
A mixture of 2,6-dichloro-1,5-naphthyridine (400 mg, 2.010 mmol, 1.00 equiv), 6-(methoxymethoxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (2459.47 mg, 2.010 mmol, 1 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (163.72 mg, 0.201 mmol, 0.1 equiv), dioxane (20.00 mL, 236.082 mmol, 117.47 equiv), and (phosphoperoxy)potassium; dipotassium (1279.80 mg, 6.030 mmol, 3 equiv) in water (4.00 mL, 222.037 mmol, 110.48 equiv) was stirred for 1 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with water (30 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (1x40 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (310 mg, 43.48%) as a solid. **LCMS** (ES, *m/z*):355 $[M+H]^+$.

Synthesis of Intermediate B103 and B104



A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (200 mg, 0.564 mmol, 1.00 equiv), N-tert-butylpyrrolidin-3-amine (88.20 mg, 0.620 mmol, 1.1 equiv), DIEA (218.57 mg, 1.692 mmol, 3 equiv) and DMSO (10 mL, 140.786 mmol, 249.75 equiv) was stirred overnight at 100 °C under nitrogen atmosphere. The mixture was cooled to room temperature, then quenched with water (20 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, washed with sub-saturated brine (3x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1(min): 7.01) to afford a solid. The resultant solid was purified by prep-chiral-HPLC (Column: CHIRALPAK IA-3, 4.6*50mm 3um; Mobile Phase A: MTBE(0.1%DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (3S)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl] -1,5-naphthyridin-2-yl}pyrrolidin-3-amine (65 mg, 25.04%) and (3R)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (63 mg, 24.26%) as solids. **LCMS** (ES, *m/z*): 461 $[M+H]^+$. The absolute stereochemistry of the compounds was arbitrarily assigned.

Synthesis of Compound 153

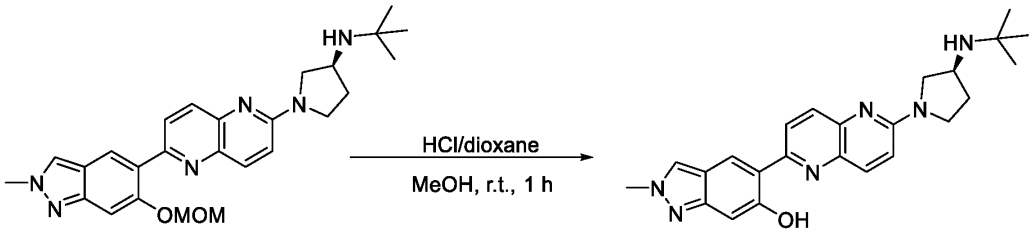


B103 **153**

A mixture 5-{6-[(3R)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (65 mg, 0.156 mmol, 1.00 equiv), methanol (2 mL, 62.418 mmol, 399.98 equiv), and HCl (gas) in 1,4-dioxane (2 mL, 65.824 mmol, 421.81 equiv) was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60

mL/min; Gradient: 5% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 7.37;) to afford 5-{6-[(3R)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (21 mg, 32.26%) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 12.5, 9.2 Hz, 2H), 7.14 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.50 (ddd, J = 18.1, 12.0, 7.2 Hz, 2H), 3.17 – 3.09 (m, 1H), 2.23 – 2.15 (m, 1H), 1.83 – 1.66 (m, 2H), 1.10 (s, 9H).

Synthesis of Compound 154

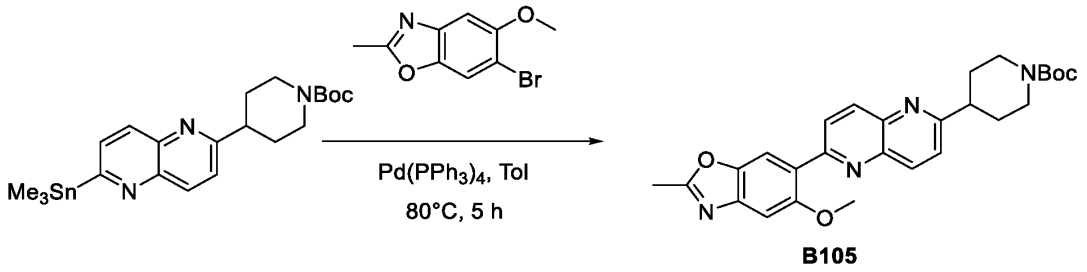


B104 **154**

A mixture of 5-{6-[(3S)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -2-methylindazol-6-ol (65 mg, 0.156 mmol, 1.00 equiv), methanol (2 mL, 62.418 mmol, 399.98 equiv), and HCl (gas) in 1,4-dioxane (2 mL, 65.824 mmol, 421.81 equiv) was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 7.00;) to afford 5-{6-[(3S)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (19.1 mg, 29.21%) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.55 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 12.7, 9.2 Hz, 2H), 7.14 (d, J = 9.2 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.57 – 3.45 (m, 2H), 3.18 – 3.09 (m, 1H), 2.21 – 2.14 (m, 1H), 1.84 – 1.65 (m, 2H), 1.10 (s, 9H).

Example 49: Synthesis of Compound 147

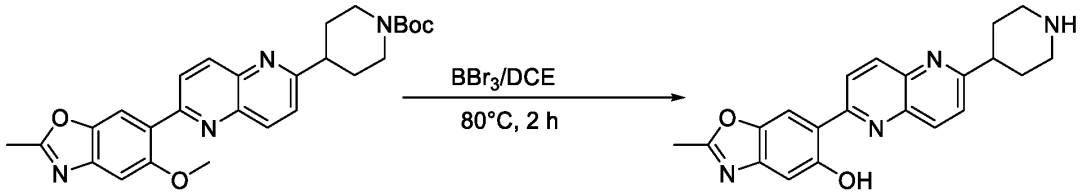
Synthesis of Intermediate B105



B105

To a mixture of tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (150.0 mg, 0.315 mmol, 1.0 equiv) and 6-bromo-5-methoxy-2-methyl-1,3-benzoxazole (76.25 mg, 0.32 mmol, 1.0 equiv) in toluene (2.00 mL) was added $Pd(PPh_3)_4$ (36.4 mg, 0.032 mmol, 0.1 equiv). The reaction mixture was stirred for 5 h at 80 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC/silica gel column chromatography, eluted with PE/EA (2/8) to afford tert-butyl 4-[6-(5-methoxy-2-methyl-1,3-benzoxazol-6-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (60 mg, 40.1%) as a solid. **LCMS** (ES, *m/z*): 475 $[M+H]^+$.

Synthesis of Compound 147

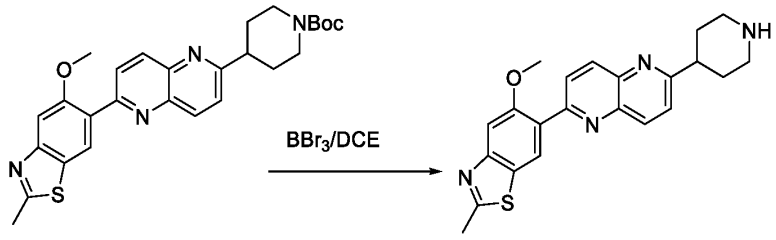


B105 147

To a solution of tert-butyl 4-[6-(5-methoxy-2-methyl-1,3-benzoxazol-6-yl)-1,5-naphthyridin-2-yl] piperidine-1-carboxylate (60 mg, 0.126 mmol, 1.00 equiv) in DCE (1 mL) was added BBr_3 (316.74 mg, 1.26 mmol, 10 equiv). The reaction mixture was stirred for 2 h at 80 °C, then quenched with methanol at 0°C and the resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (5% ACN up to 50% in 8 min); Detector, uv) to afford 2-methyl-6-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]-1,3-benzoxazol-5-ol (1.5 mg, 3.3%) as a solid. **LCMS** (ES, *m/z*): 361 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.34 (s, 1H), 8.66 (d, *J* = 9.3 Hz, 1H), 8.56 (s, 1H), 8.52 (d, *J* = 9.1 Hz, 1H), 8.45 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.19 (s, 1H), 3.17 - 2.98 (m, 3H), 2.61 - 2.74 (m, 5H), 1.84 - 1.88 (m, 2H), 1.77 - 1.82 (m, 2H).

Example 50: Synthesis of Compound 213

Synthesis of Compound 213

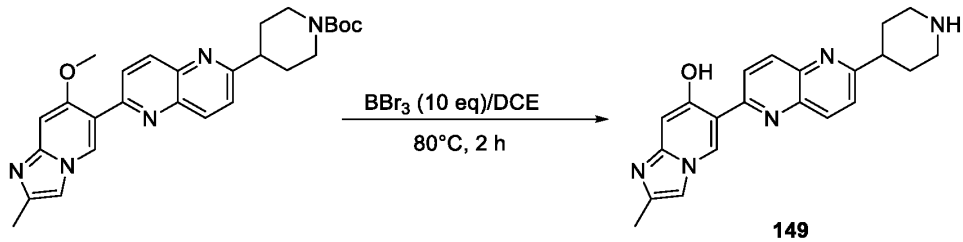


213

To a stirred solution of tert-butyl 4-[6-(5-methoxy-2-methyl-1,3-benzothiazol-6-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (55 mg, 0.112 mmol, 1.00 equiv) in DCE (1 mL, 12.631 mmol, 112.68 equiv) was added BBr_3 (0.2 mL, 2.116 mmol, 18.87 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with methanol (5 mL), then filtered, and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10MMOL/L NH4HCO3) and ACN (10% ACN up to 46% in 8 min); Detector, uv 220nm product was obtained which Alpha) to afford 2-(5-methoxy-2-methyl-1,3-benzothiazol-6-yl)-6-(piperidin-4-yl)-1,5-naphthyridine (13.6 mg, 31.07%) as a solid. **LCMS** (ES, *m/z*): 377 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.17 (s, 1H), 8.93 (s, 1H), 8.63 (d, *J* = 9.3 Hz, 1H), 8.54 (d, *J* = 9.1 Hz, 1H), 8.47 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.45 (s, 1H), 3.14 – 3.00 (m, 3H), 2.82 (s, 3H), 2.73 – 2.62 (m, 2H), 1.89 (d, *J* = 11.5 Hz, 2H), 1.77 (tt, *J* = 13.1, 6.7 Hz, 2H).

Example 51: Synthesis of Compound 149

Synthesis of Compound 149



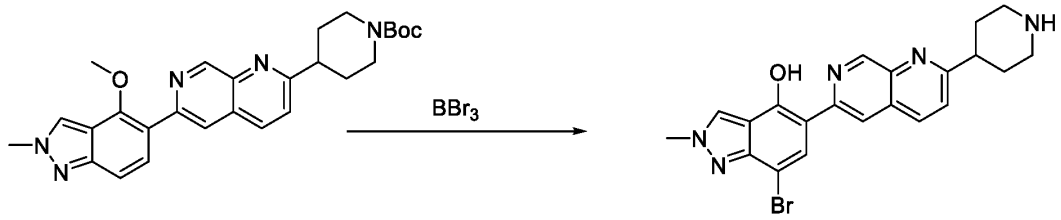
149

To a stirred solution of tert-butyl 4-(6-{7-methoxy-2-methylimidazo[1,2-a]pyridin-6-yl} -1,5-naphthyridin-2-yl)piperidine-1-carboxylate (60 mg, 0.127 mmol, 1.00 equiv) in DCE (1 mL,

12.631 mmol, 99.70 equiv) was added BBr_3 (0.2 mL, 2.116 mmol, 16.70 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with methanol (5 mL). After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm, 5μm; mobile phase, Water (10MMOL/L NH4HCO3) and ACN (5% ACN up to 30% in 8 min); Detector, uv 220nm product was obtained which Alpha) to afford 2-methyl-6-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]imidazo[1,2-a]pyridin-7-ol (12.1 mg, 26.57%) as a solid. **LCMS** (ES, *m/z*): 360 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ9.35 (s, 1H) 8.51 (s, 2H), 8.44 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 6.69 (s, 1H), 3.13 – 2.97 (m, 3H), 2.66 (td, *J* = 12.1, 2.7 Hz, 2H), 2.29 (s, 3H), 1.88 (d, *J* = 11.8 Hz, 2H), 1.75 (qd, *J* = 12.2, 4.0 Hz, 2H).

Example 52: Synthesis of Compound 141

Synthesis of Compound 141

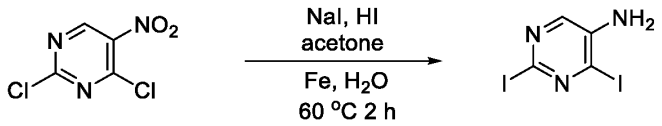


141

A stirred mixture of 6-(7-bromo-4-methoxy-2-methylindazol-5-yl) -2-(piperidin-4-yl)-1,7-naphthyridine (74.00 mg, 0.164 mmol, 1.00 equiv) and BBr_3 (0.50 mL, 5.289 mmol, 32.33 equiv) in DCM (2.00 mL) was stirred overnight at room temperature under nitrogen atmosphere. The reaction was quenched with methanol (5mL) at 0 °C. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 30¡Á150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:5 B to 45 B in 8 min; 220 nm; RT1:6.85) to afford tert-butyl 4-[6-(7-bromo-4-hydroxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl] piperidine-1-carboxylate (24.9 mg, 28.27%) as a solid. **LCMS** (ES, *m/z*): 438 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.67 (d, *J* = 2.6 Hz, 2H), 8.40 (d, *J* = 8.6 Hz, 1H), 8.19 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 4.19 (d, *J* = 3.7 Hz, 3H), 3.18 (s, 2H), 3.16 – 3.02 (m, 1H), 2.74 (dd, *J* = 13.1, 10.5 Hz, 1H), 2.49 (s, 1H), 1.97 – 1.89 (m, 2H), 1.83 (dd, *J* = 12.2, 3.9 Hz, 2H), 1.81 – 1.74 (m, 2H).

Example 53: Synthesis of Compound 155

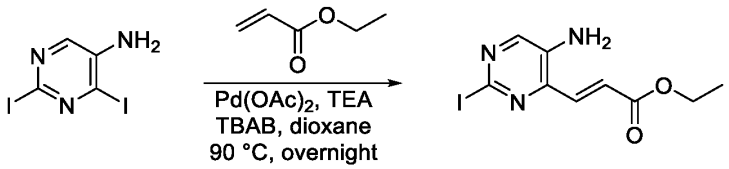
Synthesis of Intermediate B106



B106

A mixture of 2,4-dichloro-5-nitropyrimidine (10.00 g, 51.554 mmol, 1.00 equiv), NaI (30.91 g, 206.212 mmol, 4.00 equiv), and HI (3.00 mL, 39.894 mmol, 0.77 equiv) in acetone (100.00 mL) was stirred for 3 h at room temperature under nitrogen atmosphere. To the reaction mixture was added Fe (14.40 g, 257.857 mmol, 5.00 equiv) and water (5.00 mL). The resulting mixture was stirred for an additional 2 h at 60 °C. The resulting mixture was filtered, the filter cake washed with ethyl acetate (2 x 20 mL), and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (2:1) to afford 2,4-diiodopyrimidin-5-amine (5 g, 27.96%) as a solid.

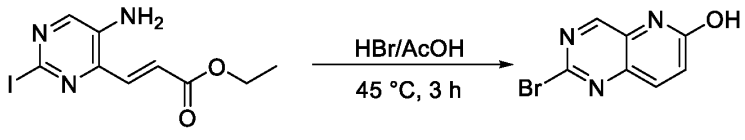
Synthesis of Intermediate B107



B106 **B107**

A mixture of 2,4-diiodopyrimidin-5-amine (5.00 g, 14.413 mmol, 1.00 equiv), ethyl acrylate (7.22 g, 72.116 mmol, 5.00 equiv), TBAB (6.97 g, 21.620 mmol, 1.50 equiv), $Pd(AcO)_2$(0.16 g, 0.721 mmol, 0.05 equiv), and TEA (5.83 g, 57.654 mmol, 4.00 equiv) in dioxane (50.00 mL) was stirred overnight at 90 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford ethyl (2E)-3-(5-amino-2-iodopyrimidin-4-yl) prop-2-enoate (2g,43.48%) as a solid.

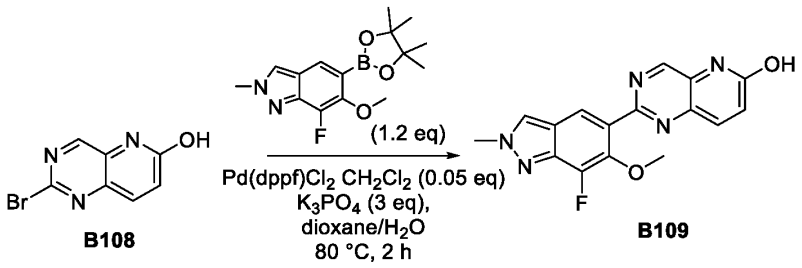
Synthesis of Intermediate B108



B107 **B108**

A mixture of ethyl (2E)-3-(5-amino-2-iodopyrimidin-4-yl) prop-2-enoate (2.00 g, 6.268 mmol, 1.00 equiv) in HBr in AcOH (40%) (20.00 mL) was stirred for 3 h at 45 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in methanol (5 mL). The residue was neutralized to pH 7 with saturated $NaHCO_3$ (aq.) and a solid precipitated. The precipitated solid was collected by filtration and washed with methanol (1x2 mL) to afford 2-bromopyrido[3,2-d] pyrimidin-6-ol (1.2 g, 84.70%) as a solid.

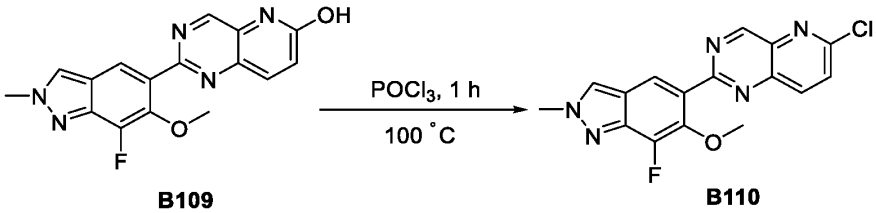
Synthesis of Intermediate B109



B108 B109

A mixture of 2-bromopyrido[3,2-d] pyrimidin-6-ol (310 mg, 1.344 mmol, 1.00 equiv), 7-fluoro-6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indazole (493.76 mg, 1.613 mmol, 1.2 equiv), $Pd(dppf)Cl_2CH_2Cl_2$ (54.74 mg, 0.067 mmol, 0.05 equiv), and K_3PO_4 (855.89 mg, 4.032 mmol, 3 equiv) in dioxane (2.5 mL, 29.510 mmol, 21.96 equiv) and water (0.62 mL, 34.415 mmol, 25.61 equiv) was stirred for 2 h at 80 °C under nitrogen atmosphere. The mixture cooled to room temperature, then poured into water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford 2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)pyrido[3,2-d]pyrimidin-6-ol (250 mg, 56.04%) as a solid.

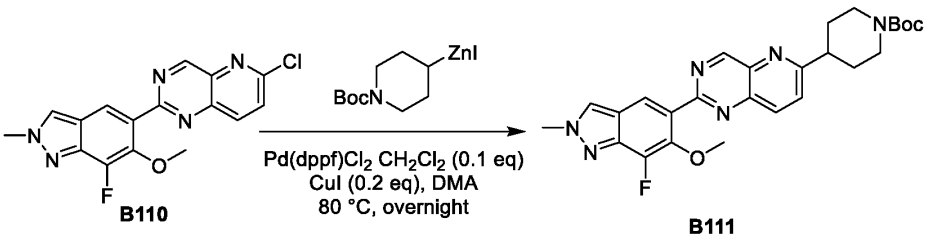
Synthesis of Intermediate B110



B109 B110

A solution of 2-(7-fluoro-6-methoxy-2-methylindazol-5-yl) pyrido[3,2-d] pyrimidin-6-ol (250 mg, 0.753 mmol, 1.00 equiv) in $POCl_3$ (12.5 mL) was stirred for 1 h at 100 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with water/ice (200 mL) at 0 °C. The mixture was basified to pH 8 with saturated Na_2CO_3. The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The resulting mixture was concentrated under vacuum to afford 5-{6-chloropyrido[3,2-d] pyrimidin-2-yl}-7-fluoro-6-methoxy-2-methylindazole (220 mg, 84.98%) as a solid.

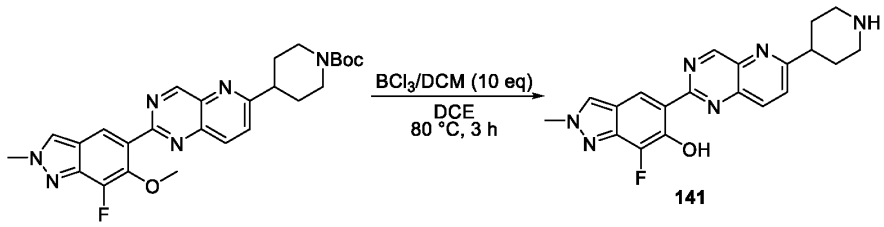
Synthesis of Intermediate B111



B110 B111

A mixture of 5-{6-chloropyrido[3,2-d] pyrimidin-2-yl}-7-fluoro-6-methoxy-2-methylindazole (220 mg, 0.627 mmol, 1.00 equiv) and CuI (23.89 mg, 0.125 mmol, 0.2 equiv) in DMA (22 mL, 236.615 mmol, 377.26 equiv) was stirred for 30 min at 80 °C under nitrogen atmosphere. To the reaction mixture was added [1-(tert-butoxycarbonyl) piperidin-4-yl] (iodo)zinc (708.50 mg, 1.881 mmol, 3 equiv) dropwise over 10 min at 80 °C. The resulting mixture was stirred overnight at 80 °C. The reaction mixture was cooled to room temperature, then filtered, and the filtrate poured into water (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)pyrido[3,2-d]pyrimidin-6-yl]piperidine-1-carboxylate (160 mg, 50.76%) as a solid.

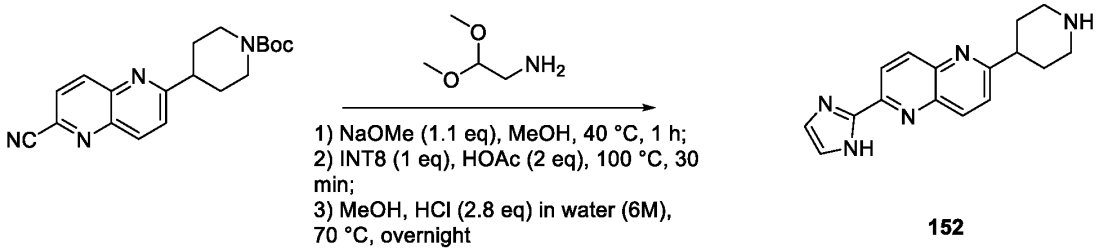
Synthesis of Compound 141



To a stirred solution of tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)pyrido[3,2-d]pyrimidin -6-yl]piperidine-1-carboxylate (150 mg, 0.305 mmol, 1.00 equiv) in DCE (2 mL, 25.263 mmol, 82.96 equiv) was added BBr_3 (0.5 mL, 5.289 mmol, 17.37 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with methanol (10mL), then filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, Xselect CSH OBD Column 30*150mm 5um, n; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (5% ACN up to 45% in 8 min); Detector, uv 220nm product was obtained which Alpha) to afford 7-fluoro-2-methyl-5-[6-(piperidin-4-yl)pyrido[3,2-d]pyrimidin-2-yl]indazol-6-ol (21.1 mg, 18.31%) as a solid. **LCMS** (ES, *m/z*): 379 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.23 (s, 1H), 9.75 (s, 1H), 8.96 (s, 1H), 8.63 (d, *J* = 2.6 Hz, 1H), 8.54 (d, *J* = 8.8 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 4.19 (s, 3H), 3.12 (d, *J* = 11.7 Hz, 3H), 2.26 (s, 2H), 1.92 (d, *J* = 12.7 Hz, 2H), 1.78 (td, *J* = 13.1, 12.7, 3.2 Hz, 2H).

Example 54: Synthesis of Compound 152

Synthesis of Compound 152

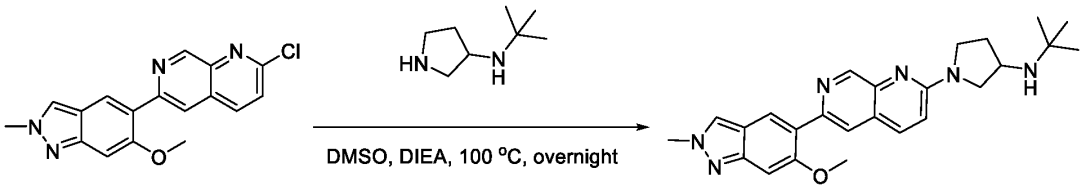


A mixture of tert-butyl 4-(6-cyano-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (50 mg, 0.148 mmol, 1.00 equiv) and NaOMe (8.78 mg, 0.163 mmol, 1.1 equiv) in MeOH (1 mL) was stirred for 1 h at 40 °C under nitrogen atmosphere. To the reaction mixture was added 2,2-

dimethoxyethanamine (15.53 mg, 0.148 mmol, 1 equiv) and HOAc (17.75 mg, 0.296 mmol, 2 equiv) dropwise at room temperature. The resulting mixture was stirred for an additional 30 min at 100 °C. To the reaction mixture was added methanol (2 mL, 49.398 mmol, 334.34 equiv) and HCl (2.8eq, aq, 4M) dropwise at room temperature. The resulting mixture was stirred overnight at 70 °C, then concentrated under reduced pressure to give a residue. The residue was purified twice by Prep-HPLC (Column: YMC-Actus Triart C18, 30x150 mm, 5um; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 3% B in 2 min, 3% B to 43% B in 8 min; Wave Length: 220 nm; RT1(min): 7.18.; Column: YMC-Actus Triart C18, 30x150 mm, 5um; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 3% B to 43% B in 8 min, 43% B; Wave Length: 220 nm; RT1(min): 6.42.) to afford 2-(1H-imidazol-2-yl)-6-(piperidin-4-yl)-1,5-naphthyridine (8.3 mg, 19.49%) as a solid. **LCMS** (ES, *m/z*): 280[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-*d6*, *ppm*): δ 12.99 (s, 1H), 8.46 – 8.35 (m, 2H), 8.33 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 60.5 Hz, 2H), 3.12 – 2.94 (m, 3H), 2.83 (s, 1H), 2.64 (td, *J* = 11.9, 2.5 Hz, 2H), 1.86 (d, *J* = 12.7 Hz, 2H), 1.73 (qd, *J* = 12.3, 3.9 Hz, 2H).

Example 55: Synthesis of Compound 218

Synthesis of Intermediate B112

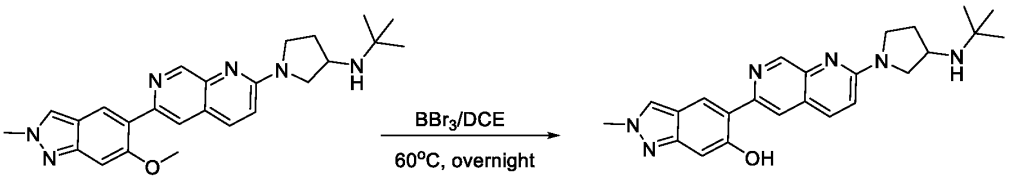


B112

To a stirred solution of 2-chloro-6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridine (150 mg, 0.462 mmol, 1 equiv) and N-tert-butylpyrrolidin-3-amine (98.55 mg, 0.693 mmol, 1.5 equiv) in DMSO (2 mL) was added DIEA (179.08 mg, 1.386 mmol, 3 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100°C under nitrogen atmosphere. The resulting mixture was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (2x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH

(10:1) to afford N-tert-butyl-1-[6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl]pyrrolidin-3-amine (70 mg, 35.20%) as a solid.

Synthesis of Compound 218

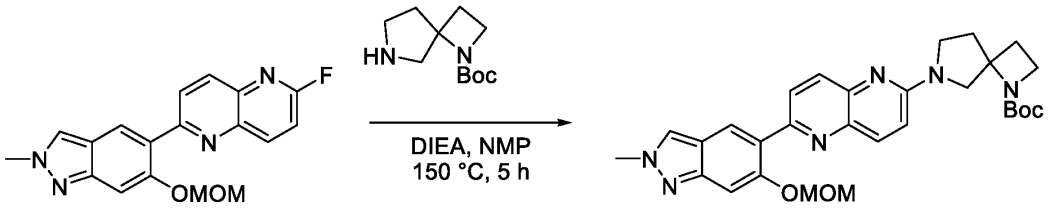


B112 218

To a stirred solution of N-tert-butyl-1-[6-(6-methoxy-2-methylindazol-5-yl)-1,7-naphthyridin-2-yl] pyrrolidin-3-amine (60 mg, 0.139 mmol, 1 equiv) in DCE (2 mL) was added BBr_3 (69.82 mg, 0.278 mmol, 2 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 60 °C under nitrogen atmosphere. The reaction mixture was cooled to 0°C, then quenched with methanol at 0 °C and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was basified to pH 9 with NH_3/MeOH. The resulting mixture was extracted with CH_2Cl_2 (2 x 5mL). The organic layers were combined, washed with brine (2x5 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water(10 mmol/L NH_4HCO_3) and ACN (10% ACN up to 45% in 10 min); Detector, uv 220nm product was obtained which Alpha) to afford 5-{2-[3-(tert-butylamino)pyrrolidin-1-yl]-1,7-naphthyridin-6-yl}-2-methylindazol-6-ol (6.1 mg, 10.51%) as a solid. **LCMS** (ES, *m/z*): 417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.35 (s, 1H), 8.90 (s, 1H), 8.48 (s, 1H), 8.37 – 8.31(s, 2H), 8.11 (d, *J* = 9.2 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 6.85 (s, 1H), 4.10 (s, 3H), 3.87 (s, 1H), 3.73 (s, 1H), 3.55 – 3.46 (m, 2H), 3.14 (t, *J* = 9.1 Hz, 1H), 2.18 (d, *J* = 9.1 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.09 (s, 9H).

Example 56: Synthesis of Compound 178

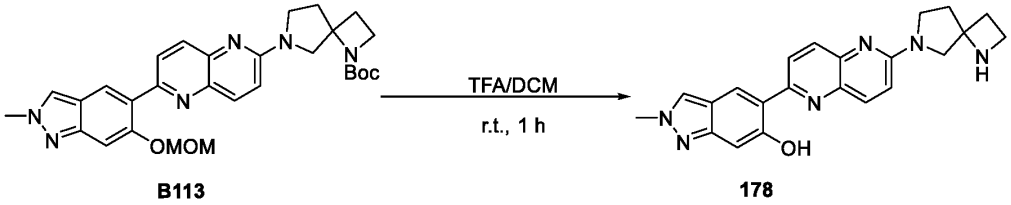
Synthesis of Intermediate B113



B113

To a stirred mixture of 2-fluoro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (230 mg, 0.680 mmol, 1 equiv) and tert-butyl 1,6-diazaspiro[3.4]octane-1-carboxylate (173.18 mg, 0.816 mmol, 1.2 equiv) in NMP (11.5 mL, 119.256 mmol, 175.43 equiv) was added DIEA (263.57 mg, 2.040 mmol, 3 equiv) dropwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 150 °C for 5 h, then cooled to room temperature. The resulting mixture was diluted with water (35 mL) and extracted with ethyl acetate (3 x40 mL). The organic layers were combined, washed with brine (3x10 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by reverse flash chromatography (with the following conditions: column, C18 silica gel; mobile phase, MeOH in water, 10% to 50% gradient in 10 min; detector, UV 254 nm) to afford tert-butyl 6-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}-1,6-diazaspiro[3.4]octane-1-carboxylate (100 mg, 27.72%) as a solid.

Synthesis of Compound 178



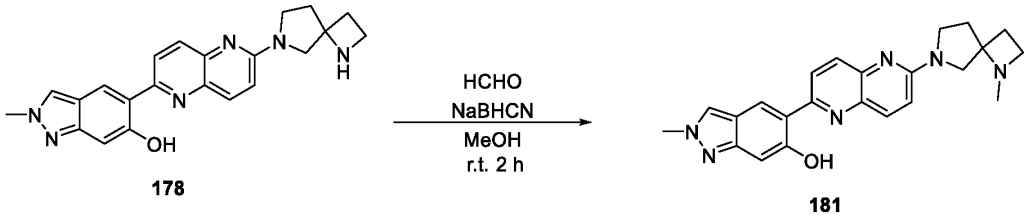
B113 **178**

To a stirred mixture of tert-butyl 6-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin -2-yl}-1,6-diazaspiro[3.4]octane-1-carboxylate (40 mg, 0.075 mmol, 1 equiv) in DCM (1 mL) was added TFA (0.05 mL) dropwise at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 h, then concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 60% B in 8 min, 60% B; Wave Length: 220

nm; RT1(min): 6.78; Number Of Runs: 0) to afford 5-(6-{1,6-diazaspiro[3.4]octan -6-yl}-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol as a solid. **LCMS** (ES, *m/z*): 387 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.54 (s, 1H), 8.40 (d, *J* = 9.3 Hz, 1H), 8.35 (s, 1H), 8.09 (dd, *J* = 16.0, 9.2 Hz, 2H), 7.14 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 0.9 Hz, 1H), 4.12 (s, 3H), 3.64 (d, *J* = 11.1 Hz, 2H), 3.60 (d, *J* = 7.2 Hz, 2H), 3.46 – 3.32 (m, 1H), 3.31 (s, 1H), 2.89 (s, 1H), 2.41 – 2.32 (m, 1H), 2.25 (ddd, *J* = 10.8, 8.5, 5.6 Hz, 1H), 2.15 (t, *J* = 7.0 Hz, 2H).

Example 57: Synthesis of Compound 181

Synthesis of Compound 181

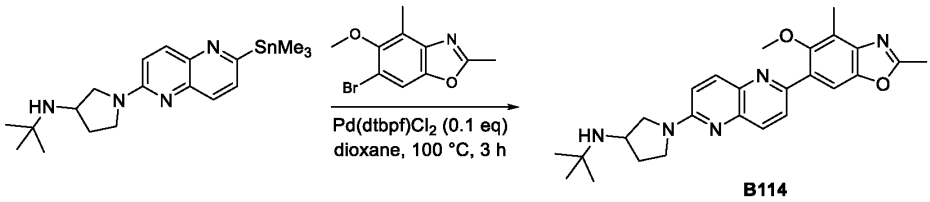


178 181

To a stirred mixture of 5-(6-{1,6-diazaspiro[3.4]octan-6-yl}-1,5-naphthyridin-2-yl)-2-methylindazol-6-ol (50 mg, 0.129 mmol, 1.00 equiv) and HCHO (3.88 mg, 0.129 mmol, 1 equiv) in methanol (0.5 mL) was added $NaBH_3CN$ (33.27 mg, 0.529 mmol, 4.09 equiv) in portions at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 h, then concentrated under vacuum to give a residue. The residue was purified by prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 65% B in 8 min, 65% B; Wave Length: 220 nm; RT1(min): 6.57; Number Of Runs: 0) to afford 2-methyl-5-(6-{1-methyl-1,6-diazaspiro[3.4] octan-6-yl}-1,5-naphthyridin-2-yl)indazol-6-ol (1.1 mg, 2.12%) as a solid. **LCMS** (ES, *m/z*): 401 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.55 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.11 (dd, *J* = 18.2, 9.2 Hz, 2H), 7.18 (d, *J* = 9.3 Hz, 1H), 6.88 (s, 1H), 4.12 (s, 3H), 3.73 (s, 1H), 3.56 (dd, *J* = 18.7, 10.3 Hz, 2H), 3.09 (s, 3H), 2.20 (s, 5H), 2.08 (s, 2H).

Example 58: Synthesis of Compound 214 and 215

Synthesis of Intermediate B114

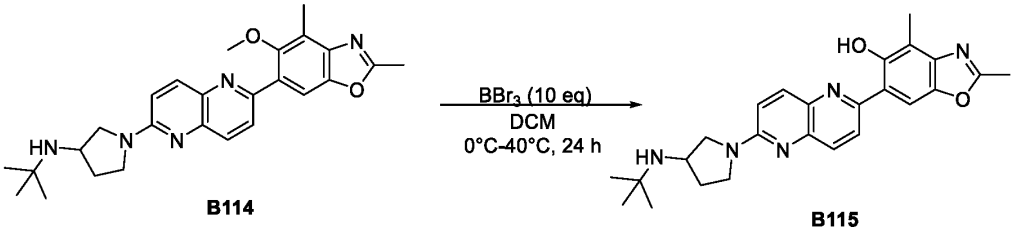


B114

To a stirred mixture of N-tert-butyl-1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (200 mg, 0.462 mmol, 1 equiv) and 6-bromo-5-methoxy-2,4-dimethyl-1,3-benzoxazole (142 mg, 0.554 mmol, 1.2 equiv) in dioxane (20 mL) was added $Pd(DtBPF)Cl_2$ (30 mg, 0.046 mmol, 0.1 equiv) in portions. The reaction mixture was stirred for 3 h at 100°C under N_2 atmosphere, then cooled to room temperature. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford N-tert-butyl-1-[6-(5-methoxy -2,4-dimethyl -1,3-benzoxazol-6-yl) -1,5-naphthyridin -2-yl]pyrrolidin-3-amine (105 mg, 51.04%) as a solid.

LCMS (ES, *m/z*): 446 $[M+H]^+$.

Synthesis of Intermediate B115

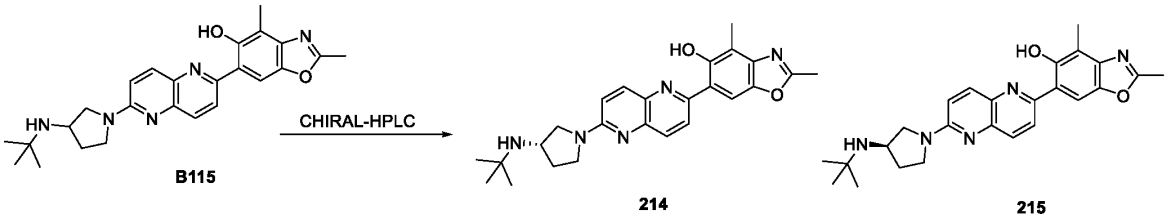


B114 B115

A solution of N-tert-butyl-1-[6-(5-methoxy-2,4-dimethyl -1,3-benzoxazol-6-yl)-1,5-naphthyridin-2-yl] pyrrolidin-3-amine (100 mg, 0.224 mmol, 1 equiv) in DCM (10 mL) was stirred at 0°C. To the solution was added BBr_3 (562 mg, 2.240 mmol, 10 equiv) in portions over 10 min at 0°C. The resulting mixture was stirred for an additional 24 h at 40 °C, then quenched with methanol (15 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 35% B to 55% B in 10 min, 55% B; Wave Length: 220 nm; RT1(min): 8.15) to afford 6-{6-[3-(tert-butylamino) pyrrolidin-1-yl]-1,5-naphthyridin -2-

yl}-2,4 -dimethyl-1,3-benzoxazol-5-ol (50 mg, 51.63%) as a solid. **LCMS** (ES, *m/z*): 432 $[M+H]^+$.

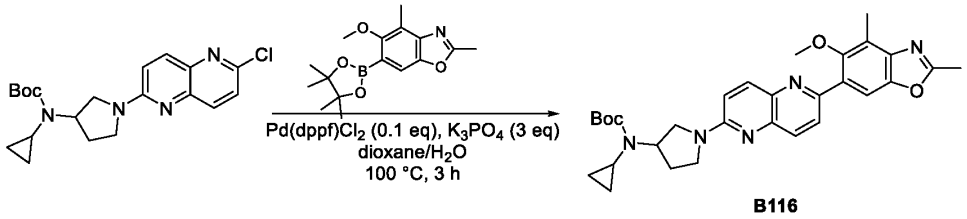
Synthesis of Compounds 214 and 215



6-{6-[3-(tert-butylamino) pyrrolidin-1-yl]-1,5-naphthyridin -2-yl}-2,4 -dimethyl-1,3-benzoxazol-5-ol was further purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2 x 25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 7 min; Wave Length: 220/254 nm; RT_1(min): 5.1; RT_2(min): 5.9; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.5 mL) to afford two enantiomers as solids. The absolute stereochemistry of the enantiomers was arbitrarily assigned. The first peak eluting from the HPLC column was assigned to be Compound **214**, **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.42 (d, J = 9.3 Hz, 1H), 8.26 (s, 1H), 8.14 (d, J = 9.2 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 3.86 (s, 1H), 3.72 (s, 1H), 3.61 – 3.42 (m, 2H), 3.14 (s, 1H), 2.61 (s, 3H), 2.40 (s, 3H), 2.19 (s, 1H), 1.76 (s, 1H), 1.09 (s, 9H) (16.9 mg, 33.80%); and the second peak was assigned to be Compound **215**, **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.99 (s, 1H), 8.42 (d, J = 9.3 Hz, 1H), 8.26 (s, 1H), 8.14 (d, J = 9.3 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 3.87 (s, 1H), 3.72 (s, 1H), 3.55 – 3.46 (m, 2H), 3.14 (s, 1H), 2.61 (s, 3H), 2.40 (s, 3H), 2.18 (s, 1H), 1.76 (s, 1H), 1.10 (s, 9H) (18 mg, 36.00%). **LCMS** (ES, *m/z*): 432 $[M+H]^+$.

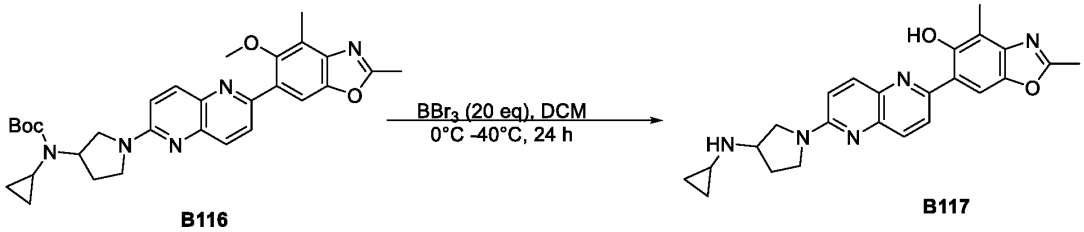
Example 59: Synthesis of Compounds 216 and 217

Synthesis of Intermediate B116



To a stirred solution of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl) pyrrolidin-3-yl] -N-cyclopropyl carbamate (200 mg, 0.514 mmol, 1 equiv) and 5-methoxy-2,4-dimethyl -6-(4,4,5,5-tetramethyl -1,3,2-dioxa borolan-2-yl)-1,3-benzoxazole (234 mg, 0.771 mmol, 1.5 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (42 mg, 0.051 mmol, 0.1 equiv) and K_3PO_4 (327 mg, 1.542 mmol, 3 equiv) in dioxane (16 mL) and H_2O (4 mL) was stirred for 3 h at 100°C under N_2 atmosphere. The mixture was allowed to cool down to room temperature. The resulting mixture was extracted with EtOAc (2 x 20mL). The combined organic layers were washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-cyclopropyl-N-{1-[6-(5-methoxy-2,4-dimethyl -1,3-benzoxazol-6-yl)-1,5-napht hyridin-2-yl]pyrrolidin-3-yl}carbamate (200 mg, 73.43%) as a solid. **LCMS** (ES, *m/z*): 530 $[M+H]^+$.

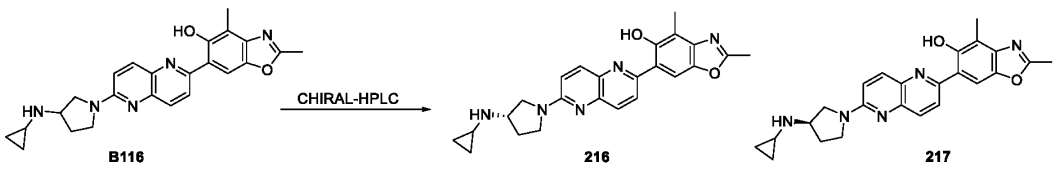
Synthesis of Intermediate B117



B116 **B117**

A solution of tert-butyl N-cyclopropyl-N-{1-[6-(5-methoxy -2,4-dimethyl-1,3-benzoxazol-6-yl) -1,5- naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (180 mg, 0.340 mmol, 1 equiv) in DCM (18 mL) was stirred for 10 min at 0 °C . To the solution was added BBr_3 (851 mg, 3.400 mmol, 10 equiv) dropwise over 15 min at 0 °C. The resulting mixture was stirred for an additional 24 h at 40 °C, then quenched with water (20 mL) at 0 °C. The reaction mixture was neutralized to pH 7 with saturated $NaHCO_3$, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C_{18}, 30 x 150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 40% B to 76% B in 8 min, 76% B; Wave Length: 220 nm; RT1(min): 7.55) to afford 6-{6-[3-(cyclopro pylamino) pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,4-dimethyl-1,3-benzoxazol-5-ol (100 mg, 70.82%) as a solid. **LCMS** (ES, *m/z*): 416 $[M+H]^+$.

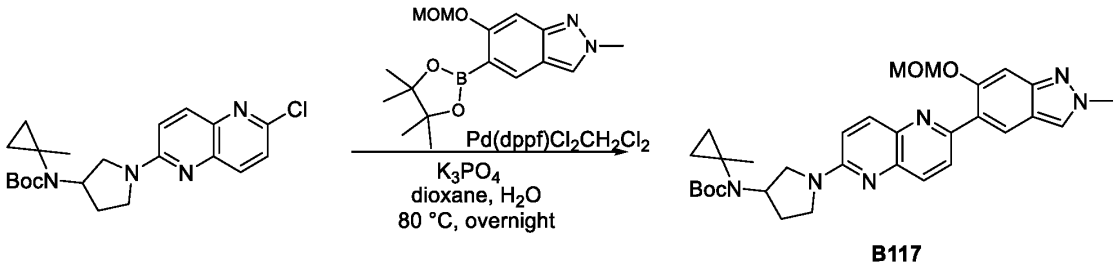
Synthesis of Compounds 216 and 217



6-{6-[3-(cyclopropylamino) pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,4-dimethyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2 x 25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 7 min; Wave Length: 220/254 nm; RT1(min): 5.2; RT2(min): 6.1; Sample Solvent: DCM--HPLC; Injection Volume: 0.45 mL) to afford two enantiomers as solids. The absolute stereochemistry of the enantiomers was arbitrarily assigned. The first peak eluting from the HPLC column was assigned to be Compound **216**, **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 15.00 (s, 1H), 8.42 (d, *J* = 9.2 Hz, 1H), 8.26 (s, 1H), 8.14 (d, *J* = 9.3 Hz, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 7.17 (d, *J* = 9.3 Hz, 1H), 3.75 (s, 1H), 3.66 (s, 1H), 3.59 (s, 1H), 3.51 (s, 2H), 2.57 (s, 3H), 2.40 (s, 3H), 2.13 (s, 2H), 1.93 (s, 1H), 0.41 (d, *J* = 6.7 Hz, 2H), 0.28 – 0.22 (m, 2H) (25 mg, 25.00%); and the second peak was assigned to be Compound **217**, **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 14.98 (s, 1H), 8.41 (d, *J* = 9.2 Hz, 1H), 8.25 (s, 1H), 8.19 – 8.11 (m, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.67 (s, 1H), 3.58 (s, 1H), 3.57 (s, 1H), 3.51 (t, *J* = 5.4 Hz, 1H), 3.42 (s, 1H), 2.61 (s, 3H), 2.40 (s, 3H), 2.13 (s, 2H), 1.93 (s, 1H), 0.42 (dd, *J* = 6.5, 1.4 Hz, 2H), 0.25 (s, 2H) (22.5 mg, 22.50%). **LCMS** (ES, *m/z*): 416 $[M+H]^+$.

Example 60: Synthesis of Compound 219-221

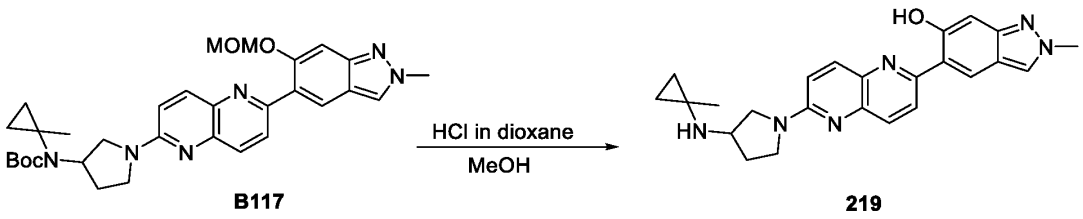
Synthesis of Intermediate B117



To a stirred mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-(1-methylcyclopropyl)carbamate (200 mg, 0.496 mmol, 1 equiv) and 6-(methoxymethoxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (189.52 mg, 0.595 mmol, 1.2

equiv) in 1,4-dioxane and water (0.8 mL) was added $Pd(dppf)Cl_2CH_2Cl_2$ (40.44 mg, 0.050 mmol, 0.1 equiv) and K_3PO_4 (316.09 mg, 1.488 mmol, 3 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 80 °C overnight, then concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-(1-{6-[6-(methoxymethoxy)- 2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (250 mg, 90.15%) as a solid.

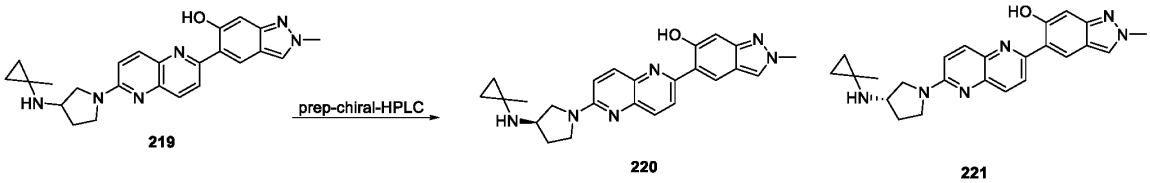
Synthesis of Compound 219



B117 **219**

To a stirred mixture of tert-butyl N-(1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (40 mg, 0.072 mmol, 1 equiv) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL) in portions at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 h, then concentrated under vacuum to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (10% ACN up to 55% in 8 min)) to afford 2-methyl-5-(6-{3-[(1-methylcyclopropyl)amino] pyrrolidin-1-yl}-1,5-naphthyridin-2-yl)indazol-6-ol (14.7 mg, 49.53%) as a solid. **LCMS** (ES, *m/z*): 415 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.98 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, *J* = 13.1, 9.2 Hz, 2H), 7.14 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.78 (s, 1H), 3.65 (s, 2H), 3.54 (s, 1H), 2.13 (dd, *J* = 11.9, 6.3 Hz, 1H), 1.89 (d, *J* = 11.4 Hz, 1H), 1.27 (s, 3H), 0.47 (q, *J* = 10.5 Hz, 2H), 0.33 (d, *J* = 3.4 Hz, 2H).

Synthesis of Compounds 220 and 221

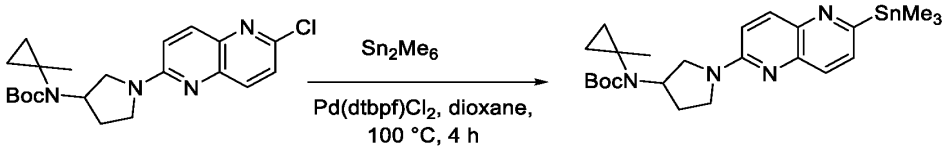


219 **220** **221**

2-methyl-5-(6-{3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl}-1,5-naphthyridin -2-yl)indazol-6-ol (100 mg, 0.241 mmol, 1 equiv) was purified by prep-chiral-HPLC (Column: CHIRAL ART Cellulose-SB, 4.6*100 mm, 3μm; Mobile Phase A: MtBE(0.1%DEA): MeOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford Compound **220** (2-methyl-5-{6-[(3R)-3- [(1-methylcyclopropyl)amino]pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (25.2 mg, 25.20%)) and Compound **221** (2-methyl-5-{6-[(3S)-3-[(1-methylcyclopropyl) amino]pyrrolidin-1-yl]-1,5-naphthyridin -2-yl}indazol-6-ol (22.5 mg, 22.50%)) as solids. The absolute stereochemistry of the compounds was arbitrarily assigned. **220: LCMS** (ESI, *m/z*): 415[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.97 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.79 (s, 1H), 3.66 (s, 2H), 3.55 (s, 1H), 3.31 (s, 1H), 2.15 (s, 1H), 1.91 (s, 1H), 1.26 (d, *J* = 19.3 Hz, 4H), 0.49 (s, 2H), 0.35 (s, 2H). **221: LCMS** (ESI, *m/z*): 415[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 13.97 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.79 (s, 1H), 3.66 (s, 2H), 3.54 (s, 1H), 3.32 (s, 1H), 2.14 (s, 1H), 1.91 (s, 1H), 1.26 (d, *J* = 16.1 Hz, 4H), 0.48 (s, 2H), 0.34 (s, 2H).

Example 61: Synthesis of Compounds 222 and 223

Synthesis of Intermediate B118

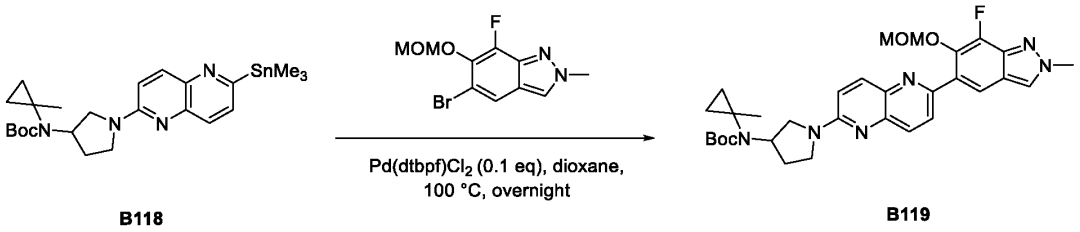


B118

To a stirred mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-(1-methylcyclopropyl)carbamate (600 mg, 1.489 mmol, 1 equiv) and Pd(DtBPF)Cl_2 (97.05 mg, 0.149 mmol, 0.10 equiv) in dioxane (30 mL) was added Sn_2Me_6 (731.83 mg, 2.234 mmol, 1.5 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 100 °C under nitrogen atmosphere, then quenched with saturated KF at room temperature. The resulting mixture was extracted with ethyl acetate (2 x 20 mL). The organic layers were combined, washed with brine (2x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl-N-(1-

methylcyclopropyl)-N-{1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (800 mg, 101.12%) as an oil.

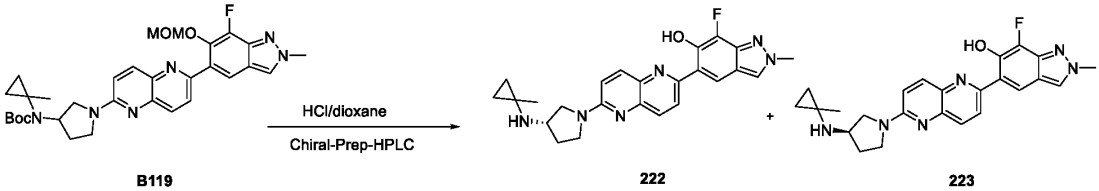
Synthesis of Intermediate B119



B118 B119

To a stirred mixture of 5-bromo-7-fluoro-6-(methoxymethoxy)-2-methylindazole (195.9 mg, 0.678 mmol, 1.2 equiv) and $Pd(DtBPF)Cl_2$ (36.80 mg, 0.056 mmol, 0.1 equiv) in dioxane (15 mL) was added tert-butyl-N-(1-methylcyclopropyl)-N-{1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (300 mg, 0.565 mmol, 1 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 100 °C under nitrogen atmosphere, then quenched with water at room temperature. The resulting mixture was extracted with ethyl acetate (2 x20 mL). The organic layers were combined, washed with brine (2x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3:1) to afford tert-butyl N-(1-{6-[7-fluoro-6-(methoxymethoxy)-2-methylindazol-5-yl] -1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (130 mg, 39.92%) as a solid. **LCMS** (ES, *m/z*): 577 $[M+H]^+$.

Synthesis of Compounds 222 and 223



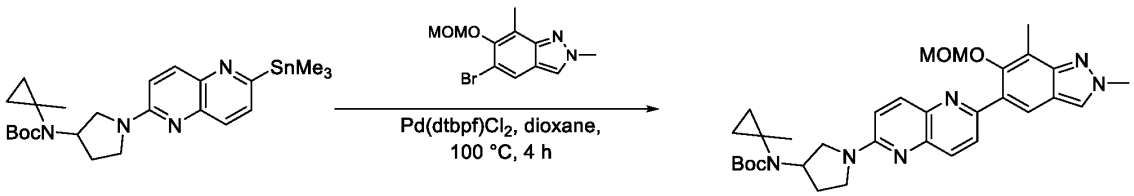
B119 222 223

To a stirred solution of tert-butyl N-(1-{6-[7-fluoro-6-(methoxymethoxy)-2-methylindazol-5-yl] -1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (100 mg, 0.173 mmol, 1 equiv) in methanol (2 mL) was added HCl (gas) in 1,4-dioxane (2 mL) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere, then filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-

HPLC ((SHIMADZU (HPLC-01)): Column, CHIRAL ART Cellulose-SB, 2*25 cm, 5 um; mobile phase, MtBE (0.1% DEA) and MeOH- (hold 15% MeOH- in 10 min); Detector, UV 220nm product was obtained which Alpha) to afford 7-fluoro-2-methyl-5-{6-[(3S)-3- [(1-methylcyclopropyl)amino]pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (12.9 mg, 17.20%) and 7-fluoro-2-methyl-5-{6-[(3R)-3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl] -1,5-naphthyridin-2-yl}indazol-6-ol (13.3 mg, 17.73%) as solids. The absolute stereochemistry of the compounds was arbitrarily assigned. **222: LCMS** (ES, *m/z*): 433 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.44 (s, 1H), 8.48 (d, *J* = 2.7 Hz, 1H), 8.41 (dd, *J* = 5.1, 4.2 Hz, 2H), 8.14 (d, *J* = 9.3 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 4.16 (s, 3H), 3.79 (s, 1H), 3.67 (s, 2H), 3.54 (d, *J* = 9.6 Hz, 1H), 3.34 (s, 1H), 2.14 (s, 1H), 1.91 (s, 1H), 1.27 (s, 3H), 0.49 (d, *J* = 11.6 Hz, 2H), 0.35 (s, 2H). **223: LCMS** (ES, *m/z*): 433 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.44 (s, 1H), 8.48 (d, *J* = 2.7 Hz, 1H), 8.41 (dd, *J* = 5.1, 4.2 Hz, 2H), 8.14 (d, *J* = 9.3 Hz, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 4.16 (s, 3H), 3.79 (s, 1H), 3.67 (s, 2H), 3.54 (d, *J* = 9.6 Hz, 1H), 3.34 (s, 1H),2.15 (s, 1H), 1.90 (s, 1H), 1.26 (d, *J* = 17.8 Hz, 3H), 0.53 – 0.46 (m, 2H), 0.38 – 0.34 (m, 2H).

Example 62: Synthesis of Compound 224-226

Synthesis of Intermediate B120

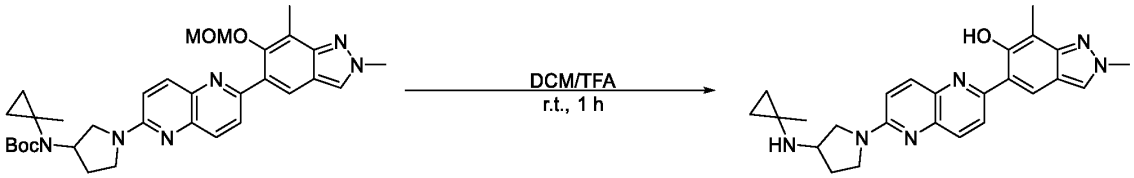


B120

A mixture of 5-bromo-6-(methoxymethoxy)-2,7-dimethylindazole (135.78 mg, 0.476 mmol, 1.1 equiv) and Pd(DtBPF)Cl_2 (28.21 mg, 0.043 mmol, 0.1 equiv) in 1,4-dioxane (10 mL) was stirred for 45 min at 100 °C under nitrogen atmosphere. To the reaction mixture was added tert-butyl N-(1-methylcyclopropyl)-N-{1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (460 mg, 0.433 mmol, 1 equiv, 50%) in 1,4-dioxane (10 mL) dropwise over 15 min at 100 °C. The resulting mixture was stirred for an additional 4 h at 100 °C. The reaction mixture was cooled to room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with

CH_2Cl_2/MeOH (10:1) to afford tert-butyl N-(1-{6-[6-(methoxymethoxy)-2,7-dimethylindazol -5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (175 mg, 51.53%) as a solid. **LCMS** (ESI, *m/z*): 573[M+H]$^+$.

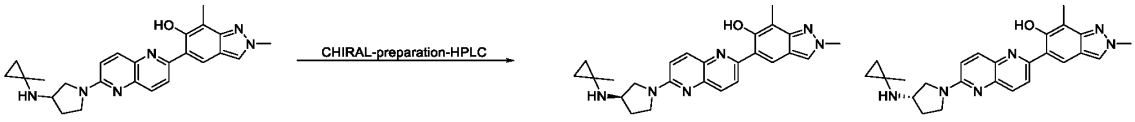
Synthesis of Intermediate 224



B120 **224**

To a stirred solution of tert-butyl N-(1-{6-[6-(methoxymethoxy)-2,7-dimethylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (160 mg, 0.279 mmol, 1 equiv) in DCM (16 mL) was added TFA (1.6 mL) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 1 h at room temperature under air atmosphere. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 65% B in 8 min; Wave Length: 220 nm; RT1(min): 7.87.) to afford 2,7-dimethyl-5-(6-{3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl}-1,5-naphthyridin-2-yl) indazol-6-ol (48 mg, 39.59%) as a solid. **LCMS** (ESI, *m/z*): 429[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 14.34 (s, 1H), 8.47 – 8.35 (m, 2H), 8.32 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.13 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.72 – 3.58 (m, 2H), 3.53 (t, *J* = 8.6 Hz, 1H), 2.38 (s, 3H), 2.20 – 2.07 (m, *J* = 5.5 Hz, 1H), 1.88 (p, *J* = 6.8 Hz, 1H), 1.26 (s, 3H), 1.23 (d, *J* = 2.7 Hz, 1H), 1.20-1.02 (m, 1H), 0.56 – 0.39 (m, 2H), 0.33 (d, *J* = 3.2 Hz, 2H).

Synthesis of Compound 225 and 226

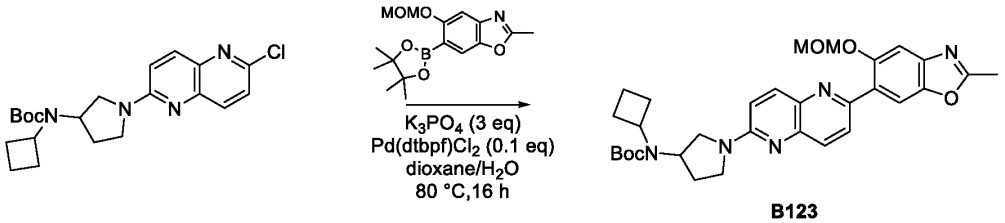


224 **225** First Peak **226** Second Peak

The racemic (2,7-dimethyl-5-(6-{3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl}-1,5-naphthyridin -2-yl)indazol-6-ol (38 mg, 0.088 mmol, 1 equiv, 98.751%)) was purified by Chiral-Prep-HPLC (Column: CHIRAL ART Cellulose-SB, 2x25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 8 min; Wave Length: 220/254 nm; RT1(min): 6.2; RT2(min): 7.2; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.5 mL; Number Of Runs: 11; Column temperature: room temperature) to afford two isolated solids. The first isolated solid (First Peak:14 mg) was further purified by Prep-HPLC (Column: Xselect CSH C18 OBD Column 30x150mm 5μm, n; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 90% B in 8 min; Wave Length: 220 nm; RT1(min): 6.58.) to afford 2,7-dimethyl-5-{6-[(3R)-3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (6.1 mg, 16.14%) as a solid. **LCMS** (ESI, *m/z*): 429[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 14.33 (s, 1H), 8.42 – 8.35 (m, 2H), 8.32 (s, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.77 (d, *J* = 8.6 Hz, 1H), 3.72 – 3.58 (m, 2H), 3.53 (q, *J* = 8.0 Hz, 1H), 3.30 (d, *J* = 4.4 Hz, 1H), 2.38 (s, 3H), 2.13 (dq, *J* = 12.8, 6.3 Hz, 1H), 1.88 (dd, *J* = 12.4, 6.8 Hz, 1H), 1.27 (s, 3H), 0.58 – 0.39 (m, 2H), 0.39 – 0.25 (m, 2H). The second isolated solid (Second Peak: 12 mg) was purified by Prep-HPLC (Column: Xselect CSH C18 OBD Column 30x150mm 5μm, n; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 90% B in 8 min; Wave Length: 220 nm; RT1(min): 6.58.) to afford 2,7-dimethyl-5-{6-[(3S)-3-[(1-methylcyclopropyl) amino]pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}indazol-6-ol (6.6 mg, 17.53%) as a solid. **LCMS** (ESI, *m/z*): 429 [M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6): δ 14.33 (s, 1H), 8.48 – 8.34 (m, 2H), 8.32 (s, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.76 (d, *J* = 8.9 Hz, 1H), 3.72 – 3.58 (m, 2H), 3.53 (q, *J* = 7.9 Hz, 1H), δ 3.31 (s, 1H), 2.38 (s, 3H), 2.19 – 2.07 (m, 1H), 1.96 – 1.81 (m, 1H), 1.26 (s, 3H), 0.48 (tt, *J* = 10.9, 6.0 Hz, 2H), 0.39 – 0.27 (m, 2H). The absolute stereochemistry of the compounds was arbitrarily assigned.

Example 64: Synthesis of Compound 228

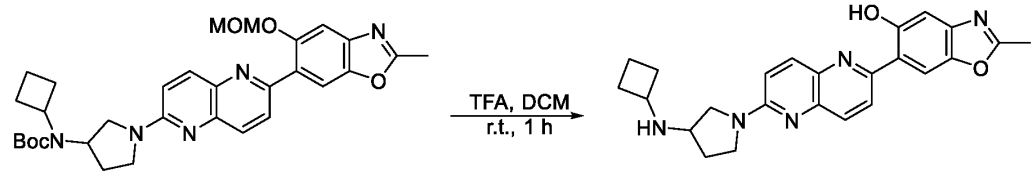
Synthesis of Intermediate B123



B123

A mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-cyclobutylcarbamate (450 mg, 1.117 mmol, 1 equiv), 5-(methoxymethoxy)-2-methyl-6-(4,4,5,5-tetramethyl -1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (891 mg, 2.792 mmol, 2.5 equiv), K_3PO_4 (711 mg, 3.351 mmol, 3 equiv), and $Pd(DtBPF)Cl_2$ (73 mg, 0.112 mmol, 0.1 equiv) in 1,4-dioxane (9 mL) and water (1.8 mL) was stirred for 16 h at 80°C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was extracted with ethyl acetate (1 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-cyclobutyl-N-(1-{6-[5-(methoxymethoxy)-2-methyl -1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (340 mg, 54.39%) as a solid. **LCMS** (ES, *m/z*): 560 $[M+H]^+$.

Synthesis of Compound 228



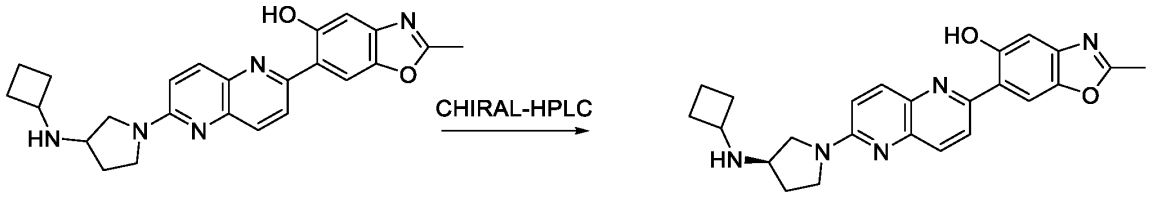
B123 **228**

A mixture of tert-butyl N-cyclobutyl-N-(1-{6-[5-(methoxymethoxy)-2-methyl-1,3-benzoxazol -6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (340 mg, 0.608 mmol, 1 equiv) in DCM (2 mL) and TFA (1 mL) was stirred for 1 h at room temperature . The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 70% B in 8 min, 70% B; Wave Length: 220 nm; RT1(min): 6.13) to afford 6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -2-methyl-1,3-benzoxazol-5-ol (11 mg, 4.34%) as a solid. **LCMS** (ES, *m/z*): 416 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.53

(s, 1H), 8.45 – 8.39 (m, 2H), 8.15 – 8.05 (m, 1H), 8.09 (s, 1H), 7.18 (m, 1H),7.09 (m, 1H), 3.70 (s, 2H), 3.55 (d, J = 9.5 Hz, 1H), 3.39 (s, 2H), 3.27 (s, 1H), 2.61 (s, 3H), 2.54 (s, 3H), 1.82 (d, J = 6.0 Hz, 1H), 1.73 (s, 2H), 1.60 (s, 2H).

Example 65: Synthesis of Compound 229

Synthesis of Compound 228

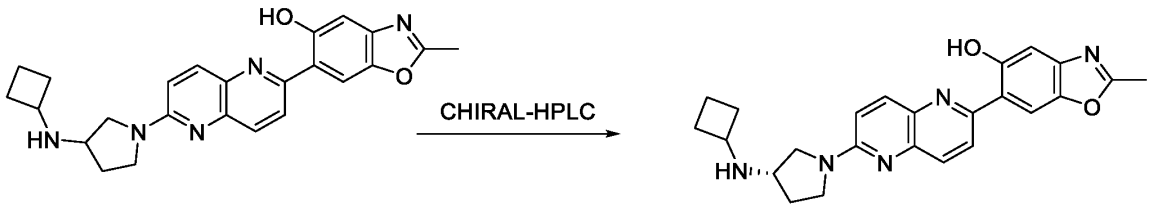


228 **229**

6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -2-methyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2x25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 6.3; RT2(min): 7.9; Sample Solvent: MeOH: DCM=1: 2; Injection Volume: 0.45 mL; Number Of Runs: 17) to afford Compound **228** (First Peak) (36.6 mg, 30.44%) as a solid. **LCMS** (ES, *m/z*): 416 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.51 (s, 1H), 8.46 – 8.39 (m, 2H), 8.14 (d, J = 18.4, 9.2 Hz, 1H), 8.08 (d, J = 18.4, 9.2 Hz, 1H), 7.16 (d, J = 9.3 Hz, 1H), 7.12 (s, 1H), 3.71 (s, 2H), 3.58 (d, J = 8.7 Hz, 1H), 3.55 (d, J = 8.7 Hz, 1H),3.44 (s, 2H), 2.61 (s, 3H), 2.15 (s, 3H), 1.87 (s, 1H), 1.76 (s, 2H), 1.60 (dt, J = 18.7, 9.2 Hz, 2H). The absolute stereochemistry of the compound was arbitrarily assigned.

Example 66: Synthesis of Compound 230

Synthesis of Compound 230

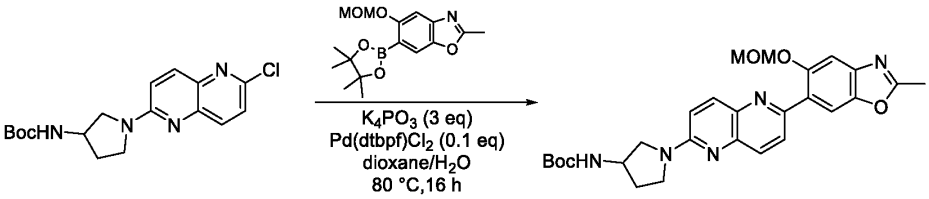


228 **230**

6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -2-methyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2x25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 8.5 min; Wave Length: 220/254 nm; RT1(min): 6.3; RT2(min): 7.9; Sample Solvent: MeOH: DCM=1: 2; Injection Volume: 0.45 mL; Number Of Runs: 17) to afford Compound **230** (Second Peak) (29.9 mg, 24.54%) as a solid. **LCMS** (ES, *m/z*): 416 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.50 (s, 1H), 8.43 (d, J = 9.4 Hz, 2H), 8.15 (d, J = 9.2 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.18 (d, J = 9.3 Hz, 1H), 7.12 (s, 1H), 3.76 (dd, J = 10.9, 6.0 Hz, 2H), 3.69 (s, 1H), 3.57 (q, J = 8.1, 7.6 Hz, 1H), 3.43 (s, 2H), 2.61 (s, 3H), 2.48 (s, 3H), 2.24 – 2.12 (m, 1H), 1.83 (s, 2H), 1.73 – 1.57 (m, 2H). The absolute stereochemistry of the compound was arbitrarily assigned.

Example 67: Synthesis of Compound 231-234

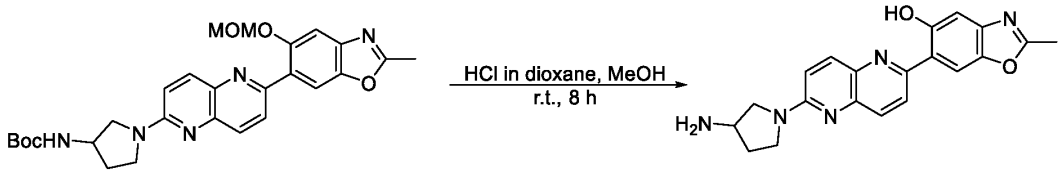
Synthesis of Intermediate B124



B124

A mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]carbamate (400 mg, 1.147 mmol, 1 equiv), 5-(methoxymethoxy)-2-methyl -6-(4,4,5,5-tetramethyl-1,3,2-dioxab orolan-2-yl)-1,3-benzoxazole (549 mg, 1.720 mmol, 1.5 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (93 mg, 0.115 mmol, 0.1 equiv), and K_3PO_4 (730 mg, 3.441 mmol, 3 equiv) in dioxane (12 mL) and water (3 mL) was stirred for 16 h at 100 °C under N_2 atmosphere. The reaction mixture was cooled to room temperature, then extracted with ethyl acetate (2 x 30 mL). The organic layers were combined, washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford tert-butyl N-(1-{6-[5-(methoxymethoxy)-2-me thyl-1,3-benzoxazo l-6-yl]-1,5 -naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (400 mg, 69.00%) as a solid. **LCMS** (ES, *m/z*): 506 $[M+H]^+$.

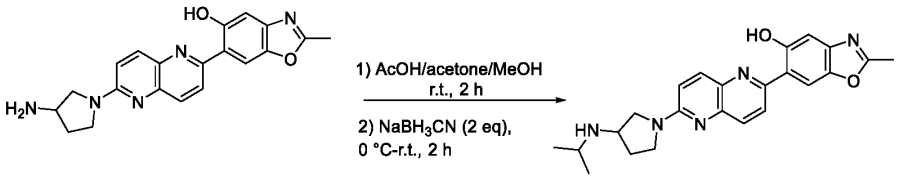
Synthesis of Compound 234



B124 234

A mixture of tert-butyl N-(1-{6-[5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl] -1,5-naph thyridin-2-yl}pyrrolidin-3-yl)carbamate (320 mg, 0.633 mmol, 1 equiv) and HCl (gas) in 1,4-dioxane (3.2 mL, 105.318 mmol, 166.39 equiv) in methanol (32 mL) was stirred for 8 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC ((Column: YMC-Actus Triart C18, 30 x 150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 55% B in 8 min, 55% B; Wave Length: 220 nm; RT1(min): 7.35) to afford 6-[6-(3-aminopyrrolidin-1-y l)-1,5-naphthyridin-2-yl]-2-meth yl-1,3- benzoxazol-5-ol (12.3 mg, 28.68%) as a solid. **LCMS** (ES, *m/z*): 362 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.54 (s, 1H), 8.46 – 8.39 (m, 2H), 8.12 (d, *J* = 9.3 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 7.12 (s, 1H), 3.70 (dd, *J* = 10.3, 5.8 Hz, 2H), 3.62 (dd, *J* = 10.8, 5.6 Hz, 2H), 3.32 (s, 1H), 2.61 (s, 3H), 2.09 (dt, *J* = 13.0, 6.5 Hz, 3H), 1.82 – 1.74 (m, 1H).

Synthesis of Compound 231

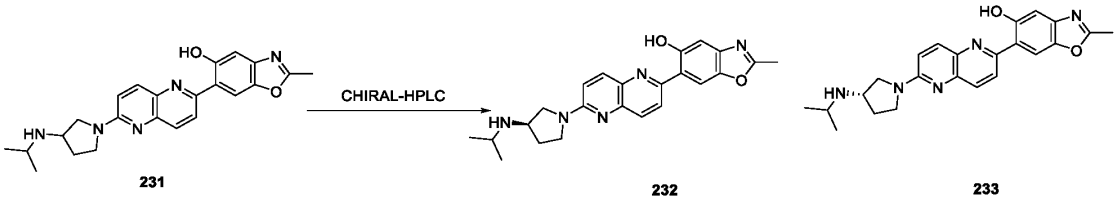


234 231

A mixture of 6-[6-(3-aminopyrrolidin-1-yl)-1,5-naphthyridin-2-yl]-2-methyl-1,3-benzoxazol-5-ol (400 mg, 1.107 mmol, 1 equiv) and acetone (1.7 mL) in AcOH (1.7 mL) and MeOH (8.5 mL) was stirred for 2 h at room temperature. To the reaction mixture was added $NaBH_3CN$ (139 mg, 2.214 mmol, 2 equiv) in portions over 10 min at 0 °C. The resulting mixture was stirred for an additional 4 h at room temperature, then quenched with water at 0 °C to form a precipitate. The precipitated solid was collected by filtration and washed with DCM (3 x 20 mL). The resulting mixture was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate

was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: Xselect CSH C_{18} OBD Column 30 x 150mm 5μm, n; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 6.58) to afford 6-{6-[3-(isopropylamino) pyrrolidin-1-yl] -1,5-naphthyridin-2-yl}-2-methyl-1,3-benzoxazol-5-ol (17.2 mg, 3.85%) as a solid. **LCMS** (ES, *m/z*): 404 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.45 – 8.38 (m, 2H), 8.10 (ddd, *J* = 14.1, 9.2, 0.8 Hz, 2H), 7.16 (d, *J* = 9.3 Hz, 1H), 7.11 (s, 1H), 3.78 (d, *J* = 8.2 Hz, 1H), 3.70 (s, 1H), 3.60 – 3.48 (m, 2H), 3.31 (s, 1H), 2.86 (p, *J* = 6.2 Hz, 1H), 2.61 (s, 3H), 2.16 (dq, *J* = 12.4, 6.2 Hz, 1H), 1.80 (dt, *J* = 14.3, 7.3 Hz, 2H), 1.02 (dd, *J* = 6.2, 4.5 Hz, 6H).

Synthesis of Compounds 232 and 233

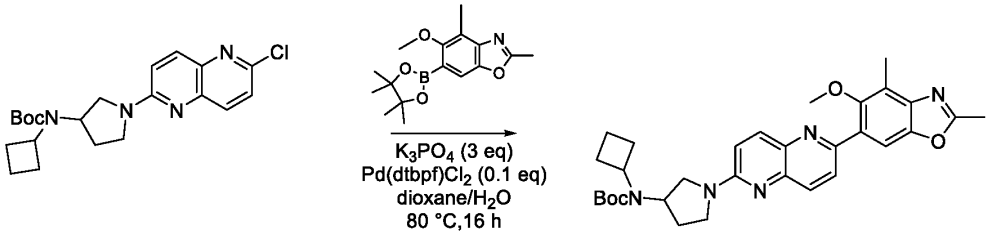


231 232 233

6-{6-[3-(isopropylamino) pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2 x 25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 7 min; Wave Length: 220/254 nm; RT1(min): 4.9; RT2(min): 6.2; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.45 mL) to afford Compound **232** (First Peak) (20.4 mg, 25.50%) and Compound **233** (Second Peak) (20.7 mg, 25.87%) as solids. **232: LCMS** (ES, *m/z*): 404 $[M+H]^+$. **^{1}H NMR**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.46 – 8.39 (m, 2H), 8.11 (dd, *J* = 15.0, 9.2 Hz, 2H), 7.17 (d, *J* = 9.3 Hz, 1H), 7.12 (s, 1H), 3.80 (s, 1H), 3.71 (s, 1H), 3.55 (d, *J* = 11.3 Hz, 2H), 3.32 (s, 1H), 2.86 (s, 1H), 2.61 (s, 3H), 2.16 (dd, *J* = 12.2, 6.2 Hz, 1H), 1.81 (s, 2H), 1.03 (dd, *J* = 6.2, 4.4 Hz, 6H). **233: LCMS** (ES, *m/z*): 404 $[M+H]^+$. **^{1}H NMR**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.46 – 8.39 (m, 2H), 8.11 (dd, *J* = 15.0, 9.3 Hz, 2H), 7.17 (d, *J* = 9.3 Hz, 1H), 7.12 (s, 1H), 3.80 (s, 1H), 3.71 (s, 1H), 3.53 (s, 2H), 3.32 (s, 1H), 2.86 (s, 1H), 2.61 (s, 3H), 2.19 – 2.12 (m, 1H), 1.81 (s, 2H), 1.02 (dd, *J* = 6.2, 4.4 Hz, 6H). The absolute stereochemistry of the compounds was arbitrarily assigned.

Example 68: Synthesis of Compound 235

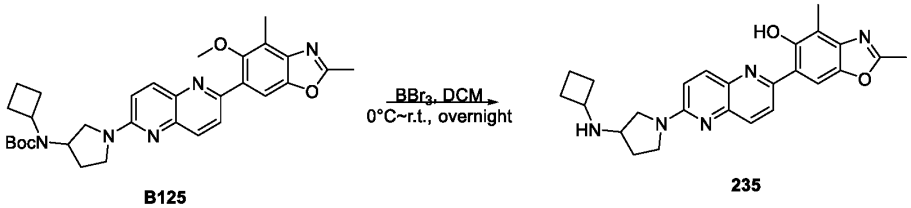
Synthesis of Intermediate B125



B125

A mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-cyclobutylcarbamate (450 mg, 1.117 mmol, 1 equiv), 5-methoxy-2,4-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (406.31 mg, 1.340 mmol, 1.2 equiv), K_3PO_4 (711 mg, 3.351 mmol, 3 equiv), and Pd(DtBPF)Cl_2 (72.79 mg, 0.112 mmol, 0.1 equiv) in 1,4-dioxane (9 mL) and water (1.8 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was extracted with ethyl acetate (1 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-cyclobutyl-N-{1-[6-(5-methoxy-2,4-dimethyl-1,3-benzoxazol-6-yl) -1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (500 mg, 82.35%) as a solid. **LCMS** (ES, *m/z*): 544 $[M+H]^+$.

Synthesis of Compound 235



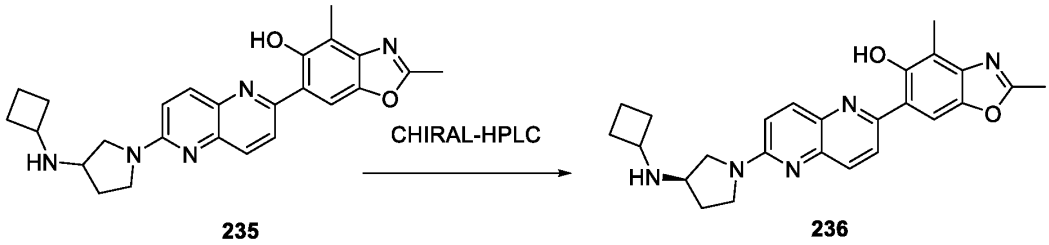
B125 **235**

A mixture of tert-butyl N-cyclobutyl-N-{1-[6-(5-methoxy-2,4-dimethyl-1,3-benzoxazol-6-yl) -1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (50 mg, 0.092 mmol, 1 equiv) and BBr_3 (461 mg, 1.840 mmol, 20 equiv) in DCM (1 mL) was stirred for 4 h at 0 °C~r.t.. The reaction mixture was quenched with methanol (10 mL) at 0 °C, then acidified to pH 9 with saturated $NaHCO_3$ (aq.). The resulting mixture was concentrated under reduced pressure to give a residue. The resulting residue was extracted with CH_2Cl_2 (1 x 10 mL), dried over anhydrous Na_2SO_4, and

filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: Xselect CSH C18 OBD Column 30x150mm 5μm, n; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 25% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 7.77) to afford 6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,4-dimethyl-1,3-benzoxazol-5-ol (12 mg, 29.71%) as a solid. **LCMS** (ES, *m/z*): 430 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.99 (s, 1H), 8.41 (d, *J* = 9.3 Hz, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 9.3 Hz, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 9.3 Hz, 1H), 3.68(d,2H),3.54 (d, *J* = 9.5 Hz, 1H), 3.40 (s, 1H), 3.27 (d, *J* = 7.6 Hz, 2H), 2.61 (s, 3H), 2.40 (s, 3H), 2.20 – 2.06 (m, 3H), 1.87 – 1.80 (m, 1H), 1.76 – 1.68 (m, 2H), 1.60 (dddd, *J* = 18.1, 15.0, 12.3, 7.0 Hz, 2H).

Example 69: Synthesis of Compound 236

Synthesis of Compound 236

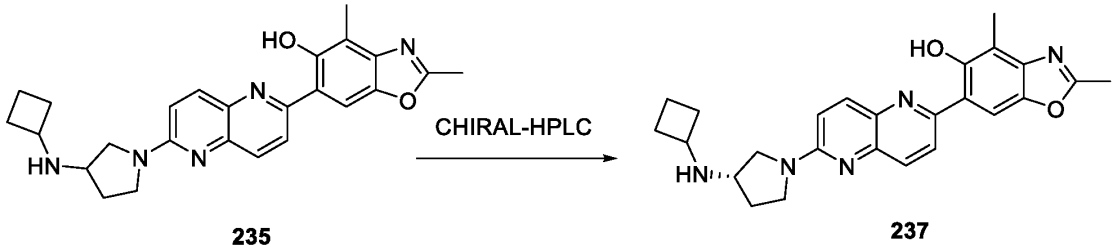


235 **236**

6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,4-dimethyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2 x 25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 6.5 min; Wave Length: 220/254 nm; RT1(min): 4.9; RT2(min): 5.8; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.26 mL; Number Of Runs: 25) to afford Compound **236** (First Peak) (84.9 mg, 44.59%) as a solid. **LCMS** (ES, *m/z*): 430 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.99 (s, 1H), 8.41 (d, *J* = 9.3 Hz, 1H), 8.25 (s, 1H), 8.14 (d, *J* = 26.1, 9.2 Hz, 1H), 8.07 (d, *J* = 26.1, 9.2 Hz, 1H),7.15 (d, *J* = 9.3 Hz, 1H), 3.69 (d, *J* = 6.4 Hz, 2H), 3.54 (d, *J* = 9.0 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.25 (q, *J* = 7.7 Hz, 2H), 2.61 (s, 3H), 2.40 (s, 3H), 2.20 – 2.05 (m, 4H), 1.86 – 1.79 (m, 2H), 1.75 – 1.49 (m, 2H). The absolute stereochemistry of the compound was arbitrarily assigned.

Example 70: Synthesis of Compound 237

Synthesis of Compound 237

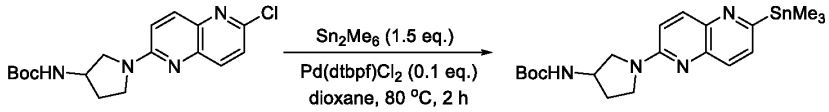


235 **237**

6-{6-[3-(cyclobutylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,4-dimethyl-1,3-benzoxazol-5-ol was purified by CHIRAL-HPLC (Column: CHIRAL ART Cellulose-SB, 2 x 25 cm, 5 μm; Mobile Phase A: MtBE(0.1% DEA)-HPLC, Mobile Phase B: MeOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 6.5 min; Wave Length: 220/254 nm; RT1(min): 4.9; RT2(min): 5.8; Sample Solvent: MeOH: DCM=1: 1; Injection Volume: 0.26 mL; Number Of Runs: 25) to afford Compound **237** (Second Peak) (89.9 mg, 46.75%) as a solid. **LCMS** (ES, *m/z*): 430 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.99 (s, 1H), 8.41 (d, J = 9.3 Hz, 1H), 8.25 (s, 1H), 8.14 (d, J = 9.3 Hz, 1H), 8.07 (dd, J = 9.1, 0.7 Hz, 1H), 7.15 (d, J = 9.3 Hz, 1H), 3.69 (d, J = 6.4 Hz, 2H),3.54 (d, J = 8.9 Hz, 1H), 3.30 (s, 1H), 3.25 (d, J = 7.6 Hz, 2H), 2.61 (s, 3H), 2.47 (d, J = 3.7 Hz, 3H), 2.40 (s, 4H), 2.20 – 2.05 (m, 1H), 1.87 – 1.79 (m, 2H), 1.72 – 1.50 (m, 2H). The absolute stereochemistry of the compound was arbitrarily assigned.

Example 71: Synthesis of Compound 238

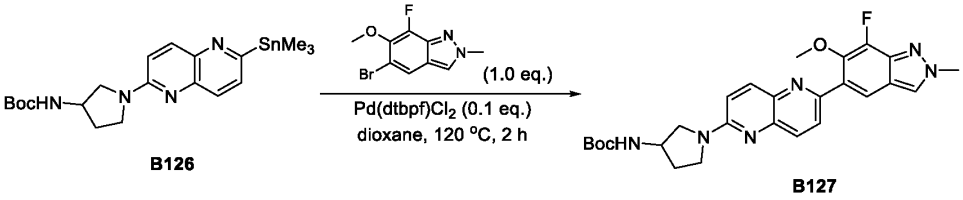
Synthesis of Intermediate B126



B126

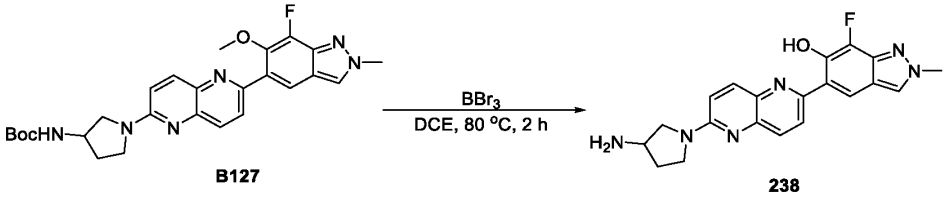
A mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl) pyrrolidin-3-yl] carbamate (800 mg, 2.29 mmol, 1.00 equiv), Sn_2Me_6 (1127.1 mg, 3.44 mmol, 1.50 equiv), $Pd(dtbpf)Cl_2$ (149.5 mg, 0.23 mmol, 0.10 equiv), and dioxane (24 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was washed with KF (aq.) (1 x 50 mL). The organic layers were combined, washed with ethyl acetate (3x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl N-{1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl] pyrrolidin-3-yl} carbamate (1 g). **LCMS** (ES, *m/z*):479 $[M+H]^+$.

Synthesis of Intermediate B127



A mixture of 5-bromo-7-fluoro-6-methoxy-2-methylindazole (380 mg, 1.47 mmol, 1.00 equiv) and $Pd(dtbpf)Cl_2$ (95.6 mg, 0.14 mmol, 0.10 equiv) in dioxane (14 mL) was stirred for 30 min at 120 °C under nitrogen atmosphere. To the reaction mixture was added tert-butyl N-{1-[6-(trimethylstannyl)-1,5- naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (700 mg, 1.47 mmol, 1.00 equiv) in dioxane (10 mL) dropwise at 120 °C. The resulting mixture was stirred for 2 h at 120 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford tert-butyl N-{1-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5-naphthyridin-2-yl] pyrrolidin-3-yl} carbamate (500 mg, 69.20%) as a solid. **LCMS** (ES, *m/z*):493 $[M+H]^+$.

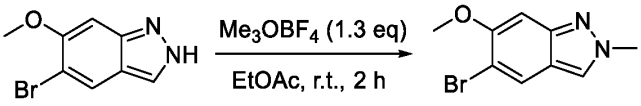
Synthesis of Compound 238



A mixture of tert-butyl N-{1-[6-(7-fluoro-6-methoxy-2-methylindazol-5-yl)-1,5- naphthyridin-2-yl] pyrrolidin-3-yl} carbamate (40 mg, 0.08 mmol, 1.00 equiv), DCE (1.20 mL), and BBr_3 (0.40 mL) was stirred for 2 h at 80 °C under nitrogen atmosphere, then basified to pH 8 with NH_3 in methanol. The mixture was purified by Prep-HPLC ((2 SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (5% ACN up to 50% in 8 min) to afford 5-[6-(3-aminopyrrolidin-1-yl)-1,5-naphthyridin-2-yl]-7-fluoro-2-methylindazol -6-ol (10 mg, 31.76%) as a solid. **LCMS** (ES, *m/z*):379 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.42 (s, 1H), 8.48 (d, J = 2.6 Hz, 1H), 8.43 – 8.36 (m, 2H), 8.13 (d, J = 9.3 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.15 (d, J = 9.2 Hz, 1H), 4.16 (s, 3H), 3.70 (dd, J = 10.5, 5.8 Hz, 2H), 3.67 – 3.52 (m, 2H), 3.21-3.08 (m, 1H), 2.11 (dt, J = 12.5, 6.5 Hz, 1H), 1.83 – 1.71 (m, 1H).

Example 74: Synthesis of Compounds 127, 153, and 154

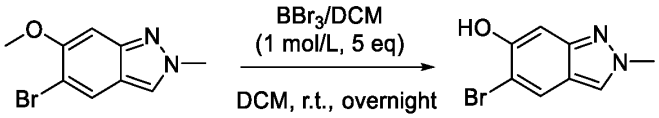
Synthesis of Intermediate B131



B131

5-bromo-6-methoxy-2H-indazole (8.90 g, 1.00 equiv) and Me_4OBF_4 (7.61 g, 1.30 equiv) were combined in ethyl acetate (180.00 mL) at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with a half-saturation sodium bicarbonate solution (150 mL), then extracted with ethyl acetate (3 x 50 mL) and washed with sat. NaCl (1 x 50 mL). The organic layers were combined, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford 5-bromo-6-methoxy-2-methylindazole (8.64 g) as a solid. **LCMS** (ES, *m/z*): 241 $[M+H]^+$.

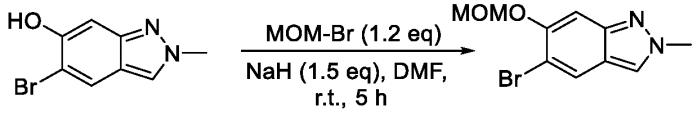
Synthesis of Intermediate B132



B131 **B132**

To a stirred solution of 5-bromo-6-methoxy-2-methylindazole (8.41 mL, 35.000 mmol, 1.00 equiv) in DCM (90.00 mL) was added BBr_3 (175.21 g, 175.210 mmol, 5.00 equiv) dropwise at room temperature. The reaction mixture was stirred for 3 h at room temperature, then quenched with methanol (150 mL). The resulting mixture was concentrated under reduced pressure to give a residue. To the residue was added DCM, and the solution was adjusted to pH 8 with a saturated sodium bicarbonate solution. A precipitate formed that was filtered and dried to afford 5-bromo-2-methylindazol-6-ol (7.032 g) as a solid. **LCMS** (ES, *m/z*): 227 $[M+H]^+$.

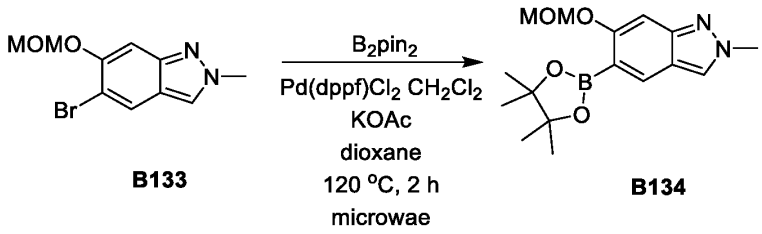
Synthesis of Intermediate B133



B132 **B133**

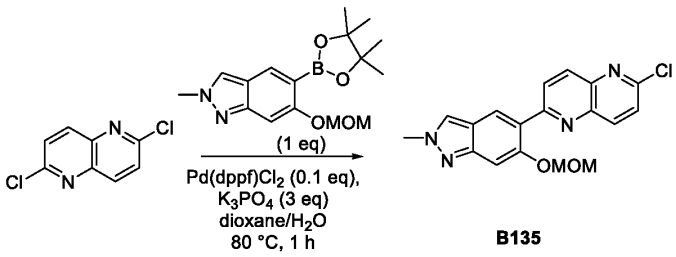
To a stirred solution of 5-bromo-2-methylindazol-6-ol (5.96 g) in DMF (120.00 mL) was added NaH (1.58 g, 1.50 equiv) at 0°C. The reaction mixture was stirred at 0 °C for 30 minutes. To the reaction mixture was added bromomethoxymethane (4.28 g, 1.30 equiv) dropwise at 0 °C over the course of 10 minutes. The reaction mixture was stirred for an additional 3 h at 0 °C. The reaction mixture was quenched with water/ice (150 mL) at room temperature and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with NaCl (aq) (5 x 100 mL), dried over anhydrous Na_2SO_4, and filtered to afford 5-bromo-6-(methoxymethoxy)-2-methylindazole(6.9g) as a solid. **LCMS** (ES, *m/z*): 271 $[M+H]^+$.

Synthesis of Intermediate B134



5-bromo-6-(methoxymethoxy)-2-methylindazole (5.70 g, 1.00 equiv), B_2pin_2 (10.21 g, 2.00 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (1.71 g, 0.10 equiv), and KOAc (6.20 g, 3.00 equiv) were combined in dioxane (68.40 mL) at 20 °C. The reaction mixture was irradiated with microwave radiation for 2 h at 120 °C. The resulting mixture was extracted with ethyl acetate (3 x 30 mL), then filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 6-(methoxymethoxy)-2-methyl-5-(4,4,5-trimethyl-1,3,2-dioxaborolan-2-yl) indazole (crude product 18.22 g) as an oil. **LCMS** (ES, *m/z*): 319 $[M+H]^+$.

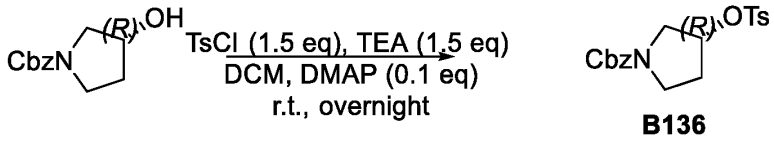
Synthesis of Intermediate B135



A mixture of 2,6-dichloro-1,5-naphthyridine (400 mg, 2.010 mmol, 1.00 equiv), 6-(methoxymethoxy)-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (2459.47 mg, 2.010 mmol, 1 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (163.72 mg, 0.201 mmol, 0.1 equiv), dioxane (20.00 mL, 236.082 mmol, 117.47 equiv), and (phosphoperoxy)potassium; dipotassium (1279.80

mg, 6.030 mmol, 3 equiv) in water (4.00 mL, 222.037 mmol, 110.48 equiv) was stirred for 1 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then quenched with water (30 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (1x40 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (4:1) to afford 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (310 mg, 43.48%) as a solid. **LCMS** (ES, *m/z*):355 $[M+H]^+$.

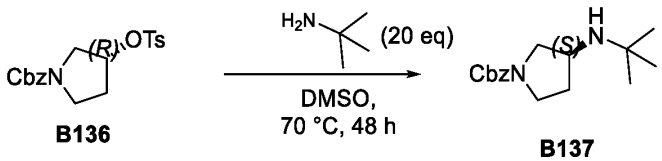
Synthesis of Intermediate B136



B136

Benzyl (3R)-3-hydroxypyrrolidine-1-carboxylate (2 g, 9.039 mmol, 1 equiv), DCM (50 mL) and TEA (1.37 g, 13.558 mmol, 1.5 equiv) were combined at room temperature. To the reaction mixture was added TsCl (2.58 g, 13.558 mmol, 1.5 equiv) in DCM (50 mL) dropwise at 0 °C, followed by DMAP (0.11 g, 0.904 mmol, 0.1 equiv) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with water (100 mL) at 0 °C. The resulting mixture was extracted with ethyl acetate (3 x 70 mL). The organic layers were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (5:1) to afford benzyl (3R)-3-[(4-methylbenzenesulfonyl)oxy]pyrrolidine-1-carboxylate (2.3 g, 67.77%) as a solid. **LCMS** (ES, *m/z*):376 $[M+H]^+$.

Synthesis of Intermediate B137

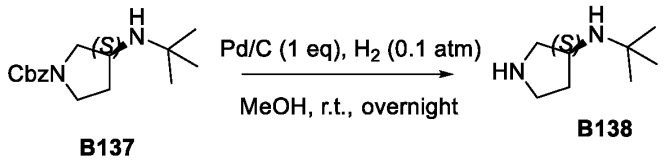


B136 **B137**

Benzyl (3R)-3-[(4-methylbenzenesulfonyl)oxy] pyrrolidine-1-carboxylate (2.3 g, 6.126 mmol, 1 equiv), erbumine (4.48 g, 61.260 mmol, 10 equiv), and DMSO (46 mL) were combined at room

temperature. The reaction mixture was stirred for 2 days at 70 °C, then cooled to room temperature. The reaction mixture was quenched with water (50 mL) at room temperature and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with half-saturation brine (3x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (5:1) to afford benzyl (3S)-3-(tert-butylamino)pyrrolidine-1-carboxylate (2.2 g, 129.94%) as a solid. **LCMS** (ES, *m/z*):277 $[M+H]^+$.

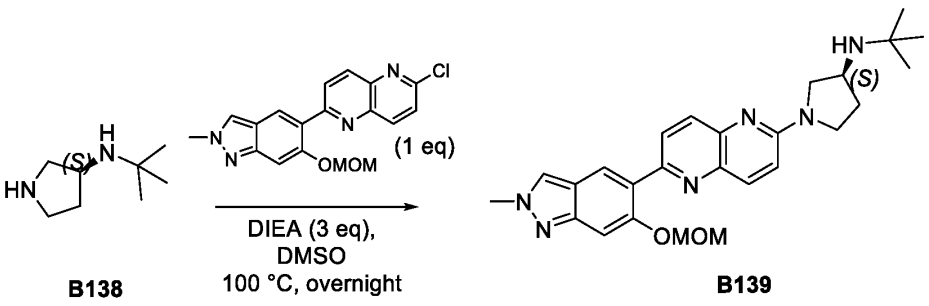
Synthesis of Intermediate B138



B137 **B138**

Benzyl (3S)-3-(tert-butylamino)pyrrolidine-1-carboxylate (1.3 g, 4.704 mmol, 1 equiv), Pd/C (0.60 g, 5.645 mmol, 1.2 equiv), and methanol (13 mL) were combined at room temperature. The resulting mixture was stirred overnight at 30 °C under H_2 (0.1atm). The mixture was cooled to room temperature, then filtered, and the filter cake washed with methanol (3x15 mL). The filtrate was concentrated under reduced pressure to give an oil (650 mg, 97.5% yield). **LCMS** (ES, *m/z*):143 $[M+H]^+$.

Synthesis of Intermediate B139

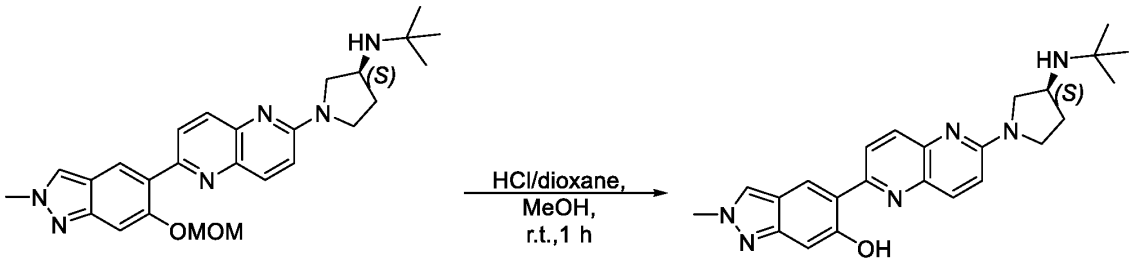


B138 **B139**

Into a 20 mL vial were added (3S)-N-tert-butylpyrrolidin-3-amine (100 mg, 0.703 mmol, 1 equiv), 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (249.42 mg, 0.703 mmol, 1 equiv), DIEA (272.58 mg, 2.109 mmol, 3 equiv) and DMSO (10 mL) at room temperature. The resulting mixture was stirred for overnight at 100 °C. The mixture was allowed to cool down to room temperature. The reaction was quenched by the addition of Water (30 mL) at room temperature. The resulting mixture was extracted with EtOAc (3 x 20 mL). The

combined organic layers were washed with half saturation brine (3x20 mL), dried over anhydrous Na2SO4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (10:1) to afford (3S)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (70 mg, 21.62%) as a solid. **LCMS** (ES, *m/z*):461 $[M+H]^+$.

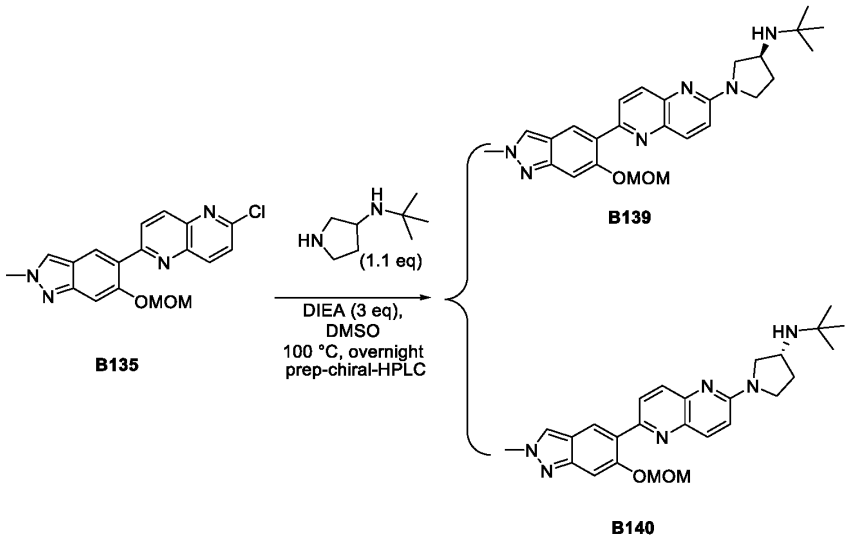
Synthesis of Compound 153



B139 **153**

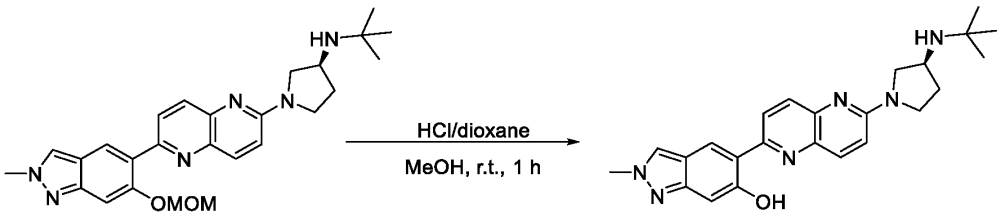
A mixture of (3S)-N-tert-butyl-1-{6-[6-(methoxymethoxy) -2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (70 mg, 0.152 mmol, 1 equiv), MeOH (3 mL), and HCl (gas) in 1,4-dioxane (3 mL, 98.736 mmol, 649.66 equiv) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 55% B in 8 min, 55% B; Wave Length: 220 nm; RT1(min): 7.42;) to afford 5-{6-[(3S)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -2-methylindazol-6-ol (20 mg, 31.59%) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$.

Synthesis of Intermediates B139 and B140



2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (200 mg, 0.564 mmol, 1.00 equiv), N-tert-butylpyrrolidin-3-amine (88.20 mg, 0.620 mmol, 1.1 equiv), DIEA (218.57 mg, 1.692 mmol, 3 equiv), and DMSO (10 mL, 140.786 mmol, 249.75 equiv) were combined at room temperature. The resulting mixture was stirred overnight at 100 °C, then cooled to room temperature. The reaction mixture was quenched with water (20 mL) at room temperature and extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, washed with sub-saturation brine (3x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1(min): 7.01), followed by prep-chiral-HPLC (Column: CHIRALPAK IA-3, 4.6*50mm 3um; Mobile Phase A: MTBE(0.1%DEA): EtOH=80: 20; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford (3S)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (65 mg, 25.04%) and (3R)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (63 mg, 24.26%) as solids. **LCMS** (ES, *m/z*):461 $[M+H]^+$. The absolute stereochemistry of the compounds was arbitrarily assigned.

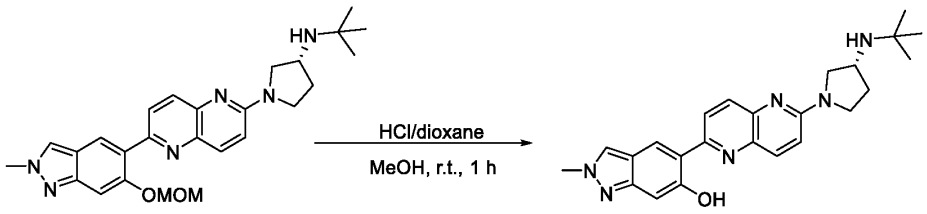
Synthesis of Compound 153



B139 **153**

A mixture of 5-{6-[(3S)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (65 mg, 0.156 mmol, 1.00 equiv), methanol (2 mL, 62.418 mmol, 399.98 equiv), and HCl (gas) in 1,4-dioxane (2 mL, 65.824 mmol, 421.81 equiv) was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 7.37;) to afford 5-{6-[(3S)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (21 mg, 32.26%) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, *J* = 12.5, 9.2 Hz, 2H), 7.14 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.50 (ddd, *J* = 18.1, 12.0, 7.2 Hz, 2H), 3.17 – 3.09 (m, 1H), 2.23 – 2.15 (m, 1H), 1.83 – 1.66 (m, 2H), 1.10 (s, 9H).

Synthesis of Compound 154



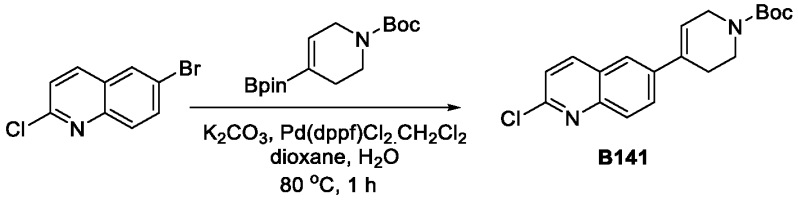
B140 **154**

A mixture of (3R)-N-tert-butyl-1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (63 mg, 0.137 mmol, 1 equiv), methanol (2 mL, 49.398 mmol, 361.14 equiv), and HCl (gas) in 1,4-dioxane (2 mL, 65.824 mmol, 481.23 equiv) was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart

C18, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 75% B in 8 min, 75% B; Wave Length: 220 nm; RT1(min): 7.00;) to afford 5-{6-[(3R)-3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (19.1 mg, 33.16%) as a solid. **LCMS** (ES, *m/z*):417 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.99 (s, 1H), 8.55 (s, 1H), 8.39 (d, J = 9.2 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 12.7, 9.2 Hz, 2H), 7.14 (d, J = 9.2 Hz, 1H), 6.87 (s, 1H), 4.12 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.57 – 3.45 (m, 2H), 3.18 – 3.09 (m, 1H), 2.21 – 2.14 (m, 1H), 1.84 – 1.65 (m, 2H), 1.10 (s, 9H).

Example 75: Synthesis of Compound 109

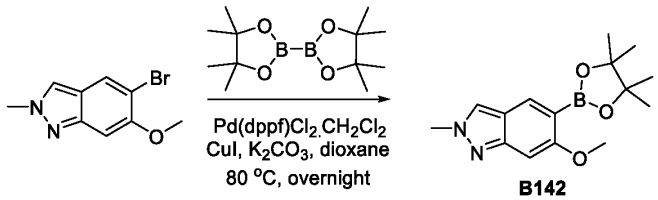
Synthesis of Intermediate B141



B141

To a mixture of 6-bromo-2-chloroquinoline (1.23 g, 5.072 mmol, 1.00 equiv) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.57 g, 5.072 mmol, 1 equiv) in dioxane (12.00 mL) and water (3.00 mL) was added K_2CO_3 (2.10 g, 15.216 mmol, 3 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (413.19 mg, 0.507 mmol, 0.1 equiv). After stirring for 1 h at 80 °C under a nitrogen atmosphere, the resulting mixture was diluted with water (20 mL), extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (1x50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl 4-(2-chloroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (770 mg, 44.02%) as a solid. **LCMS** (ES, m/z): 345 $[M+H]^+$.

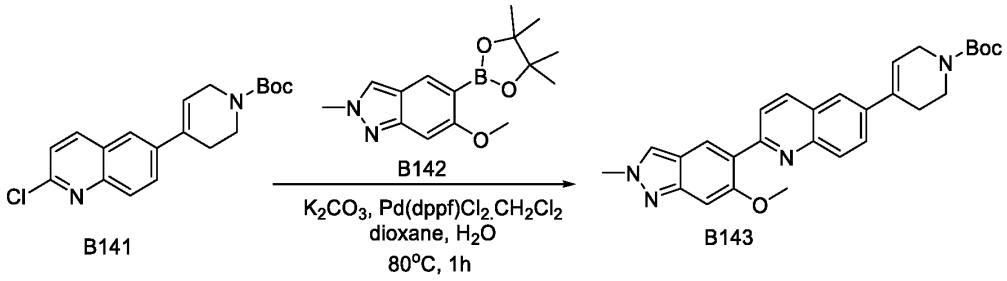
Synthesis of Intermediate B142



B142

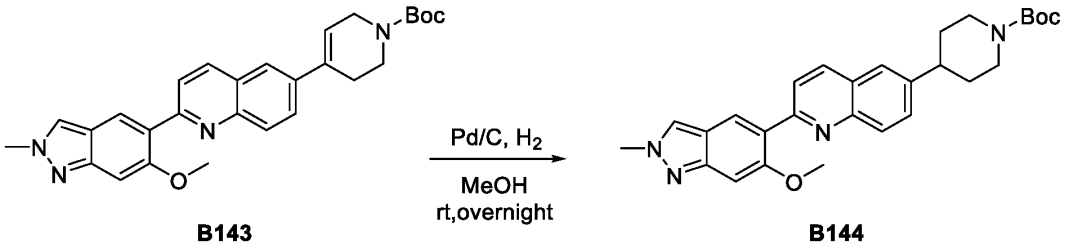
To a mixture of 5-bromo-6-methoxy-2-methylindazole (756.00 mg, 3.136 mmol, 1.00 equiv) and bis(pinacolato)diboron (1194.45 mg, 4.704 mmol, 1.5 equiv) in dioxane (15.00 mL) was added K_2CO_3 (433.38 mg, 3.136 mmol, 1 equiv), CuI (59.72 mg, 0.314 mmol, 0.1 equiv), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (255.45 mg, 0.314 mmol, 0.1 equiv). After stirring overnight at 100 °C under a nitrogen atmosphere, the resulting mixture was diluted with water (30 mL), extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with brine (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:5) to afford 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (480 mg, 53.12%) as a solid. **LCMS** (ES, m/z): 289 $[M+H]^+$.

Synthesis of Intermediate B143



To a mixture of 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (144.00 mg, 0.500 mmol, 1.00 equiv) and tert-butyl 4-(2-chloroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (172.33 mg, 0.500 mmol, 1.00 equiv) in dioxane (4.00 mL) and water (1.00 mL) was added K_2CO_3 (207.20 mg, 1.499 mmol, 3 equiv) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (40.71 mg, 0.050 mmol, 0.10 equiv). After stirring for 1 h at 80 °C under a nitrogen atmosphere, the resulting mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (1x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (301 mg). **LCMS** (ES, m/z): 471 $[M+H]^+$.

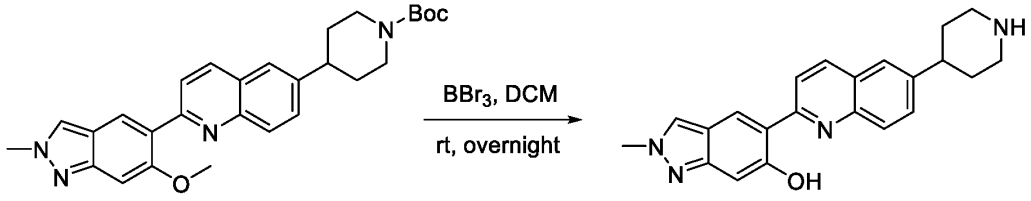
Synthesis of Intermediate B144



B143 **B144**

To a stirred solution of tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200.00 mg, 0.425 mmol, 1.00 equiv) in methanol (5.00 mL) was added Pd/C (226.15 mg, 2.125 mmol, 5 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature, then filtered, and the filter cake washed with ethyl acetate (3x15 mL). The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2/MeOH (12:1) to afford tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (62 mg, 30.87%) as a solid. **LCMS** (ES, m/z): 473 $[M+H]^+$.

Synthesis of Compound 109



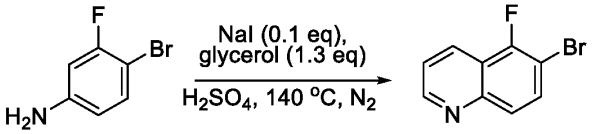
B144 **109**

To a stirred solution of tert-butyl 4-[2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (53.00 mg, 0.112 mmol, 1.00 equiv) in DCM (4.00 mL, 62.920 mmol) was added BBr_3 (561.91 mg, 2.240 mmol, 20.00 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred overnight at room temperature, then quenched with methanol (2 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150mm 5um; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:10 B to 30 B in 10 min; UV 220 nm; RT1:8.77) to afford 2-methyl-5-[6-(piperidin-4-yl)quinolin-2-yl]indazol-6-ol (15 mg, 37.31%) as a solid. **LCMS** (ES, m/z): 359 $[M+H]^+$. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 8.56 (s, 1H), 8.39 (d, J = 8.9 Hz,

1H), 8.31 – 8.22 (m, 2H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.80 – 7.71 (m, 2H), 6.98 (s, 1H), 4.17 (s, 3H), 3.32 – 3.27 (m, 2H), 3.03 – 2.87 (m, 3H), 2.08 – 1.97 (m, 2H), 1.94 – 1.79 (m, 2H).

Example 76: Synthesis of Compound 115

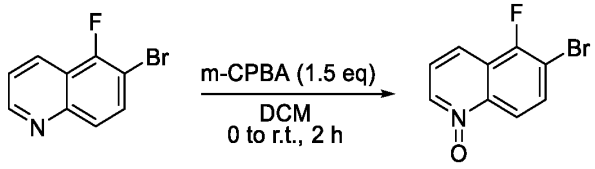
Synthesis of Intermediate B145



B145

4-bromo-3-fluoroaniline (22.00 g, 115.789 mmol, 1.00 equiv), NaI (1.74 g, 11.579 mmol, 0.10 equiv), and glycerol (13.86 g, 150.526 mmol, 1.30 equiv) were combined in H_2SO_4 (88.00 mL) at room temperature. The resulting mixture was stirred for 4 h at 140 °C under nitrogen atmosphere. The reaction mixture was quenched with water (20 mL) at room temperature, then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 6-bromo-5-fluoroquinoline (8.4 g, 32.09%) as a solid. **LCMS** (ES, *m/z*):226 $[M+H]^+$.

Synthesis of Intermediate B146

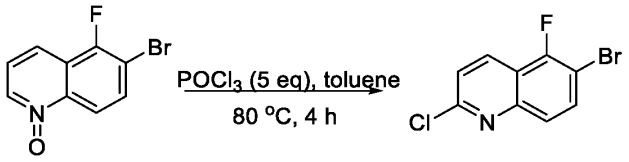


B145 **B146**

To a stirred solution of 6-bromo-5-fluoroquinoline (8.40 g, 37.160 mmol, 1.00 equiv) in DCM (115.00 mL) was added m-CPBA (9.62 g, 55.740 mmol, 1.50 equiv) in portions at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 3 h at room temperature under nitrogen atmosphere, then quenched with water at room temperature, and neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with CH_2Cl_2 (2 x 100mL). The organic layers were combined, washed with water (3x100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to

afford 6-bromo-5-fluoro-1lambda5-quinolin-1-one (8.8g,97.84%) as a solid. **LCMS** (ES, *m/z*):242 $[M+H]^+$.

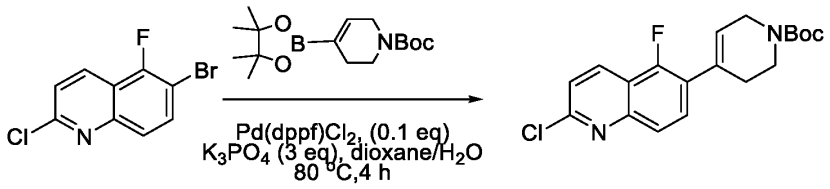
Synthesis of Intermediate B147



B146 **B147**

To a stirred solution of 6-bromo-5-fluoro-1λ5-quinolin-1-one (8.80 g, 36.357 mmol, 1.00 equiv) in toluene (88.00 mL) was added phosphorus oxychloride (27.87 g, 181.785 mmol, 5.00 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere. The resulting mixture was diluted with water (80 mL), then neutralized to pH 7 with saturated $NaHCO_3$ (aq.). The resulting mixture was extracted with ethyl acetate (3 x 80 mL). The organic layers were combined, washed with saturated NaCl (aq) (3x40 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford 6-bromo-2-chloro-5-fluoroquinoline (6 g, 63.35%) as a solid. **LCMS** (ES, *m/z*):260 $[M+H]^+$.

Synthesis of Intermediate B148

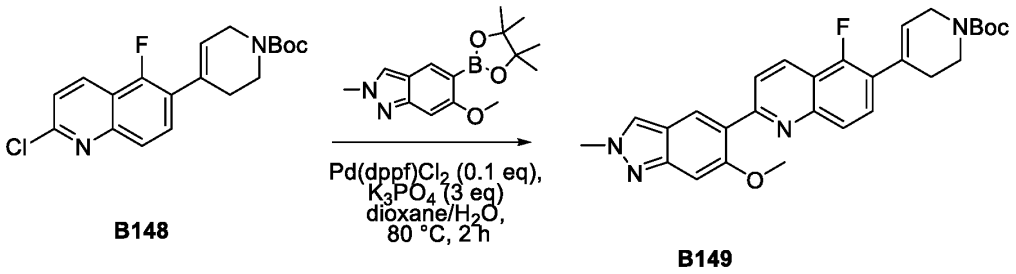


B147 **B148**

To a stirred mixture of 6-bromo-2-chloro-5-fluoroquinoline (2.00 g, 7.678 mmol, 1.00 equiv), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (2.37 g, 7.678 mmol, 1.00 equiv), and $Pd(dppf)Cl_2$ (0.63 g, 0.773 mmol, 0.10 equiv) in dioxane (16.60 mL) was added K_3PO_4 (4.89 g, 23.037 mmol, 3.00 equiv) in water (3.40 mL) dropwise at room temperature. The resulting mixture was stirred for 16 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to

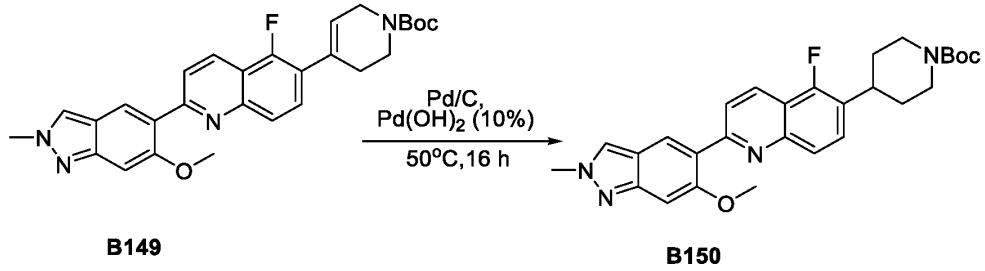
afford tert-butyl 4-(2-chloro-5-fluoroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (1.5g, 53.85%) as a solid. **LCMS** (ES, *m/z*): 363 $[M+H]^+$.

Synthesis of Intermediate B149



Tert-butyl 4-(2-chloro-5-fluoroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (200.00 mg, 0.551 mmol, 1.00 equiv), 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole(158.83 mg, 0.551 mmol, 1.00 equiv), $Pd(dppf)Cl_2 CH_2Cl_2$ (44.90 mg, 0.055 mmol, 0.10 equiv), and K_3PO_4 (351.02 mg, 1.653 mmol, 3.00 equiv) were combined in water (2.50 mL) and dioxane (12.50 mL) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl 4-[5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200mg,74.26%) as a solid. **LCMS** (ES, *m/z*):489 $[M+H]^+$.

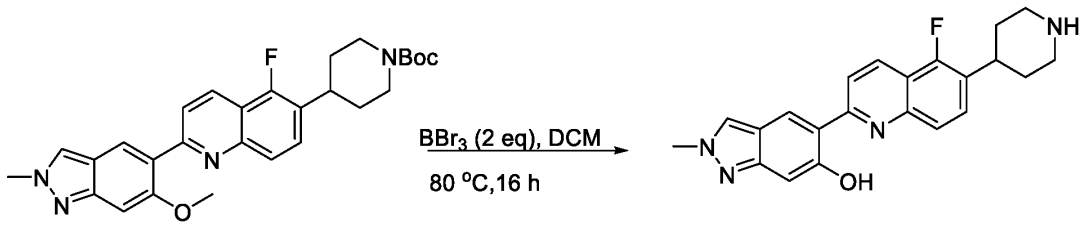
Synthesis of Intermediate B150



Tert-butyl 4-[5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (200.00 mg, 0.409 mmol, 1.00 equiv), Pd/C (30.00 mg, 0.282 mmol, 0.69 equiv), and $Pd(OH)_2/C$ (30.00 mg, 0.214 mmol, 0.52 equiv) were combined in methanol (15.00 mL) at room temperature. The resulting mixture was stirred for 20 h at room temperature under hydrogen atmosphere. The resulting mixture was filtered, and the filter cake washed with methanol (2x10 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl 4-

[5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (200 mg, 99.59%) as an oil. **LCMS** (ES, *m/z*):491 $[M+H]^+$.

Synthesis of Compound 115

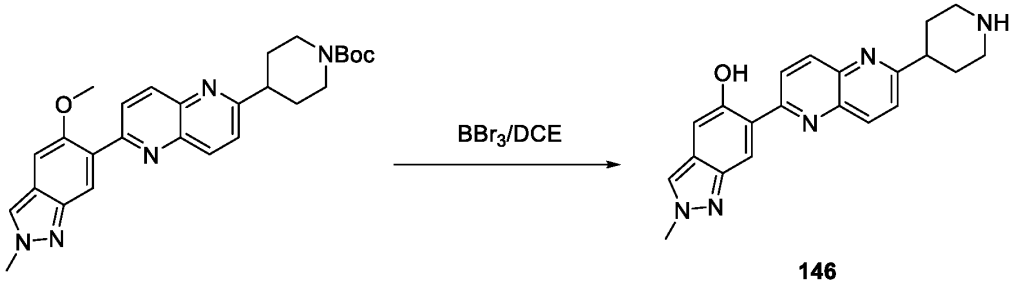


B150 **115**

To a stirred solution of tert-butyl 4-[5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (150.00 mg, 0.306 mmol, 1.00 equiv) in DCM (15 .00 mL) was added BBr_3 (153.20 mg, 0.612 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 16 h at 80 °C. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water(10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 45% B in 8 min, 45% B; Wave Length: 220 nm; RT1(min): 7.72) to afford 5-[5-fluoro-6-(piperidin-4-yl)quinolin-2-yl]-2-methylindazol-6-ol (9.1 mg, 7.90%) as a solid. **LCMS** (ES, *m/z*):377 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 13.94 (s, 1H), 8.69 (s, 1H), 8.56 (d, J = 8.9 Hz, 1H), 8.45 – 8.33 (m, 2H), 7.99 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 11.8 Hz, 1H), 6.91 (s, 1H), 4.13 (s, 3H), 3.25 – 2.96 (m, 3H), 2.84 – 2.63 (m, 2H), 1.86 (d, J = 12.4 Hz, 2H), 1.71 (dd, J = 12.3, 3.8 Hz, 2H).

Example 77: Synthesis of Compound 146

Synthesis of Compound 146



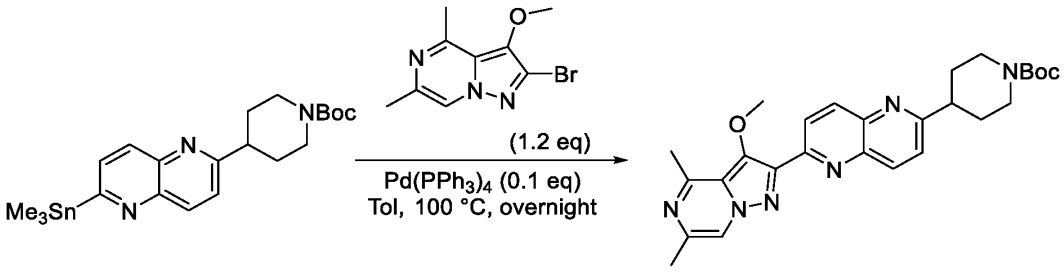
146

To a stirred solution of tert-butyl 4-[6-(5-methoxy-2-methylindazol-6-yl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (40 mg, 0.08 mmol, 1.00 equiv) in DCE (1 mL, 12.63 mmol, 149.55

equiv) was added BBr_3 (0.2 mL, 2.11 mmol, 25.05 equiv) in portions at room temperature under nitrogen atmosphere. The resulting mixture was stirred overnight at 80° C under nitrogen atmosphere. The resulting mixture was diluted with methanol (5 mL) and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm, 5μm; mobile phase, Water (10MMOL/L NH_4HCO_3) and ACN (5% ACN up to 60% in 8 min); Detector, uv 220nm product was obtained which Alpha) to afford 2-methyl-6-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]indazol-5-ol (9.8 mg, 32.3%) as a solid. **LCMS** (ES, *m/z*): 360[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 13.17 (s, 1H), 8.69 (s, 1H), 8.67 (d, *J* = 9.3 Hz, 1H), 8.54 (d, *J* = 9.1 Hz, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.08 (s, 1H), 4.18(s, 3H), 3.32 – 3.11 (m, 2H), 3.08 (m, 1H), 2.61 – 2.63(m, 2H) 1.87 (d, *J* = 11.5 Hz, 2H), 1.78 – 1.74 (m, 2H)

Example 78: Synthesis of Compound 150

Synthesis of Intermediate B151



B151

A mixture of tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (44.00 mg, 0.092 mmol, 1.00 equiv), 2-bromo-3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazine (28.40 mg, 0.111 mmol, 1.20 equiv), and $Pd(PPh_3)_4$ (10.68 mg, 0.009 mmol, 0.10 equiv) in toluene (1.00 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:3) to afford tert-butyl 4-(6-[3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl]-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (120 mg, 46.78%) as a solid. **LCMS** (ES, *m/z*):489[M+H]$^+$.

Synthesis of Compound 150

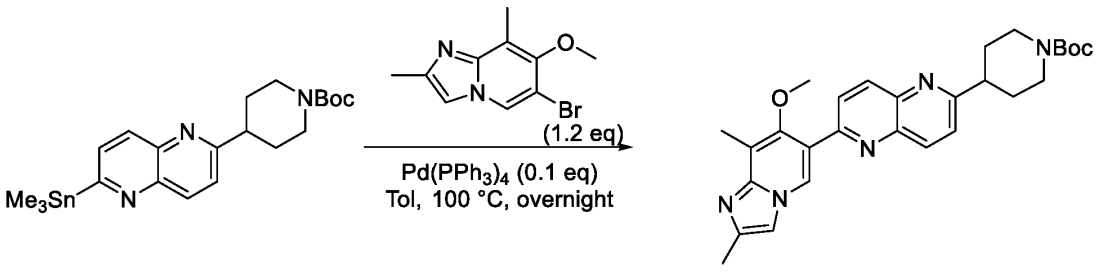


B151 150

To a stirred solution of tert-butyl 4-(6-[3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl]-1,5-naphthyridin-2-yl)piperidine-1-carboxylate (110.00 mg, 0.225 mmol, 1.00 equiv) in DCE (2.00 mL) was added BBr_3 (282.01 mg, 1.126 mmol, 5.00 equiv) dropwise at 0 °C under nitrogen atmosphere. The resulting mixture was stirred for 4 h at 80 °C under nitrogen atmosphere, then quenched with methanol (5 mL) at 0 °C. The resulting mixture was concentrated under reduced pressure at room temperature to give a residue. The residue was dissolved in $MeOH/H_2O$ (15 mL) and purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30x150 mm, 5um; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 45% B in 8 min; Wave Length: 220 nm; RT1(min): 6.97) to afford 4,6-dimethyl-2-[6-(piperidin-4-yl)-1,5-naphthyridin-2-yl]pyrazolo[1,5-a]pyrazin-3-ol(6.7mg,7.88%) as a solid. **LCMS** (ES, *m/z*):374[M+H]$^+$. **^{1}H NMR:** (400 MHz, 353K, DMSO-d_6, *ppm*): δ 8.48 (dd, *J* = 17.2, 8.8 Hz, 2H), 8.39 (d, *J* = 8.8 Hz, 1H), 8.17 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 3.13 (s, 3H), 2.78 (s, 3H), 2.69 (td, *J* = 12.0, 2.6 Hz, 2H), 2.38 (s, 3H), 1.95 – 1.86 (m, 2H), 1.77 (qd, *J* = 12.1, 4.1 Hz, 2H).

Example 79: Synthesis of Compound 151

Synthesis of Intermediate B152

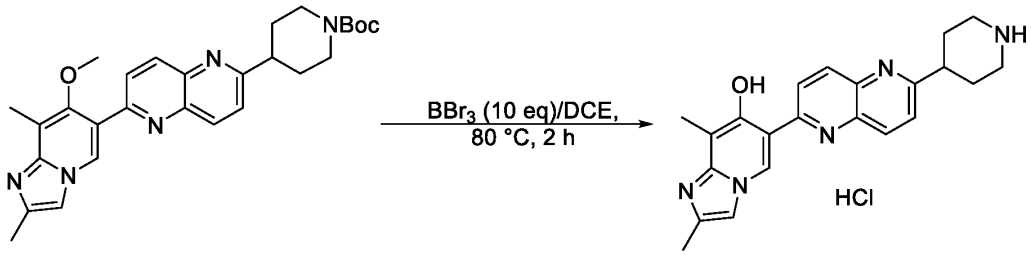


B152

A mixture of tert-butyl 4-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]piperidine-1-carboxylate (180 mg, 0.378 mmol, 1.00 equiv), 6-bromo-7-methoxy-2,8-dimethylimidazo[1,2-a]pyridine (115.72 mg, 0.454 mmol, 1.2 equiv), and $Pd(PPh_3)_4$ (43.68 mg, 0.038 mmol, 0.1 equiv)(4x11

mg) in toluene (3.6 mL) was stirred overnight at 100 °C under nitrogen atmosphere. The resulting mixture was diluted with water (20 mL), then extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (1x20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (PE / EA 3:7) to afford tert-butyl 4-(6-{7-methoxy-2,8-dimethylimidazo[1,2-a]pyridin-6-yl}-1,5-naphthyridin-2-yl) piperidine-1-carboxylate (25 mg) as an oil. **LCMS** (ES, *m/z*):488[M+H]$^+$.

Synthesis of Compound 151

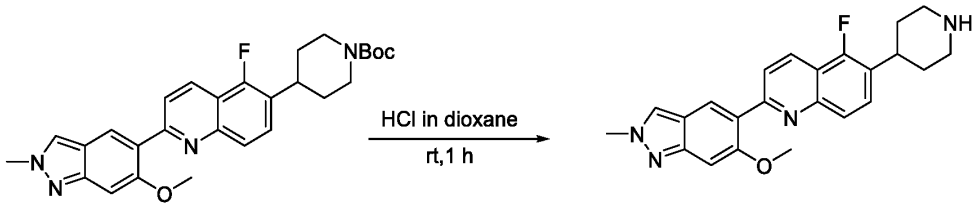


B152 **151**

To a solution of tert-butyl 4-(6-{7-methoxy-2,8-dimethylimidazo[1,2-a]pyridin-6-yl} -1,5-naphthyridin-2-yl) piperidine-1-carboxylate (60 mg, 0.123 mmol, 1.00 equiv) in DCE (1 mL, 12.631 mmol, 102.65 equiv) was added BBr_3 (308.27 mg, 1.230 mmol, 10 equiv). After stirring for 3 h at 80 °C, the reaction was quenched with methanol at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, Xselect CSH OBD Column 30x150mm 5um, n; mobile phase, Water(0.05%HCl) and ACN (3% ACN up to 20% in 8 min)) to afford 2,8-dimethyl-6-(6-(piperidin-4-yl)-1,5-naphthyridin-2-yl)imidazo[1,2-a]pyridin-7-ol hydrochloride (1.1 mg, 2.39%) as a solid. **LCMS**: (ES, *m/z*):374[M+H]$^+$. **^{1}H-NMR**: (400 MHz, 353K, DMSO-d_6, *ppm*): δ 9.78 (s, 1H), 8.86 (s, 1H), 8.71 (dd, *J* = 9.1, 0.8 Hz, 1H), 8.65 (t, *J* = 7.3 Hz, 1H), 8.63 – 8.57 (m, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 1.3 Hz, 1H), 3.34 (s, 1H), 3.25 (s, 2H), 3.19 – 3.04 (m, 2H), 2.49 (s, 6H), 2.23 (d, *J* = 13.0 Hz, 2H), 2.19 – 2.10 (m, 2H).

Example 80: Synthesis of Compound 143

Synthesis of Compound 143

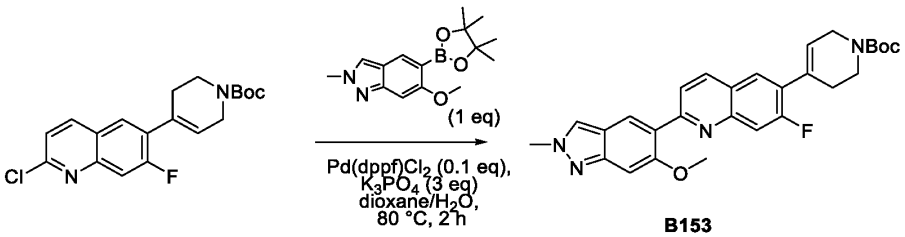


143

A mixture of tert-butyl 4-[5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin -6-yl]piperidine-1-carboxylate(50.00 mg, 0.102 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (2.00 mL) in dioxane (2.00 mL) at room temperature was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: (YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 40% B in 8 min, 40% B; Wave Length: 220 nm; RT1(min): 7.6;)) to afford 5-fluoro-2-(6-methoxy-2-methylindazol-5-yl)-6-(piperidin-4-yl)quinoline (9.1 mg, 22.87%) as a solid. **LCMS** (ES, *m/z*):391 [M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.43 – 8.23 (m, 2H), 8.01 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 12.1 Hz, 1H), 7.11 (s, 1H), 4.14 (s, 3H), 3.86 (s, 3H), 3.06 (dd, *J* = 30.2, 12.4 Hz, 3H), 2.74 – 2.61 (m, 2H), 1.83 (d, *J* = 12.1 Hz, 2H), 1.68 (dd, *J* = 12.1, 3.8 Hz, 1H).

Example 81: Synthesis of Compound 144

Synthesis of Intermediate B153

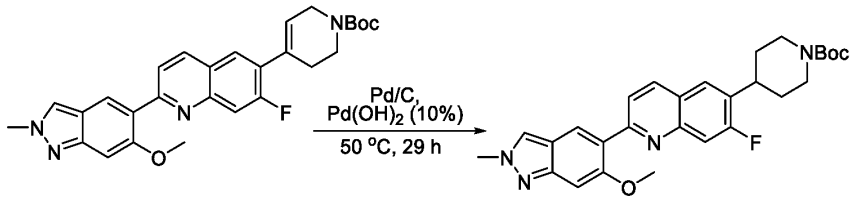


B153

To a stirred mixture of tert-butyl 4-(2-chloro-7-fluoroquinolin-6-yl)-3,6-dihydro-2H-pyridine -1-carboxylate (200.00 mg, 0.551 mmol, 1.00 equiv), 6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl -1,3,2-dioxaborolan-2-yl)indazole (158.83 mg, 0.000 mmol, 1.00 equiv), $Pd(dppf)Cl_2$ (44.90 mg, 0.055 mmol, 0.10 equiv), and K_3PO_4 (351.02 mg, 1.653 mmol, 3.00 equiv) in water (2.50 mL) and dioxane (12.50 mL) at room temperature. The resulting mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. The resulting mixture was concentrated under reduced pressure to

give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (5:1) to afford tert-butyl 4-[7-fluoro-2-(6-methoxy -2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine -1-carboxylate (150 mg, 55.70%) as a solid. **LCMS** (ES, *m/z*):489 $[M+H]^+$.

Synthesis of Intermediate B154



B153 **B154**

To a stirred solution of tert-butyl 4-[7-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin-6-yl] -3,6-dihydro-2H-pyridine-1-carboxylate (120.00 mg, 0.246 mmol, 1.00 equiv) and Pd/C (20.00 mg, 0.188 mmol, 0.77 equiv) and $Pd(OH)_2/C$ (20.00 mg, 0.142 mmol, 0.58 equiv) in MeOH (12.00 mL) was at room temperature. The resulting mixture was stirred for 29h at 50°C under hydrogen atmosphere. The resulting mixture was filtered, the filter cake was washed with MeOH (2x10 mL). The filtrate was concentrated under reduced pressure. This resulted in tert-butyl 4-[7-fluoro-2-(6-methoxy-2-methylindazol-5-yl) quinolin-6-yl]piperidine-1-carboxylate(120 mg, 99.59%) as an oil. **LCMS** (ES, *m/z*):491 $[M+H]^+$.

Synthesis of Compound 144



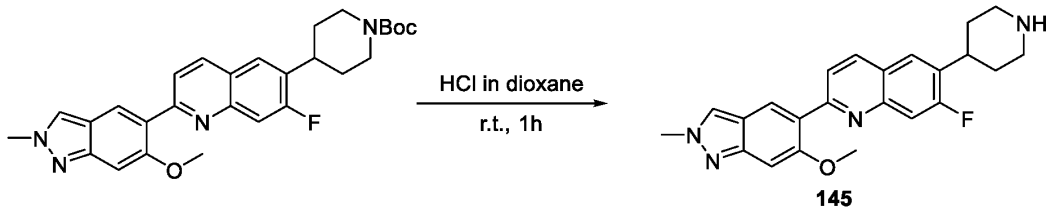
B154 **144**

To a stirred solution of tert-butyl 4-[7-fluoro-2-(6-methoxy-2-methylindazol-5-yl) quinolin-6-yl] piperidine-1-carboxylate (80.00 mg, 0.163 mmol, 1.00 equiv) in DCE (8.00 mL) was added BBr_3 (81.71 mg, 0.326 mmol, 2.00 equiv) at room temperature. The resulting mixture was stirred for 4h at 80 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC ((HPLC-01): Column: YMC-Actus Triart C18, 30*150 mm, 5μm; Mobile Phase A: Water (10MMOL/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:

60 mL/min; Gradient: 10% B to 50% B in 8 min, 50% B; Wave Length: 220 nm; RT1(min): 5.12) to afford 5-[7-fluoro-6-(piperidin-4-yl)quinolin-2-yl]-2-methylindazol-6-ol(8.1 mg, 13.19%) as a solid. **LCMS** (ES, *m/z*):377 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.88 (d, *J* = 4.4 Hz, 1H), 8.27 (s, 1H), 7.75 (d, *J* = 11.9 Hz, 1H), 7.58 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.02 (s, 1H), 4.12 (s, 3H), 2.96 (d, *J* = 10.4 Hz, 3H), 2.71 – 2.54 (m, 2H), 1.68 (dd, *J* = 23.3, 12.6 Hz, 2H), 1.42 (dt, *J* = 23.4, 11.9 Hz, 2H).

Example 82: Synthesis of Compound 145

Synthesis of Compound 145

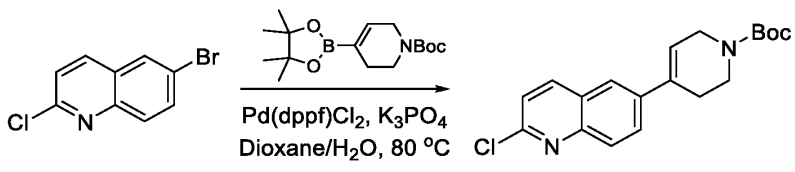


145

A mixture of tert-butyl 4-[7-fluoro-2-(6-methoxy-2-methylindazol-5-yl)quinolin 6-yl]piperidine-1-carboxylate (100.00 mg, 0.204 mmol, 1.00 equiv) and HCl (gas) in 1,4-dioxane (5.00 mL, 72.990 mmol, 429.69 equiv) in dioxane (5.00 mL) at room temperature was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10MMOL/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 35% B in 8 min, 35% B; Wave Length: 220 nm; RT1(min): 7.54) to afford 7-fluoro-2-(6-methoxy-2-methylindazol-5-yl)-6-(piperidin-4-yl)quinoline(13 mg, 16.33%) as a solid. **LCMS** (ES, *m/z*):391 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.89 (d, *J* = 4.4 Hz, 1H), 8.34 (s, 1H), 7.75 (d, *J* = 11.8 Hz, 1H), 7.65 (s, 1H), 7.48 – 7.31 (m, 2H), 7.18 (s, 1H), 4.16 (s, 3H), 3.69 (s, 3H), 2.94 (d, *J* = 15.3 Hz, 3H), 2.73 – 2.53 (m, 2H), 1.68 (dd, *J* = 29.7, 12.5 Hz, 2H), 1.50 – 1.05 (m, 2H).

Example 83: Synthesis of Compound 241

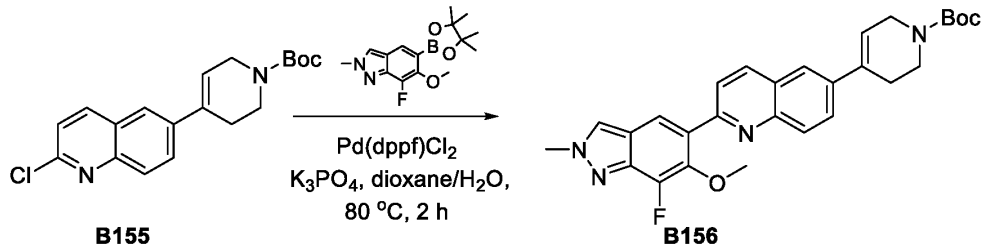
Synthesis of Intermediate B155



B155

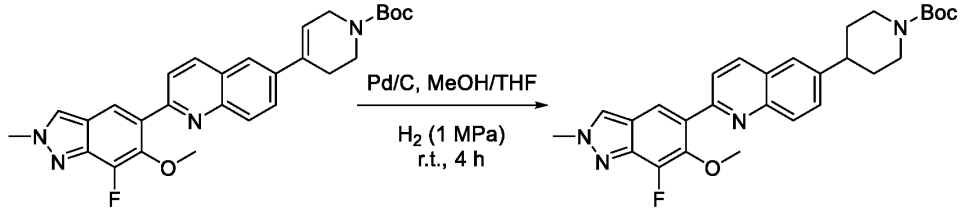
6-bromo-2-chloroquinoline (300 mg, 1.23 mmol, 1.00 equiv), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (420.78 mg, 1.36 mmol, 1.10equiv), dioxane (4 mL), K_3PO_4 (656.49 mg, 3.093 mmol, 2.5 equiv), water (0.8mL), and $Pd(dppf)Cl_2.CH_2Cl_2$ (50.39 mg, 0.062 mmol, 0.05 equiv) were combined. The reaction mixture was evacuated and flushed three times with nitrogen. The resulting solution was stirred for 2 h at 80 °C, then quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with saturated aqueous NaCl (1 x50 mL), dried over anhydrous sodium sulfate, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a resiude. The residue was purified by silica gel column chromatography, eluted with PE/EA to afford tert-butyl 4-(2-chloroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (180 mL, 42.19%) as a solid. **LCMS** (ES, *m/z*): 345 $[M+H]^+$.

Synthesis of Intermediate B156



Tert-butyl 4-(2-chloroquinolin-6-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (90 mg, 0.261 mmol, 1 equiv), dioxane (3 mL), K_3PO_4 (166.20 mg, 0.783 mmol, 3 equiv) and H_2O (0.6 mL) were combined. The reaction mixture was evacuated and flushed three times with nitrogen. The resulting mixture was stirred for 20 min at room temperature. To the reaction mixture was added 7-fluoro-6-methoxy-2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (95.88 mg, 0.313 mmol, 1.2 equiv) in dioxane added dropwise while stirring at room temperature. The reaction mixture was evacuated and flushed three times with nitrogen. The resulting mixture was stirred for 4 h at 80 °C, then quenched with water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with saturated aqueous NaCl (50 mL), dried over anhydrous sodium sulfate, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA to afford tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (100 mg, 78.43%) as a solid. **LCMS** (ES, *m/z*):489 $[M+H]^+$.

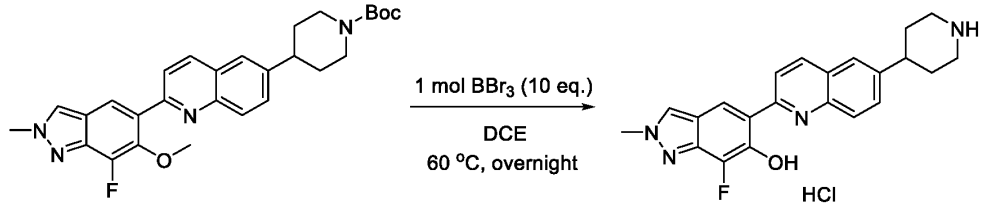
Synthesis of Intermediate B157



B156 **B157**

To a solution of tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate (90 mg, 0.184 mmol, 1 equiv) in methanol (2 mL) and THF (2 mL) was added Pd/C (100 mg, 0.940 mmol, 5.10 equiv) under nitrogen atmosphere in a 10 mL pressure tank reactor. The reaction mixture was hydrogenated at room temperature for 3 h under hydrogen atmosphere (1 MPa). The resulting mixture was filtered, the filter cake washed with methanol, and the filtrate concentrated under reduced pressure to give a residue. To the residue was added DCE (4 mL) and MnO_2(20 equiv), and the resultant mixture was stirred at 80 °C overnight. The resulting mixture was filtered, the filter cake was washed with DCM. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA to afford tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (70 mg, 77.46%) as a solid. **LCMS** (ES, *m/z*): 491 $[M+H]^+$.

Synthesis of Compound 241



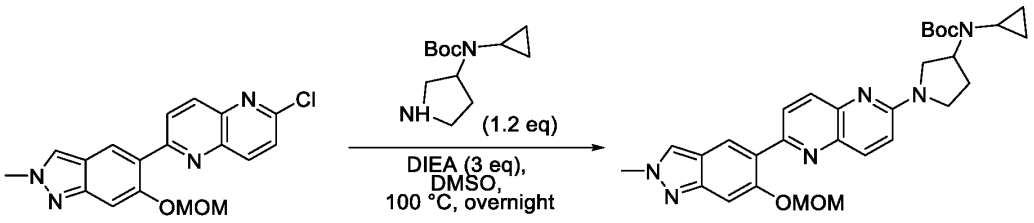
B157 **241**

A mixture of tert-butyl 4-[2-(7-fluoro-6-methoxy-2-methylindazol-5-yl)quinolin-6-yl]piperidine-1-carboxylate (60 mg, 0.122 mmol, 1 equiv), DCE (4 mL), and BBr_3 (306.40 mg, 1.220 mmol, 10 equiv) was stirred overnight at 60 °C. The reaction mixture was basified to pH 8 with NH_3 in methanol, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (0.05%HCl), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 50% B

in 8 min, 50% B; Wave Length: 220 nm; RT1(min): 7.85) to afford 7-fluoro-2-methyl-5-[6-(piperidin-4-yl)quinolin-2-yl]indazol-6-ol (10.1 mg, 21.87%) as a solid. **LCMS** (ES, *m/z*): 377 [M-HCl]$^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.70 (d, *J* = 11.7 Hz, 1H), 8.61 (d, *J* = 8.9 Hz, 1H), 8.55 (d, *J* = 2.8 Hz, 2H), 8.45 (d, *J* = 9.1 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, *J* = 8.7, 2.0 Hz, 1H), 4.18 (s, 3H), 3.43 (d, *J* = 12.4 Hz, 2H), 3.07 (q, *J* = 12.2, 11.6 Hz, 3H), 2.09 (d, *J* = 13.4 Hz, 2H), 2.02 – 1.90 (m, 3H).

Example 85: Synthesis of Compounds 182, 197, 198, and 245-247

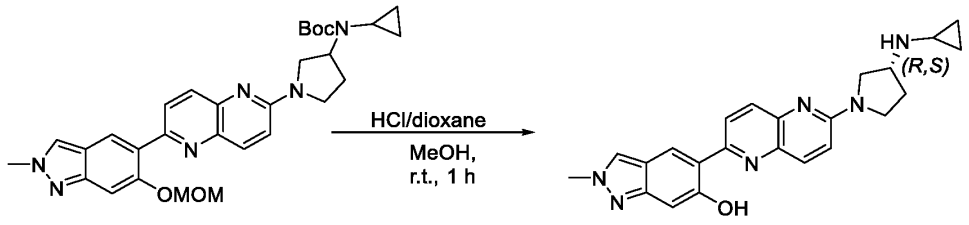
Synthesis of Intermediate B158



B158

A mixture of 2-chloro-6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridine (150 mg, 0.423 mmol, 1 equiv), tert-butyl N-cyclopropyl-N-(pyrrolidin-3-yl)carbamate (114.82 mg, 0.508 mmol, 1.2 equiv), DMSO (4 mL, 56.314 mmol, 133.20 equiv) and DIEA (163.93 mg, 1.269 mmol, 3 equiv) was stirred overnight at 100 °C. The reaction mixture was cooled to room temperature, then quenched with water (10 mL) at room temperature. The resulting mixture was extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, washed with sub-saturation brine (3x5 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 /EA (1:4) to afford tert-butyl N-cyclopropyl-N-(1-{6-[6-(methoxymethoxy)-2-methylindazol -5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (130 mg, 56.45%) as an oil. **LCMS** (ES, *m/z*): 545 [M+H]$^+$.

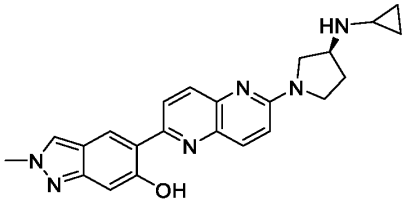
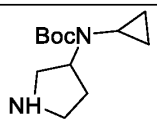
Synthesis of Compound 197

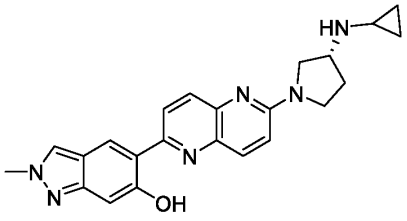
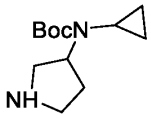
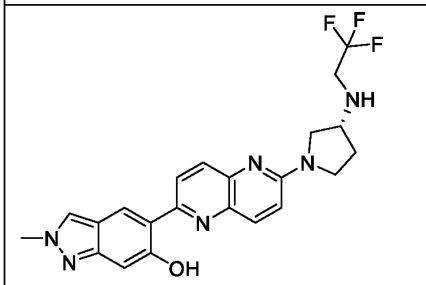
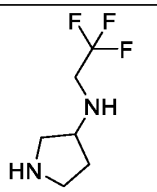
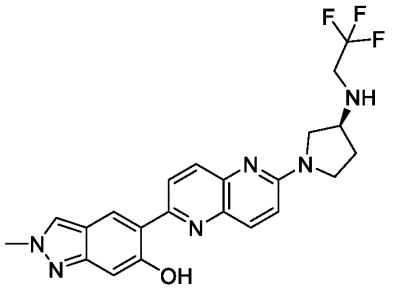
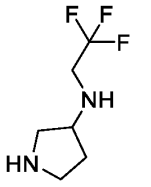


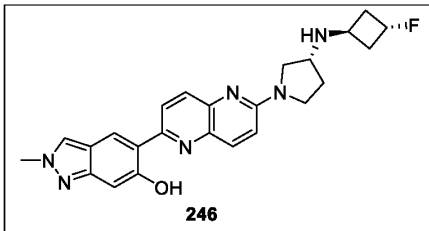
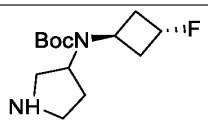
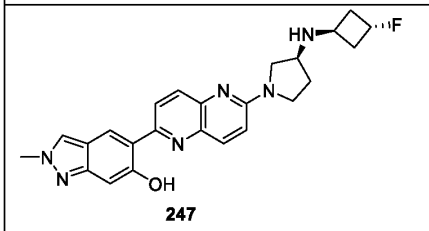
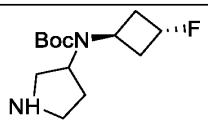
B158 **197**

A mixture of tert-butyl N-cyclopropyl-N-(1-{6-[6-(methoxymethoxy)-2-methylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (150 mg, 0.275 mmol, 1.00 equiv), methanol (3 mL, 74.097 mmol, 269.05 equiv), and HCl (gas) in 1,4-dioxane (3 mL, 98.736 mmol, 358.51 equiv) was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure, then basified to pH 8 with NH_3/MeOH. The resulting product was purified by Chiral-HPLC (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: MtBE (0.1% DEA)-HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 11 min; Wave Length: 220/254 nm; RT1(min): 9.3; RT2(min): 10.2; Sample Solvent: MeOH: DCM=2: 1; Injection Volume: 0.21 mL; Number Of Runs: 38), followed by Prep-HPLC (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 5% B to 65% B in 8 min, 65% B; Wave Length: 220 nm; RT1(min): 7.12) to afford 5-{6-[(3S)-3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylindazol-6-ol (7.9 mg, 7.02%) as a solid.

Compounds 182, 197, 198, and 245-247 were prepared according to the procedures descrbed herein, outlined in this Example 85. The table below provides intermediates used in these procedures and final compound characterization data.

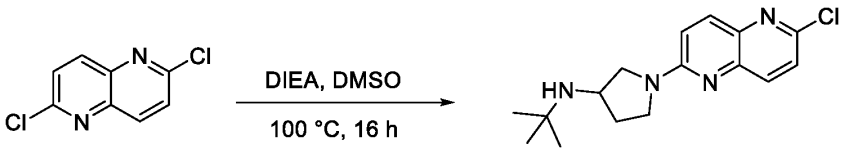
Compound No. and Structure	**Coupling Reagent**	**LCMS (ESI, *m/z*) $[M+H]^+$**	**^{1}H NMR δ**
 **198**		401	(400 MHz, DMSO-d_6) δ 13.97 (s, 1H), 8.54 (s, 1H), 8.39 (d, J = 9.3 Hz, 1H), 8.35 (s, 1H), 8.08 (dd, J = 15.9, 9.2 Hz, 2H), 7.15 (d, J = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.75 (d, J = 7.8 Hz, 1H), 3.67 (s, 1H), 3.56 (s, 2H), 3.43 (s, 1H), 2.16 (s, 2H), 1.95 (s, 1H), 0.44 (d, J = 6.9 Hz, 2H), 0.28 (s, 2H)

 **197**		401	(400 MHz, DMSO-d_6) δ13.97 (s, 1H), 8.54 (s, 1H), 8.41 – 8.31 (m, 2H), 8.13 – 8.03 (m, 2H), 7.14 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.74 (t, *J* = 5.5 Hz, 1H), 3.67 (s, 1H), 3.61 – 3.46 (m, 2H), 3.46 – 3.36 (m, 1H), 2.20 – 2.08 (m, 2H), 1.93 (s, 1H), 0.46 – 0.35 (m, 2H), 0.31 – 0.19 (m, 2H)
 **245**		443	(400 MHz, DMSO-*d*$_6$) δ 13.96 (s, 1H), 8.54 (s, 1H), 8.44 – 8.29 (m, 2H), 8.09 (dd, *J* = 18.9, 9.2 Hz, 2H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.82 – 3.64 (m, 1H), 3.61 – 3.47 (m, 1H), 3.39 (s, 1H), 3.36 (d, *J* = 2.6 Hz, 1H), 3.29 (s, 2H), 2.84 – 2.60 (m, 1H), 2.36 – 2.06 (m, 1H), 1.90 (dd, *J* = 12.5, 6.5 Hz, 1H)
 **182**		443	(400 MHz, DMSO-*d*$_6$) δ 13.96 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), 4.11 (s, 3H), 3.84 – 3.66 (m, 1H), 3.63 – 3.48 (m, 1H), 3.46 – 3.33 (m, 2H), 3.31 (d, *J* = 12.8 Hz, 2H), 2.75 (q, *J* = 7.1 Hz, 1H), 2.15 (dq, *J* = 12.9, 6.7 Hz, 1H), 1.91 (dd, *J* = 12.7, 6.5 Hz, 1H)

 246		433	(400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.3 Hz, 1H), 8.35 (s, 1H), 8.08 (ddd, *J* = 16.0, 9.2, 0.8 Hz, 2H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.87 (d, *J* = 0.8 Hz, 1H), 5.19 (ddq, *J* = 56.9, 6.6, 3.3 Hz, 1H), 4.11 (s, 3H), 3.78 – 3.63 (m, 2H), 3.54 (s, 2H), 3.35 (d, *J* = 3.6 Hz, 1H), 2.42 – 2.26 (m, 3H), 2.15 (ddd, *J* = 25.6, 10.4, 5.1 Hz, 3H), 1.81 (d, *J* = 12.9 Hz, 1H)
 247		433	(400 MHz, DMSO-d_6) δ 13.96 (s, 1H), 8.54 (s, 1H), 8.39 (d, *J* = 9.2 Hz, 1H), 8.35 (s, 1H), 8.13 – 8.03 (m, 2H), 7.15 (d, *J* = 9.3 Hz, 1H), 6.87 (s, 1H), δ 5.19 (dtt, *J* = 56.9, 6.5, 3.6 Hz, 1H), 4.11 (s, 3H) 3.76 – 3.68 (m, 2H), 3.55 (d, *J* = 9.3 Hz, 2H), 3.41 (s, 1H), 2.42 – 2.27 (m, 3H), 2.14 (ddd, *J* = 16.8, 10.5, 5.0 Hz, 3H), 1.87 – 1.76 (m, 1H)

Example 86: Synthesis of Compounds 183, 186, 187, 191, 201-203, 206-210, and 248-251

Synthesis of Intermediate B159

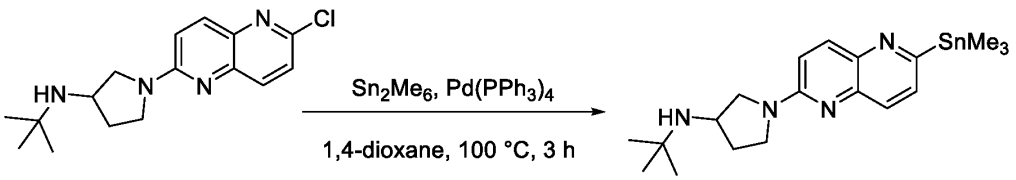


B159

To a mixture of 2,6-dichloro-1,5-naphthyridine (2 g, 10.049 mmol, 1 equiv) and N-tert-butylpyrrolidin-3-amine (1.43 g, 10.049 mmol, 1 equiv) in DMSO (20 mL) was added DIEA (3.90 g, 30.147 mmol, 3 equiv). After stirring for 16 h at 100 °C under a nitrogen atmosphere. The reaction mixture was cooled to 25°C, then poured into ice water and stirred for 0.5 h to form

a precipitate. The precipitated solid were collected by filtration and washed with water (3x30 mL) to afford N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (2 g, 65.29%) as a solid.

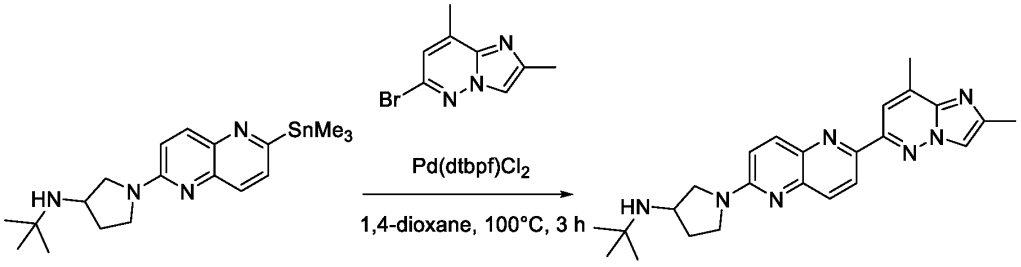
Synthesis of Intermediate B160



B159 B160

To a stirred mixture of N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (1 g, 3.281 mmol, 1 equiv) and Pd(PPh3)4 (0.38 g, 0.328 mmol, 0.1 equiv) in dioxane (10 mL) was added hexamethyldistannane (1.61 g, 4.921 mmol, 1.5 equiv) in portions. The reaction mixture was stirred for 3 h at 100 °C under N_2 atmosphere. The resulting mixture was cooled to room temperature, washed with KF (1x20 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, washed with water (3x30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford N-tert-butyl-1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl] pyrrolidin-3-amine (2 g, 98.51%) as a solid.

Synthesis of Compound 186

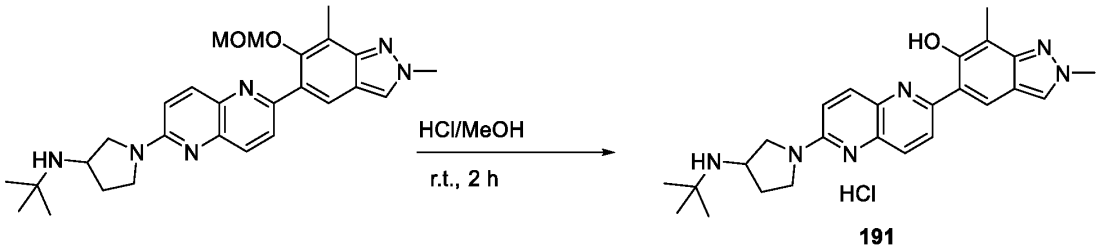


B160 186

To a mixture of N-tert-butyl-1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (100 mg, 0.231 mmol, 1 equiv) and 6-bromo-2,8-dimethylimidazo[1,2-b]pyridazine (52.19 mg, 0.231 mmol, 1 equiv) in 1,4-dioxane (2 mL) was added Pd(DtBPF)Cl_2 (15.05 mg, 0.023 mmol, 0.1 equiv) . After stirring for 3 h at 100 °C under a nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm, 5μm;

mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (5% ACN up to 57% in 8 min); Detector, uv) to afford N-tert-butyl-1-(6-{2,8-dimethylimidazo [1,2-b]pyridazin-6-yl}-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (6.0 mg, 6.25%) as a solid.

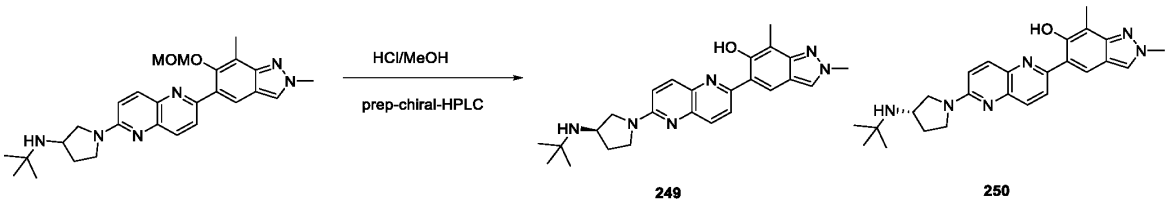
Synthesis of Compound 191



191

A mixture of N-tert-butyl-1-{6-[6-(methoxymethoxy)-2,7-dimethylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (50 mg, 0.105 mmol, 1 equiv) and HCl (gas) in 1,4-dioxane (1 mL, 32.912 mmol, 312.41 equiv) in methanol (1 mL, 24.699 mmol, 234.45 equiv) was stirred for 2 h at 25 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, Xselect CSH C18 OBD Column 30*150mm 5um, n; mobile phase, Water (0.05%HCl) and ACN (hold 3% ACN in 2 min, up to 43% in 6 min); Detector, uv) to afford 5-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin -2-yl}-2,7-dimethylindazol-6-ol hydrochloride (6.5 mg, 13.21%) as a solid.

Synthesis of Compounds 249 and 250

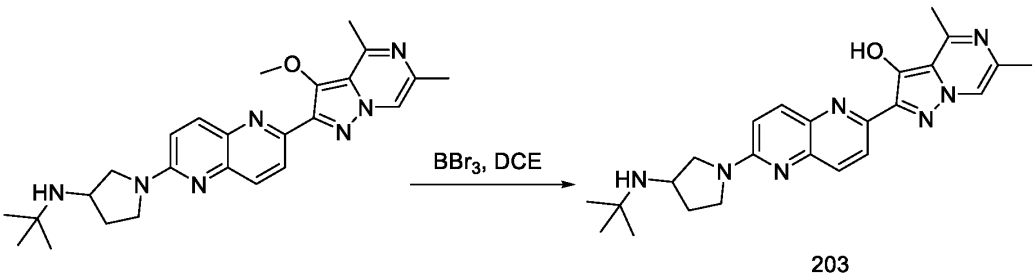


249 250

To a solution of N-tert-butyl-1-{6-[6-(methoxymethoxy)-2,7-dimethylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (80 mg, 0.169 mmol, 1 equiv) in methanol (1 mL) was added HCl (gas) in 1,4-dioxane (1 mL, 32.912 mmol, 195.25 equiv). The reaction mixture was stirred for 2 h at 25 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, YMC-Actus Triart C18, 30*150 mm,5μm; mobile phase, Water (10 mmol/L

NH_4HCO_3) and ACN (15% ACN up to 80% in 8 min)), followed by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, CHIRAL ART Cellulose-SB, 2*25 cm, 5 um; mobile phase, MtBE(0.1% DEA) and MeOH- (hold 30% MeOH- in 6.5 min)) to afford (R)-5-(6-(3-(tert-butylamino)pyrrolidin-1-yl)-1,5-naphthyridin-2-yl)-2,7-dimethyl-2H-indazol-6-ol (18.0 mg, 24.80%) and (S)-5-(6-(3-(tert-butylamino)pyrrolidin-1-yl)-1,5-naphthyridin-2-yl)-2,7-dimethyl-2H-indazol-6-ol (12.3 mg, 16.95%) as solids. The absolute stereochemistry of the compounds was arbitrarily assigned.

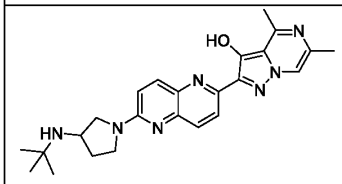
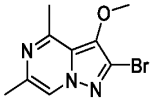
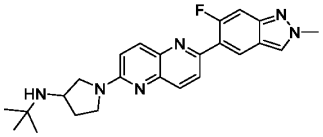
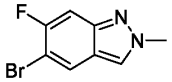
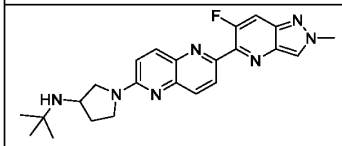
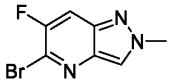
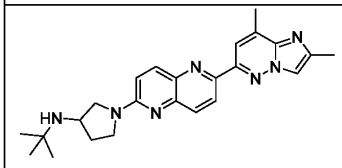
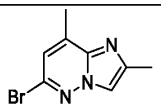
Synthesis of Compound 203

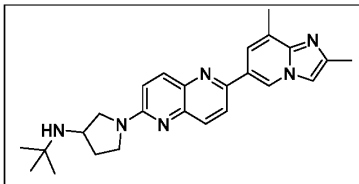
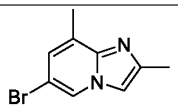
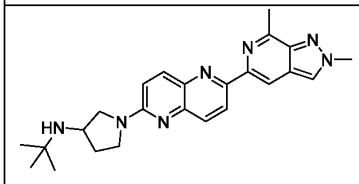
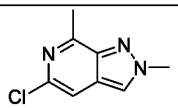
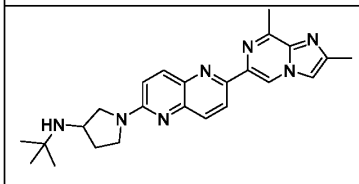
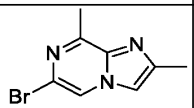
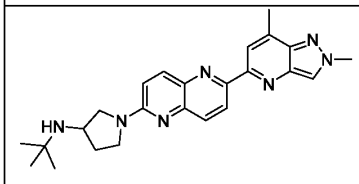
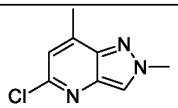


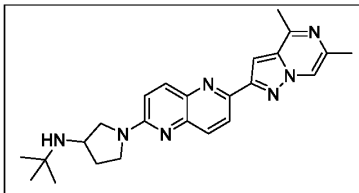
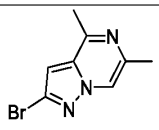
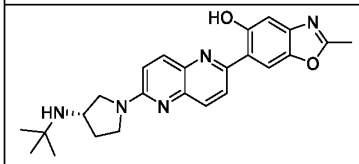
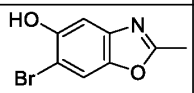
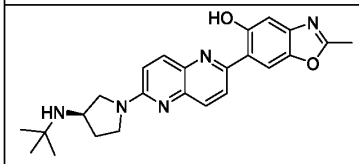
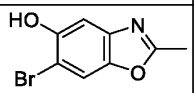
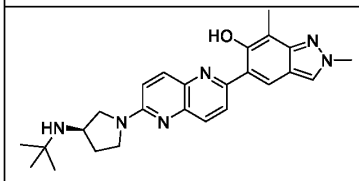
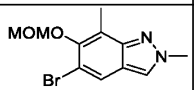
203

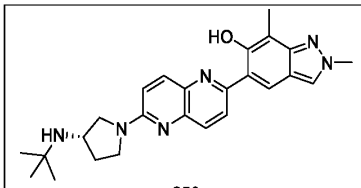
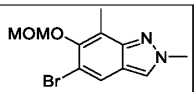
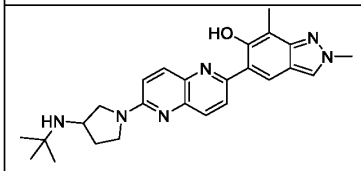
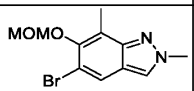
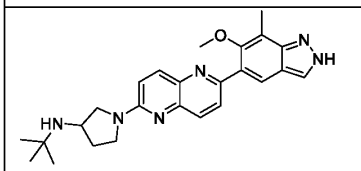
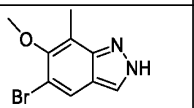
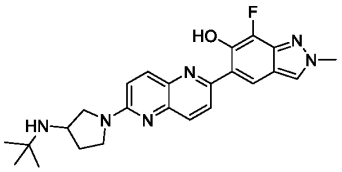
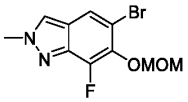
To a solution of N-tert-butyl-1-(6-{3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl} -1,5-naphthyridin-2-yl)pyrrolidin-3-amine (80 mg, 0.180 mmol, 1 equiv) in DCE (2 mL, 25.263 mmol, 140.71 equiv) was added BBr_3 (0.5 mL, 5.289 mmol, 29.46 equiv). The reaction mixture was stirred for 3 h at 80 °C under a nitrogen atmosphere. The reaction mixture was quenched with methanol at 0°C, then concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC ((2#SHIMADZU (HPLC-01)): Column, XBridge Prep OBD C18 Column, 30*150 mm, 5μm; mobile phase, Water (10 mmol/L NH_4HCO_3) and ACN (10% ACN up to 55% in 8 min); Detector, uv) to afford 2-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-4,6-dimethylpyrazolo[1,5-a]pyrazin-3-ol (6.9 mg, 8.91%) as a solid.

Compounds 183, 186, 187, 191, 201-203, 206-210, and 248-251 were prepared according to the procedures outlined herein, outlined in this Example 85. The table below provides intermediates used in these procedures and final compound characterization data.

Compound No. and Structure	Coupling Reagent	LCMS (ESI, *m/z*) $[M+H]^+$	^1H NMR δ
 203		432	(400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.29 – 8.20 (m, 2H), 8.12 – 8.02 (m, 2H), 7.16 (d, *J* = 9.3 Hz, 1H), 3.86 (s, 1H), 3.71 (s, 1H), 3.50 (dt, *J* = 18.0, 10.2 Hz, 2H), 3.14 (s, 1H), 2.75 (s, 3H), 2.35 (d, *J* = 1.1 Hz, 3H), 2.19 (s, 1H), 1.77 (s, 1H), 1.10 (s, 9H)
 183		419	(400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 8.09 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.97 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.85 (dd, *J* = 8.7, 3.1 Hz, 1H), 7.48 (d, *J* = 12.7 Hz, 1H), 7.13 (d, *J* = 9.4 Hz, 1H), 4.19 (s, 3H), 3.87 (s, 1H), 3.72 (s, 1H), 3.51 (dq, *J* = 18.1, 9.0, 8.1 Hz, 2H), 3.19 – 3.07 (m, 1H), 2.19 (q, *J* = 4.4, 3.8 Hz, 1H), 1.96 – 1.61 (m, 2H), 1.10 (s, 9H)
 207		420	(400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.19 – 7.88 (m, 4H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.24 (s, 3H), 3.87 (s, 1H), 3.73 (s, 1H), 3.50 (dd, *J* = 17.6, 9.1 Hz, 2H), 3.21 – 3.08 (m, 1H), 2.18 (q, *J* = 8.8, 7.1 Hz, 1H), 1.86 – 1.63 (m, 2H), 1.10 (s, 9H)
 186		416	(400 MHz, DMSO-*d6*) δ 8.39 (d, *J* = 8.8 Hz, 1H), 8.13 (dd, *J* = 9.3, 0.8 Hz, 1H), 8.10 – 7.95 (m, 3H), 7.16 (d, *J* = 9.3 Hz, 1H), 3.96 – 3.80 (m, 1H), 3.74 (s, 1H), 3.62 – 3.45 (m, 2H), 3.16 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.65 (d, *J* = 1.1 Hz, 3H), 2.43 (d, *J* = 0.9 Hz, 3H), 2.20 (td, *J* = 11.0, 10.4, 6.4 Hz, 1H), 1.85 – 1.71 (m, 1H), 1.65 (s, 1H), 1.11 (s, 9H)

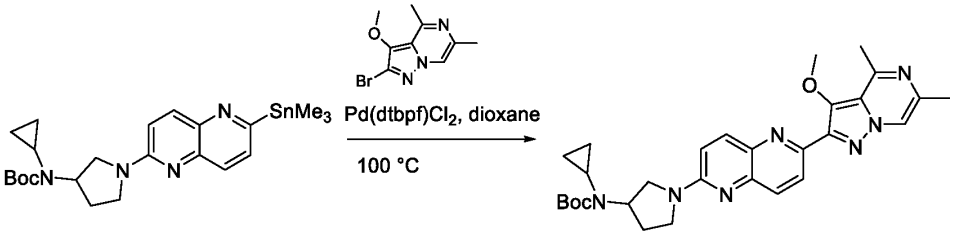
 201		415	(400 MHz, DMSO-d_6) δ 9.13 (d, J = 2.2 Hz, 1H), 8.08 (dd, J = 9.1, 6.7 Hz, 2H), 7.98 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 1.1 Hz, 1H), 7.12 (d, J = 9.3 Hz, 1H), 3.86 (s, 1H), 3.70 (s, 1H), 3.59 – 3.40 (m, 2H), 3.12 (s, 1H), 2.54 (s, 3H), 2.36 (d, J = 0.9 Hz, 3H), 2.18 (s, 1H), 1.76 (t, J = 10.0 Hz, 1H), 1.10 (s, 9H)
 208		416	(400 MHz, DMSO-d_6) δ 8.63 – 8.52 (m, 3H), 8.06 (dd, J = 9.3, 0.8 Hz, 1H), 7.98 (dd, J = 8.9, 0.8 Hz, 1H), 7.11 (d, J = 9.3 Hz, 1H), 4.27 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.49 (ddd, J = 17.5, 11.9, 7.6 Hz, 2H), 3.12 (dd, J = 10.4, 7.2 Hz, 1H), 2.83 (s, 3H), 2.25 – 2.12 (m, 1H), 1.83 – 1.72 (m, 1H), 1.69 (d, J = 12.4 Hz, 1H), 1.09 (s, 9H)
 248		416	(400 MHz, DMSO-d_6) δ 9.29 (d, J = 0.8 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 8.09 – 7.97 (m, 3H), 7.13 (d, J = 9.3 Hz, 1H), 3.86 (s, 1H), 3.70 (d, J = 9.9 Hz, 1H), 3.60 – 3.41 (m, 2H), 3.13 (dd, J = 10.4, 7.3 Hz, 1H), 2.81 (s, 3H), 2.46 – 2.38 (m, 3H), 2.18 (q, J = 4.6, 3.5 Hz, 1H), 1.85 – 1.65 (m, 2H), 1.09 (s, 9H)
 206		416	(400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.59 (d, J = 8.9 Hz, 1H), 8.31 (d, J = 1.2 Hz, 1H), 8.12 (dd, J = 9.3, 0.8 Hz, 1H), 7.98 (dd, J = 8.9, 0.8 Hz, 1H), 7.13 (d, J = 9.3 Hz, 1H), 4.24 (s, 3H), 3.87 (s, 1H), 3.72 (s, 1H), 3.61 – 3.43 (m, 2H), 3.15 (d, J = 9.6 Hz, 1H), 2.65 (d, J = 1.1 Hz, 3H), 2.27 – 2.12 (m, 1H), 1.93 – 1.58 (m, 2H), 1.10 (s, 9H)

 187		416	(400 MHz, DMSO-d_6) δ 8.49 (q, *J* = 1.0 Hz, 1H), 8.24 (d, *J* = 8.7 Hz, 1H), 8.08 (dd, *J* = 9.3, 0.8 Hz, 1H), 7.99 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.49 (d, *J* = 1.0 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 3.88 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.72 (d, *J* = 9.3 Hz, 1H), 3.51 (dt, *J* = 10.4, 7.4 Hz, 2H), 3.15 (dd, *J* = 10.5, 7.2 Hz, 1H), 2.74 (s, 3H), 2.45 (d, *J* = 1.0 Hz, 3H), 2.25 – 2.14 (m, 1H), 1.77 (dq, *J* = 12.0, 8.5 Hz, 1H), 1.63 (s, 1H), 1.11 (s, 9H)
 209		418	(400 MHz, DMSO-d_6) δ 14.52 (s, 1H), 8.48 – 8.36 (m, 2H), 8.10 (dd, *J* = 13.8, 9.2 Hz, 2H), 7.16 (d, *J* = 9.3 Hz, 1H), 7.12 (s, 1H), 3.87 (s, 1H), 3.72 (s, 1H), 3.58 (s, 1H), 3.49 (d, *J* = 8.3 Hz, 1H), 3.17 (s, 1H), 2.61 (s, 3H), 2.20 (s, 1H), 1.80 (s, 2H), 1.12 (s, 9H)
 210		418	(400 MHz, DMSO-d_6) δ 14.52 (s, 1H), 8.46 – 8.34 (m, 2H), 8.09 (dd, *J* = 12.2, 9.2 Hz, 2H), 7.20 – 7.06 (m, 2H), 3.86 (s, 1H), 3.71 (s, 1H), 3.49 (dt, *J* = 18.5, 9.0 Hz, 2H), 3.13 (s, 1H), 2.61 (s, 3H), 2.18 (s, 1H), 1.77 (d, *J* = 11.9 Hz, 2H), 1.10 (s, 9H)
 249		431	(400 MHz, DMSO-d_6) δ 14.33 (s, 1H), 8.43 – 8.34 (m, 2H), 8.33 (s, 1H), 8.12 (d, *J* = 9.3 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.86 (s, 1H), 3.71 (s, 1H), 3.48 (q, *J* = 9.3 Hz, 2H), 3.13 (s, 1H), 2.38 (s, 3H), 2.18 (s, 1H), 1.76 (s, 2H), 1.10 (s, 9H)

 250		431	(400 MHz, DMSO-d_6) δ 14.33 (s, 1H), 8.43 – 8.36 (m, 2H), 8.32 (s, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 8.05 (d, *J* = 9.1 Hz, 1H), 7.14 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.91 (d, *J* = 38.0 Hz, 1H), 3.71 (s, 1H), 3.61 – 3.42 (m, 2H), 3.13 (s, 1H), 2.38 (s, 3H), 2.18 (d, *J* = 8.4 Hz, 1H), 1.76 (s, 2H), 1.10 (s, 9H)
 191		431	(400 MHz, DMSO-d_6) δ 14.10 (s, 1H), 8.99 (s, 2H), 8.48 (d, *J* = 9.3 Hz, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 8.30 (d, *J* = 9.3 Hz, 1H), 8.23 (s, 1H), 7.33 (d, *J* = 9.4 Hz, 1H), 4.23 - 4.16(m, 1H), 4.14 (s, 3H), 4.08 (d, *J* = 7.1 Hz, 1H), 3.85 (s, 2H), 3.74(s, 1H), 2.47 (s, 1H), 2.39 (s, 3H), 2.34 - 2.31(m, 1H), 1.40 (s, 9H)
 251		431	(400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 8.15 - 8.04 (m, 2H), 8.01 - 7.86 (m, 3H), 7.10 (d, *J* = 9.3 Hz, 1H), 3.86 (s, 1H), 3.72 (s, 1H), 3.60 - 3.47 (m, 1H), 3.34 (s, 3H), 3.18 - 3.08 (m, 1H), 2.26 - 2.11 (m, 1H), 1.77 (t, *J* = 10.3 Hz, 2H), 1.10 (s, 9H)
 202		435	(400 MHz, DMSO-d_6) δ 14.43 (s, 1H), 8.48 (d, *J* = 2.7 Hz, 1H), 8.40 (dd, *J* = 5.2, 4.2 Hz, 2H), 8.11 (dd, *J* = 18.9, 9.2 Hz, 2H), 7.16 (d, *J* = 9.3 Hz, 1H), 4.16 (s, 3H), 3.86 (s, 1H), 3.72 (s, 1H), 3.59 – 3.41 (m, 2H), 3.14 (s, 1H), 2.18 (s, 1H), 1.84 – 1.67 (m, 1H), 1.10 (s, 9H)

Example 87: Synthesis of Compound 252

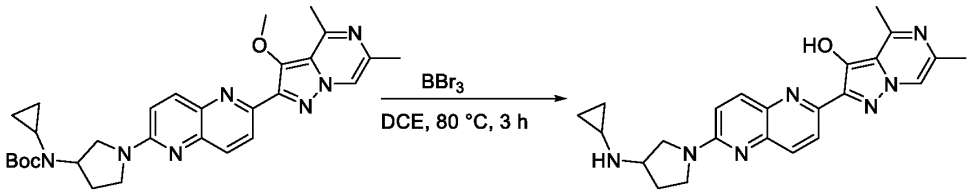
Synthesis of Intermediate B161



B161

To a mixture of tert-butyl cyclopropyl(1-(6-(trimethylstannyl)-1,5-naphthyridin-2-yl)pyrrolidin -3-yl)carbamate (100 mg, 0.19 mmol, 1 equiv) and 2-bromo-3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazine (49.2 mg, 0.19 mmol, 1 equiv) in 1,4-dioxane (2 mL) was added Pd(DtBPF)Cl_2 (12.5 mg, 0.019 mmol, 0.1 equiv). The reaction mixture was stirred for 3 h at 100°C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 19) to afford tert-butyl cyclopropyl(1-(6-(3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazin-2-yl)-1,5-naphthyridin-2-yl)pyrrolidin-3-yl)carbamate (60 mg, 58.8%) as a solid.

Synthesis of Compound 252



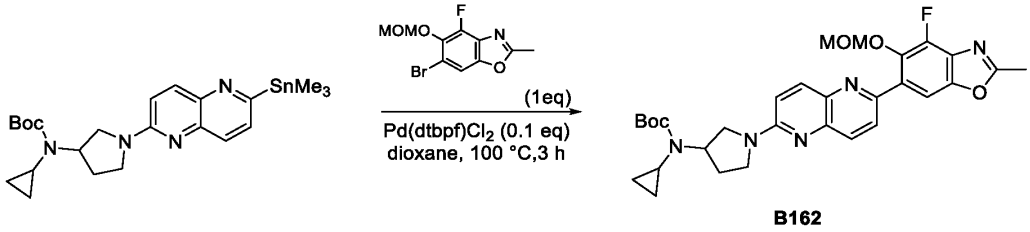
B161 252

To a solution of tert-butyl N-cyclopropyl-N-[1-(6-{3-methoxy-4,6-dimethylpyrazolo[1,5-a]pyrazine -2-yl}-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]carbamate (60 mg, 0.113 mmol, 1 equiv) in DCE (2 mL) was added BBr_3 (0.5 mL). The reaction mixture was stirred for 3 h at 80 °C under a nitrogen atmosphere, then quenched with MeOH at 0 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 1, Gradient 23) to afford 2-{6-[3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl} -4,6-dimethylpyrazolo[1,5-a]pyrazin-3-ol (3.9 mg, 8.29%) as a solid. **LCMS**: (ES, *m/z*): 416 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 8.32 – 8.19 (m, 2H), 8.13 – 7.95 (m, 2H), 7.16 (d, *J* = 9.3 Hz, 1H), 3.87 – 3.62 (m, 2H), 3.61 – 3.44 (m, 2H), 3.41 (s,

1H), 2.75 (s, 3H), 2.38 – 2.28 (m, 3H), 2.12 (dq, *J* = 6.7, 3.7 Hz, 2H), 1.92 (s, 1H), 0.45 – 0.38 (m, 2H), 0.30 – 0.20 (m, 2H).

Example 88: Synthesis of Compounds 253 and 254

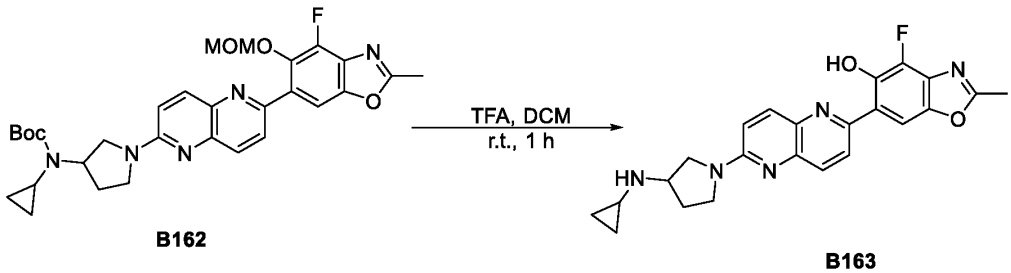
Synthesis of Intermediate B162



B162

A mixture of tert-butyl N-cyclopropyl-N-{1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-yl}carbamate (220 mg, 0.425 mmol, 1 equiv) and Pd(DtBPF)Cl_2 (28 mg, 0.043 mmol, 0.1 equiv) in dioxane (11 mL) was stirred for 30 min at 100 °C under nitrogen atmosphere. To the reaction mixture was added 6-bromo-4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazole (123 mg, 0.425 mmol, 1 equiv) in dioxane (0.7 mL) dropwise over 2 min at 100 °C. The resulting mixture was stirred for an additional 3 h at 100 °C, then cooled to room temperature. The resulting mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-cyclopropyl-N-(1-{6-[4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (120 mg, 50.06%) as a solid. **LCMS** (ES, *m/z*):564 $[M+H]^+$.

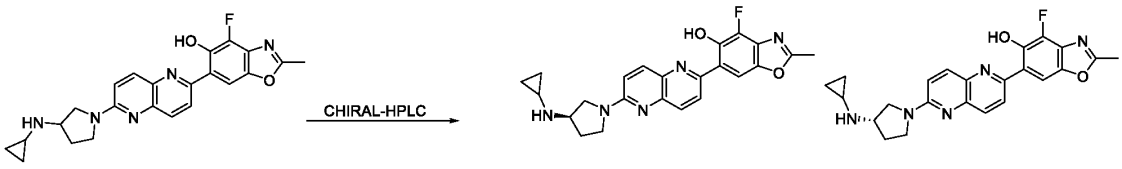
Synthesis of Intermediate B163



B162 **B163**

A solution of tert-butyl N-cyclopropyl-N-(1-{6-[4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (110 mg, 0.195 mmol, 1 equiv) in TFA (1 mL) and DCM (3 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by reverse flash chromatography (column, C18 silica gel; mobile phase, water (10 mmol/L NH_4HCO_3) and ACN, 20% to 40% gradient in 30 min; detector, UV 220 nm) to afford 6-{6-[3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-4-fluoro-2-methyl-1,3-benzoxazol-5-ol (70 mg, 85.51%) as a solid. **LCMS** (ES, *m/z*):420 $[M+H]^+$.

Synthesis of Compounds 253 and 254

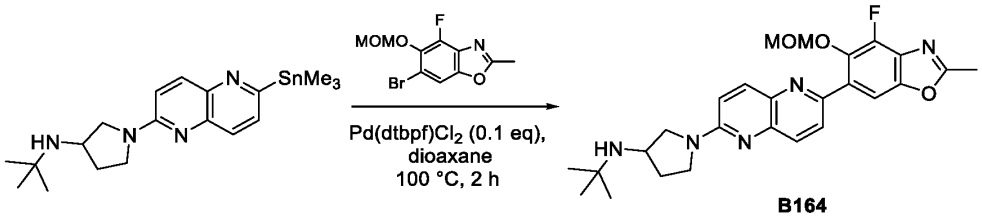


B163 253 254

6-{6-[3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-4-fluoro-2-methyl-1,3-benzoxazol-5-ol (70 mg, 0.167 mmol, 1 equiv) was purified by Chiral-Prep-HPLC (Condition 1, Gradient 11) to afford Compound **253** (First peak) (14.1 mg) and Compound **254** (Second peak) (16.8 mg) as solids. Compound **253: LCMS**: (ES, *m/z*):420 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 15.08 (s, 1H), 8.44 (d, *J* = 9.3 Hz, 1H), 8.33 (d, *J* = 1.4 Hz, 1H), 8.14 (dd, *J* = 20.8, 9.2 Hz, 2H), 7.18 (d, *J* = 9.3 Hz, 1H), 3.76~3.74(m, 1H), 3.67~3.65 (m, 1H), 3.58~3.50 (m, 2H), 3.45~3.40 (m, 1H), 2.64 (s, 3H), 2.18 – 2.10 (m, 2H), 1.94 (s, 1H), 0.47 – 0.36 (m, 2H), 0.32 – 0.19 (m, 2H). Compound **254: LCMS**: (ES, *m/z*):420 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 15.07 (s, 1H), 8.44 (dd, *J* = 9.2, 1.8 Hz, 1H), 8.32 (d, *J* = 2.1 Hz, 1H), 8.16 (dd, *J* = 9.3, 1.9 Hz, 1H), 8.13 – 8.07 (m, 1H), 7.18 (dd, *J* = 9.2, 1.6 Hz, 1H), 3.76~3.74 (m, 1H), 3.67~3.65 (m, 1H), 3.59 – 3.51 (m, 2H), 3.45~3.40 (m, 1H), 2.64 (s, 3H), 2.17 (dq, *J* = 12.5, 6.1, 4.8 Hz, 2H), 1.96 (s, 1H), 0.51 – 0.38 (m, 2H), 0.35 – 0.24 (m, 2H). The absolute stereochemistry of the compounds was arbitrarily assigned.

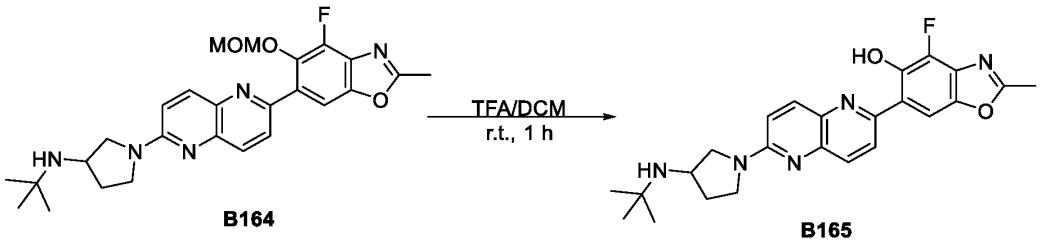
Example 89: Synthesis of Compounds 255 and 256

Synthesis of Intermediate B164



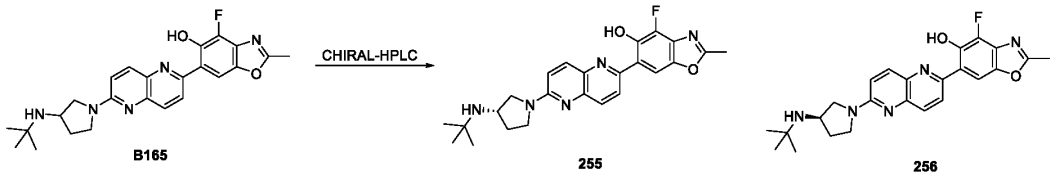
A mixture of N-tert-butyl-1-[6-(trimethylstannyl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (300 mg, 0.693 mmol, 1 equiv), 6-bromo-4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazole (201 mg, 0.693 mmol, 1 equiv), and Pd(DtBPF)Cl_2 (45 mg, 0.069 mmol, 0.1 equiv) in dioxane (3 mL) was stirred for 2 h at 100 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature. The resulting mixture was poured into water (30 mL), extracted with ethyl acetate (3 x 30 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford N-tert-butyl-1-{6-[4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (120 mg, 36.13%) as a solid. **LCMS** (ES, *m/z*):480 $[M+H]^+$.

Synthesis of Intermediate B165



A solution of N-tert-butyl-1-{6-[4-fluoro-5-(methoxymethoxy)-2-methyl-1,3-benzoxazol -6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-amine (120 mg, 0.245 mmol, 1 equiv) in TFA (1 mL) and DCM (3 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to give a resiude. The residue was purified by reverse flash (Condition 3, Gradient 1) to afford 6-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-4-fluoro-2-methyl -1,3-benzoxazol-5-ol (80 mg, 70.23%) as a solid. **LCMS** (ES, *m/z*):436 $[M+H]^+$.

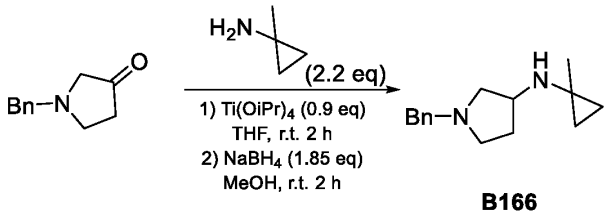
Synthesis of Compound 255 and 256



(6-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-4-fluoro-2-methyl-1,3-benzoxazol-5-ol (80 mg, 0.184 mmol, 1 equiv) was purified by Chiral-Prep-HPLC (Condition 1, Gradient 12) to afford Compound **255** (First peak) and Compound **256** (Second peak) as solids. Compound **255: LCMS**: (ES, *m/z*):436 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 15.06 (s, 1H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.31 (d, *J* = 1.4 Hz, 1H), 8.18 – 8.06 (m, 2H), 7.17 (d, *J* = 9.3 Hz, 1H), 3.86 (s, 1H), 3.71 (s, 1H), 3.53 (s, 1H), 3.48 (q, *J* = 9.1, 8.6 Hz, 1H), 3.13 (s, 1H), 2.64 (s, 3H), 2.18 (d, *J* = 8.2 Hz, 1H), 1.76 (s, 2H), 1.09 (s, 9H). Compound **256: LCMS**: (ES, *m/z*):436 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 15.06 (s, 1H), 8.43 (d, *J* = 9.2 Hz, 1H), 8.31 (d, *J* = 1.4 Hz, 1H), 8.18 – 8.06 (m, 2H), 7.17 (d, *J* = 9.3 Hz, 1H), 3.86 (s, 1H), 3.71 (s, 1H), 3.53 (s, 1H), 3.48 (q, *J* = 9.1, 8.6 Hz, 1H), 3.13 (s, 1H), 2.64 (s, 3H), 2.18 (d, *J* = 8.2 Hz, 1H), 1.76 (s, 2H), 1.09 (s, 9H). The absolute stereochemistry of the compounds was arbitrarily assigned.

Example 90: Synthesis of Compounds 257 and 258

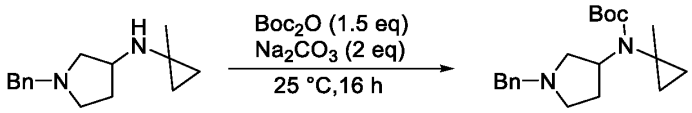
Synthesis of Intermediate B166



A mixture of 1-benzylpyrrolidin-3-one (800 mg, 4.565 mmol, 1.00 equiv), 1-methylcyclopropan-1-amine (714 mg, 10.043 mmol, 2.2 equiv), and $Ti(OiPr)_4$ (1.16 g, 4.108 mmol, 0.9eq) in THF (8 mL) was stirred for 2 h at 25 °C under N_2 atmosphere. To the reaction mixture was added $NaBH_4$ (319 mg, 8.445 mmol, 1.85 equiv) over the course of 0.5 h at 0 °C. The resulting mixture was stirred for an additional 2 h at 25 °C. The resulting mixture was concentrated under reduced pressure and extracted with ethyl acetate (1 x 20 mL). The organic layers were combined, washed with water (3 x 20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 1-benzyl-N-(1-

methylcyclopropyl)pyrrolidin-3-amine (900 mg, 68.46%) as a solid. **LCMS** (ES, *m/z*):231 $[M+H]^+$.

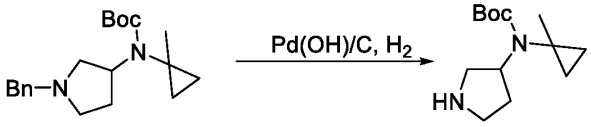
Synthesis of Intermediate B167



B166 **B167**

To a stirred mixture of 1-benzyl-N-(1-methylcyclopropyl)pyrrolidin-3-amine (800 mg, 3.473 mmol, 1.00 equiv) and Na_2CO_3 (736 mg, 6.946 mmol, 2 equiv) in THF (20 mL) was added $(Boc)_2O$ (11.4 g, 5.210 mmol, 1.5 equiv) in portions. The reaction mixture was stirred for 16 h at 25 °C. The resulting mixture was diluted with ethyl acetate (1 x 10 mL). The organic layers were combined, washed with water (3 x 20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue product was purified by reverse phase flash with the following conditions PE/EA (1/3) to afford tert-butyl N-(1-benzylpyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (480 mg, 33.46%) as an oil. **LCMS** (ES, *m/z*):331 $[M+H]^+$.

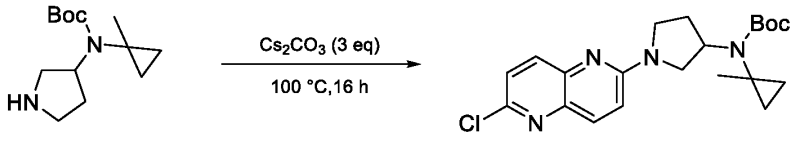
Synthesis of Intermediate B168



B167 **B168**

To a solution of tert-butyl N-(1-benzylpyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (500 mg, 1.513 mmol, 1.00 equiv) in methanol (5 mL) was added $Pd(OH)_2/C$ (10%, 50 mg) in a pressure tank. The reaction mixture was hydrogenated for 24 h at room temperature under 30 psi of hydrogen pressure, then filtered through a Celite pad, and the filtrate concentrated under reduced pressure to afford tert-butyl N-(1-methylcyclopropyl)-N-(pyrrolidin-3-yl)carbamate (320 mg, 88.00%) as an oil. **LCMS** (ES, *m/z*):241 $[M+H]^+$.

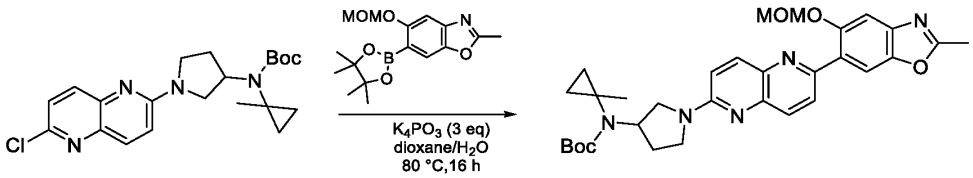
Synthesis of Intermediate B169



B168 **B169**

A solution of tert-butyl N-(1-methylcyclopropyl)-N-(pyrrolidin-3-yl)carbamate (1 g, 4.161 mmol, 1 equiv), 2,6-dichloro-1,5-naphthyridine (0.50 g, 2.497 mmol, 0.6 equiv), and Cs_2CO_3 (4.07 g, 12.483 mmol, 3 equiv) in DMSO (10 mL) was stirred for 2 h at 100 °C. The reaction mixture was cooled to room temperature, then poured into water at room temperature, and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-(1-methylcyclopropyl)carbamate (762 mg, 45.45%) as a solid. **LCMS** (ES, *m/z*):403 $[M+H]^+$.

Synthesis of Intermediate B170

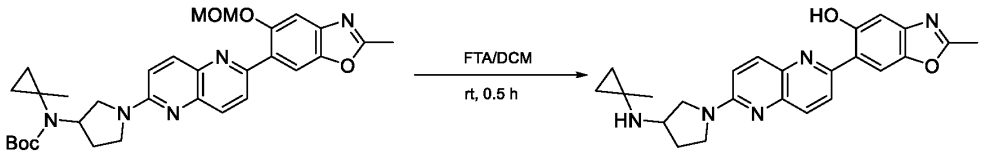


B169 **B170**

A mixture of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N- (1-methylcyclopropyl)carbamate (250 mg, 0.620 mmol, 1 equiv), 5-(methoxymethoxy)-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (198 mg, 0.620 mmol, 1 equiv), Pd(DtBPF)Cl_2 (40 mg, 0.062 mmol, 0.1 equiv), and K_3PO_4 (263 mg, 1.240 mmol, 2 equiv) in dioxane (5 mL) and water (1 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then poured into water (20 mL), and extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:5) to afford tert-butyl N-(1-{6-[5-

(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin -2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (150 mg, 42.33%) as a solid. **LCMS** (ES, *m/z*):560 $[M+H]^+$.

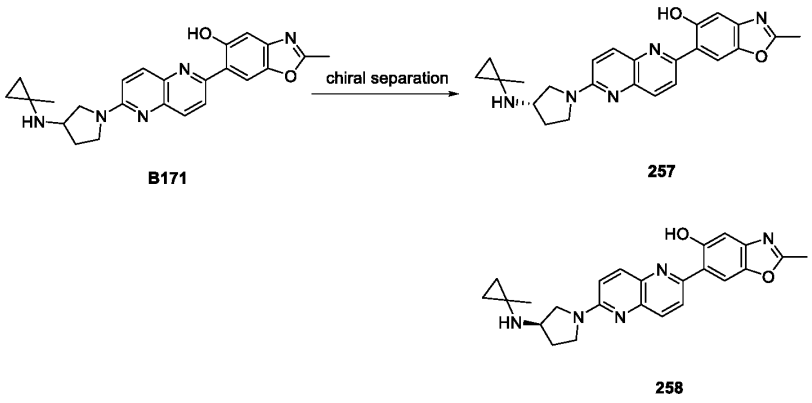
Synthesis of Intermediate B171



B170 **B171**

A solution of tert-butyl N-(1-{6-[5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)-N-(1-methylcyclopropyl)carbamate (150 mg, 0.268 mmol, 1 equiv) in TFA (1 mL) and DCM (3 mL) was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by reverse flash chromatography (Condition 3, Gradient 2) to afford 2-methyl-6-(6-{3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl} -1,5-naphthyridin-2-yl)-1,3-benzoxazol-5-ol (50 mg, 44.90%) as a solid. **LCMS** (ES, *m/z*):416 $[M+H]^+$.

Synthesis of Compound 257 and 258



B171 **257**

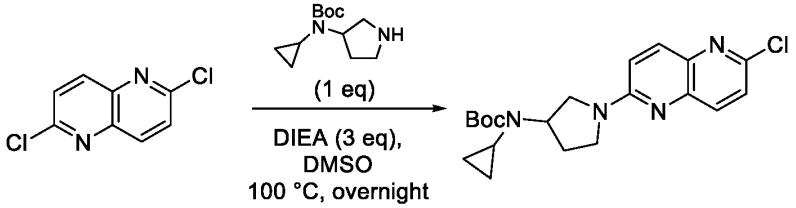
258

2-methyl-6-(6-{3-[(1-methylcyclopropyl)amino]pyrrolidin-1-yl}-1,5-naphthyridin-2-yl)-1,3-benzoxazol-5-ol was purified by PREP-CHIRAL-HPLC (Condition 1, Gradient 13) to afford Compound **257** (First peak) (13.9 mg) and Compound **258** (Second peak) (4.5 mg) as solids. Compound **257: LCMS** (ES, *m/z*):416 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.42 (t, J = 4.6 Hz, 2H), 8.10 (dd, J = 12.8, 9.2 Hz, 2H), 7.18 – 7.09 (m, 2H), 3.78 (s, 1H), 3.65 (d, J = 6.6 Hz, 2H), 3.53 (d, J = 9.4 Hz, 1H), 3.32 – 3.34(m, 1H), 2.61 (s, 3H), 2.13 (dd, J = 12.1,

6.3 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.27 (s, 3H), 0.53 – 0.45 (m, 2H), 0.35 – 0.30 (s, 2H). Compound **258: LCMS** (ES, *m/z*):416 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.42 (t, *J* = 4.6 Hz, 2H), 8.10 (dd, *J* = 12.8, 9.2 Hz, 2H), 7.18 – 7.09 (m, 2H), 3.78 (s, 1H), 3.65 (d, *J* = 6.6 Hz, 2H), 3.53 (d, *J* = 9.4 Hz, 1H), 3.32 – 3.34(m, 1H), 2.61 (s, 3H), 2.13 (dd, *J* = 12.1, 6.3 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.27 (s, 3H), 0.53 – 0.45 (m, 2H), 0.35 – 0.30 (s, 2H). The absolute stereochemistry of the compound was arbitrarily assigned.

Example 91: Synthesis of Compounds 211 and 212

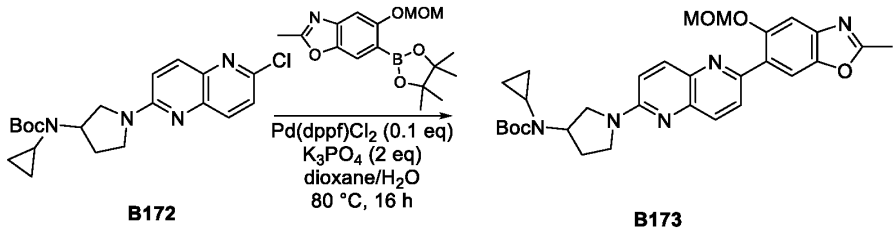
Synthesis of Intermediate B172



B172

A solution of 2,6-dichloro-1,5-naphthyridine (500 mg, 2.512 mmol, 1.00 equiv) and DIEA (974 mg, 7.536 mmol, 3 equiv) in DMSO (10 mL) was stirred overnight at 100 °C. The reaction mixture was cooled to room temperature. The resulting mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-cyclopropylcarbamate (700 mg, 71.65%) as a solid. **LCMS** (ES, *m/z*):389 $[M+H]^+$.

Synthesis of Intermediate B173



B172 **B173**

A solution of tert-butyl N-[1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-yl]-N-cyclopropylcarbamate (200 mg, 0.514 mmol, 1.00 equiv), 5-(methoxymethoxy)-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (246 mg, 0.771 mmol, 1.5 equiv), $Pd(dppf)Cl_2.CH_2Cl_2$ (42 mg, 0.051 mmol, 0.1 equiv), and K_3PO_4 (218 mg, 1.028 mmol, 2 equiv) in dioxane (5 mL) and water (1 mL) was stirred for 16 h at 80 °C under nitrogen atmosphere. The reaction mixture was cooled to room temperature, then poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford tert-butyl N-cyclopropyl-N-(1-{6-[5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (120 mg, 42.76%) as a solid. **LCMS** (ES, *m/z*): 546 $[M+H]^+$.

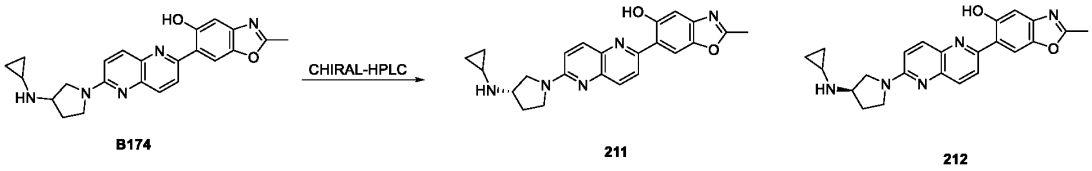
Synthesis of Intermediate B174



B173 **B174**

A solution of tert-butyl N-cyclopropyl-N-(1-{6-[5-(methoxymethoxy)-2-methyl-1,3-benzoxazol-6-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (120 mg, 0.220 mmol, 1.00 equiv) in TFA (1 mL) and DCM (3 mL) was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum to give a residue. The residue was purified by reverse flash chromatography (Condition 3, Gradient 1) to afford 6-{6-[3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methyl-1,3-benzoxazol-5-ol (75 mg, 84.94%) as a solid. **LCMS** (ES, *m/z*): 402 $[M+H]^+$.

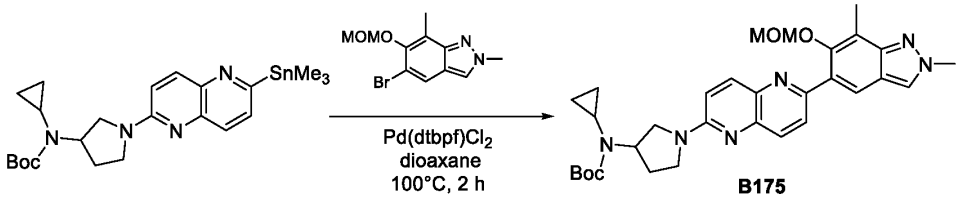
Synthesis of Compounds 211 and 212



6-{6-[3-(cyclopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methyl-1,3-benzoxazol-5-ol (75 mg, 0.187 mmol, 1 equiv) was purified by Chiral-Prep-HPLC (Condition 1, Gradient 2) to compound **211** (First peak) and compound **212** (Second peak) as solids. Compound **211: LCMS**: (ES, *m/z*):402 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.45 – 8.38 (m, 2H), 8.10 (dd, *J* = 14.2, 9.2 Hz, 2H), 7.19 – 7.09 (m, 2H), 3.75 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.66 (m, 1H), 3.57 (m, 2H), 3.52 (p, *J* = 5.8 Hz, 1H), 2.61 (s, 3H), 2.21 – 2.08 (m, 2H), 1.94 (s, 1H), 0.49 – 0.36 (m, 2H), 0.33 – 0.20 (m, *J* = 6.5, 6.1 Hz, 2H). Compound **212: LCMS**: (ES, *m/z*):402 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 14.53 (s, 1H), 8.45 – 8.38 (m, 2H), 8.10 (dd, *J* = 14.2, 9.2 Hz, 2H), 7.19 – 7.09 (m, 2H), 3.75 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.67 (m, 1H), 3.56 (m, 2H), 3.52 (p, *J* = 5.8 Hz, 1H), 2.61 (s, 3H), 2.21 – 2.08 (m, 2H), 1.94 (s, 1H), 0.49 – 0.36 (m, 2H), 0.33 – 0.20 (m, *J* = 6.5, 6.1 Hz, 2H). The absolute stereochemistry of the compounds was arbitrarily assigned.

Example 92: Synthesis of Compounds 259 and 260

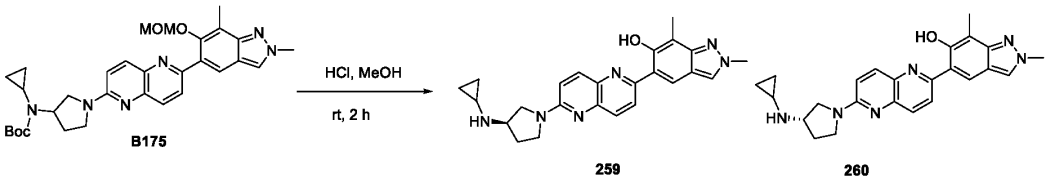
Synthesis of Intermediate B175



To a mixture of tert-butyl cyclopropyl(1-(6-(trimethylstannyl)-1,5-naphthyridin-2-yl)pyrrolidin-3-yl)carbamate (100 mg, 0.19 mmol, 1 equiv) and 5-bromo-6-(methoxymethoxy)-2,7-dimethyl-2H-indazole (53.9 mg, 0.19 mmol, 1 equiv) in 1,4-dioxane (2 mL) was added Pd(DtBPF)Cl_2 (12.5 mg, 0.019 mmol, 0.1 equiv). The reaction mixture was stirred for 2 h at 100 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 3, Gradient 19) to afford tert-butyl N-cyclopropyl-N-(1-

{6-[6-(methoxymethoxy)-2,7-dimethylindazol-5-yl]-1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (70 mg, 65.4%) as a solid.

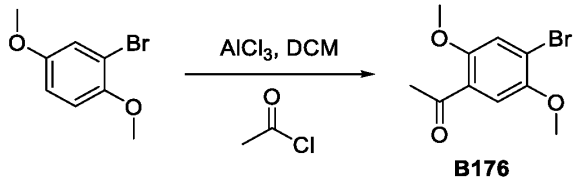
Synthesis of Compound 259 and 260



To a solution of tert-butyl N-cyclopropyl-N-(1-{6-[6-(methoxymethoxy)-2,7-dimethylindazol-5-yl] -1,5-naphthyridin-2-yl}pyrrolidin-3-yl)carbamate (70 mg, 0.125 mmol, 1 equiv) in methanol (2 mL) was added HCl (gas) in 1,4-dioxane (4M, 2 mL). The reaction mixture was stirred for 2 h at 25°C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Chiral-Prep-HPLC (Condition 1, Gradient 21), followed by Chiral-Prep-HPLC (Condition 1, Gradient 5) to afford 5-{6-[(3R)-3-(cyclopropylamino)pyrrolidin -1-yl]-1,5-naphthyridin -2-yl}-2,7-dimethylindazol-6-ol (11.8 mg, 22.72%) and 5-{6-[(3S)-3-(cyclopropylamino) pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2,7-dimethylindazol-6-ol(13.5 mg, 25.99%) as solids. Compound **259: LCMS** (ES, *m/z*): 415 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 14.33 (s, 1H), 8.44 – 8.37 (m, 2H), 8.33 (s, 1H), 8.12 (d, *J* = 9.3 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.75 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.66 (s, 1H), 3.60 – 3.48 (m, 2H), 3.43 (s, 1H), 2.38 (s, 3H), 2.15 (q, *J* = 6.3 Hz, 2H), 1.97 – 1.85 (m, 1H), 0.42 (d, *J* = 6.6 Hz, 2H), 0.36 – 0.19 (m, 2H). Compound **260: LCMS** (ES, *m/z*): 415 $[M+H]^+$. **^{1}H NMR**: (400 MHz, DMSO-d_6) δ 14.33 (s, 1H), 8.44 – 8.37 (m, 2H), 8.33 (s, 1H), 8.12 (d, *J* = 9.3 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.15 (d, *J* = 9.3 Hz, 1H), 4.13 (s, 3H), 3.75 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.66 (s, 1H), 3.60 – 3.48 (m, 2H), 3.43 (s, 1H), 2.38 (s, 3H), 2.15 (q, *J* = 6.3 Hz, 2H), 1.97 – 1.85 (m, 1H), 0.42 (d, *J* = 6.6 Hz, 2H), 0.36 – 0.19 (m, 2H). The absolute stereochemistry of the compounds was arbitrarily assigned.

Example 93: Synthesis of Compound 174

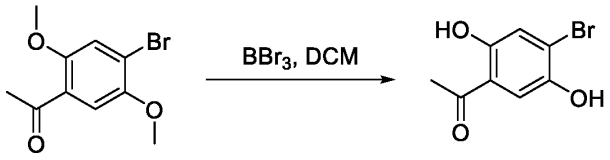
Synthesis of Intermediate B176



B176

To a stirred mixture of 2-bromo-1,4-dimethoxybenzene (10 g, 46.070 mmol, 1.00 equiv) and acetyl chloride (3.98 g, 50.677 mmol, 1.1 equiv) in DCM (100 mL, 1573.005 mmol, 34.14 equiv) was added $AlCl_3$ (6.76 g, 50.677 mmol, 1.1 equiv) in portions at 0 ℃ under nitrogen atmosphere. The reaction mixture was warmed to room temperature, then stirred for 2 h. The reaction mixture was quenched with a 1:10 w/w mixture of ice/concentrated HCl, then extracted with dichloromethane (3 x 100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 1-(4-bromo-2,5-dimethoxyphenyl)ethanone (10 g, 83.78%) as solid. **LCMS** (ES, *m/z*): 259 $[M+H]^+$.

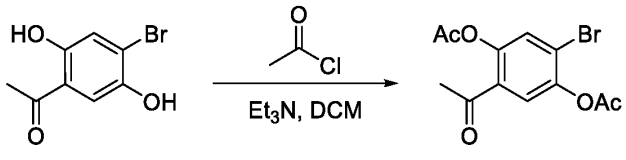
Synthesis of Intermediate B177



B176 **B177**

To a stirred solution of 1-(4-bromo-2,5-dimethoxyphenyl)ethanone (8.2 g, 31.648 mmol, 1.00 equiv) in DCM (82 mL, 1289.864 mmol, 40.76 equiv) was added BBr_3 (39.64 g, 158.240 mmol, 5.0 equiv) dropwise at 0 ℃. The resulting mixture was stirred for 1 day at room temperature, then quenched with methanol (100 mL) dropwise, and concentrated under reduced pressure to afford 1-(4-bromo-2,5-dihydroxyphenyl)ethanone (7.1 g, 97.10%) as a solid. **LCMS** (ES, *m/z*): 231 $[M+H]^+$.

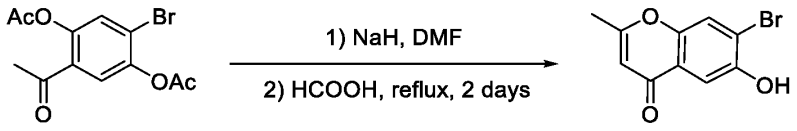
Synthesis of Intermediate B178



B177 **B178**

To a stirred mixture of 1-(4-bromo-2,5-dihydroxyphenyl)ethanone (7 g, 30.297 mmol, 1.00 equiv) and acetyl chloride (13.76 g, 175.287 mmol, 5.79 equiv) in DCM (70 mL) was added Et_3N (8.31 g, 82.123 mmol, 2.71 equiv) dropwise at 0 °C. The reaction mixture was stirred for 16 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography eluted with (PE / EA 5:1) to afford 5-acetyl-4-(acetyloxy)-2-bromophenyl acetate (5.4 g, 55.43%) as a solid. **LCMS** (ES, *m/z*): 315 $[M+H]^+$.

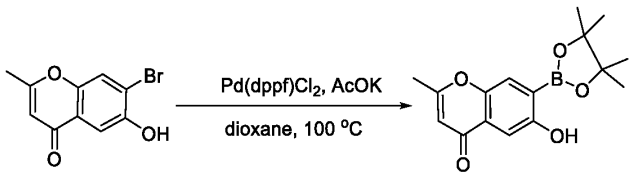
Synthesis of Intermediate B179



B178 **B179**

To a solution of 5-acetyl-4-(acetyloxy)-2-bromophenyl acetate (4.5 g, 14.280 mmol, 1.00 equiv) in DMF (27 mL, 348.887 mmol, 24.43 equiv) was added sodium hydride (60% in oil, 628.27 mg) at 0 °C. The reaction mixture was stirred for 15 min, then warmed to room temperature, and stirred for 2 h. The reaction mixture was quenched with acetic acid and water (100 mL), then extracted with ethyl acetate (3x200 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. To the residue was added HCOOH (45 mL, 1192.820 mmol, 83.53 equiv) at room temperature. The reaction mixture was stirred for 2 days at 100 °C, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel (PE / EA 5:1) to afford 7-bromo-6-hydroxy-2-methylchromen-4-one (1.54 g, 42.28%) as a solid. **LCMS** (ES, *m/z*): 255 $[M+H]^+$.

Synthesis of Intermediate B180

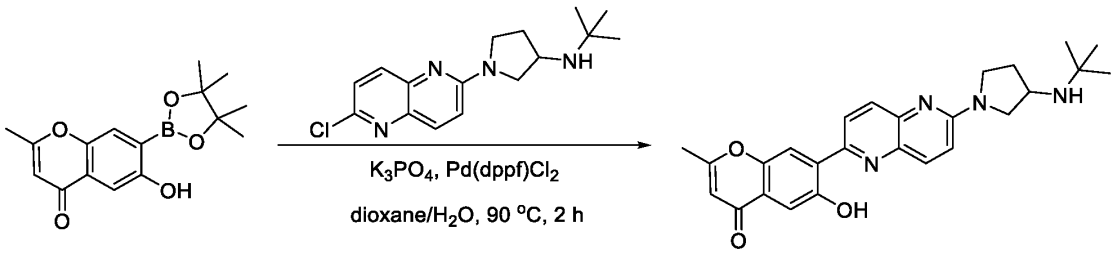


B179 **B180**

To a mixture of 7-bromo-6-hydroxy-2-methylchromen-4-one (200 mg, 0.784 mmol, 1.00 equiv) and AcOK (153.91 mg, 1.568 mmol, 2 equiv) in dioxane (2 mL, 23.608 mmol, 30.11 equiv) was

added $Pd(dppf)Cl_2$ (57.37 mg, 0.078 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 h at 100 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a solid. **LCMS** (ES, *m/z*): 303 $[M+H]^+$.

Synthesis of Compound 174

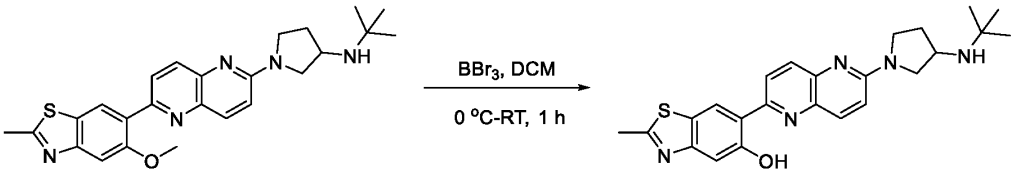


B180 **174**

To a mixture of Intermediate B180 and N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (121.07 mg, 0.397 mmol, 1.2 equiv) in dioxane (1 mL) and water (0.2 mL, 11.102 mmol, 33.54 equiv) was added K_3PO_4 (210.77 mg, 0.993 mmol, 3.0 equiv) and $Pd(dppf)Cl_2$ (24.22 mg, 0.033 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 2 h at 90 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by reverse phase flash (Condition 4, Gradient 1) to afford 6-hydroxy-7-{6-[3-(isopropylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methylchromen-4-one (18.5 mg, 12.98%) as a solid. **LCMS** (ES, *m/z*): 445$[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 8.75 (s, 2H), 8.56 (d, J = 9.1 Hz, 1H), 8.38 (s, 1H), 8.28 (d, J = 9.2 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.39 (s, 1H), 7.32 (d, J = 9.3 Hz, 1H), 6.22 (s, 1H), 4.19 (d, J = 6.3 Hz, 1H), 4.08 (dd, J = 11.6, 6.8 Hz, 1H), 3.86 – 3.78 (m, 1H), 3.74 (dd, J = 11.5, 5.6 Hz, 1H), 3.64 (dt, J = 10.5, 7.4 Hz, 1H), 2.42 (s, 3H), 2.26 (dq, J = 14.6, 7.5 Hz, 1H), 1.39 (s, 9H).

Example 94: Synthesis of Compound 190

Synthesis of Compound 190



176 190

To a stirred solution of N-tert-butyl-1-[6-(5-methoxy-2-methyl-1,3-benzothiazol-6-yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (70.0 mg, 0.156 mmol, 1.0 equiv) in DCM (1.4 mL) was added BBr_3 (293.8 mg, 1.170 mmol, 7.5 equiv) dropwise at 0 °C. The resulting mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 5, Gradient 1) to afford 6-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methyl-1,3-benzothiazol-5-ol; trifluoroacetic acid (15.2 mg, 22.42%) as a solid. **LCMS** (ES, *m/z*): 434. 2[M+H]$^+$. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.71 (s, 2H), 8.46 (d, J = 9.2 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 8.18 (d, J = 9.1 Hz, 1H), 7.41 (s, 1H), 7.31 (d, J = 9.3 Hz, 1H), 4.18 (s, 1H), 4.07 (dd, J = 11.5, 6.7 Hz, 1H), 3.86 – 3.68 (m, 2H), 3.64 (q, J = 7.8 Hz, 1H), 2.80 (s, 3H), 2.51 (p, J = 1.9 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.39 (s, 9H).

Example 95: Synthesis of Compound 175

Synthesis of Compound 175



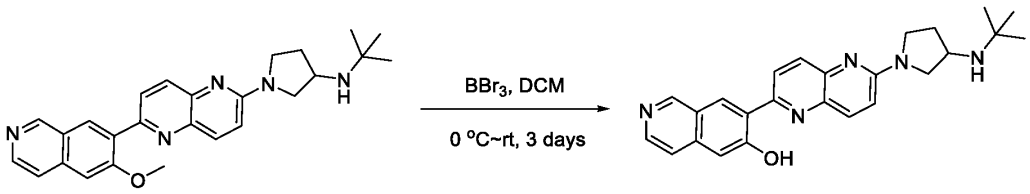
177 175

N-tert-butyl-1-[6-(5-methoxy-2-methyl-1,3-benzoxazol-6 -yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (70.0 mg, 0.162 mmol, 1.0 equiv), DCM (2 mL) and boron tribromide (325.1 mg, 1.296 mmol, 8.0 equiv) were combined at 0 °C. The resulting mixture was stirred for 24 h at room temperature, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 6, Gradient 1) to afford 6-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-2-methyl-1,3-benzoxazol-5-ol (11.4 mg, 16.70%) as a solid. **LCMS** (ES, *m/z*): 418 [M+H]$^+$. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 14.54 (s, 1H),δ 8.43 (t, J =

4.7 Hz, 2H), 8.11 (t, *J* = 9.4 Hz, 2H), 7.21 – 7.09 (m, 2H), 3.88-3.87 (m, 1H), 3.71-3.69 (m, 1H), 3.53-3.51 (m, 2H), 3.15 (d, *J* = 9.2 Hz, 1H), 2.62 (s, 3H), 2.17-2.16 (m, 1H), 1.79-1.71 (m, 2H), 1.10 (s, 9H).

Example 96: Synthesis of Compound 166

Synthesis of Compound 166

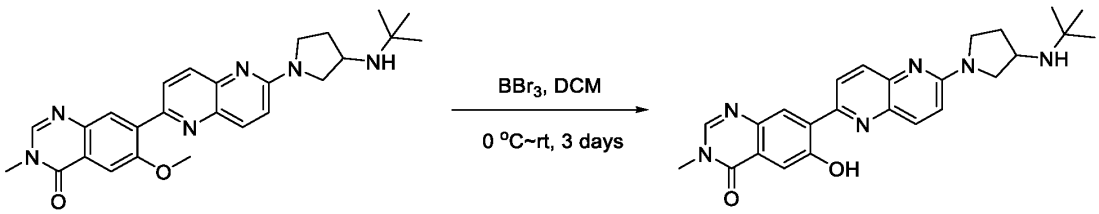


161 **166**

To a stirred solution of N-tert-butyl-1-[6-(6-methoxyisoquinolin-7-yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (50 mg, 0.117 mmol, 1.00 equiv) in DCM (0.5 mL, 7.865 mmol, 67.25 equiv) was added BBr_3 (146.49 mg, 0.585 mmol, 5.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 days at room temperature. The resulting mixture was quenched with methanol, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 1) to afford 7-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}isoquinolin-6-ol (18.7 mg, 30.31%) as a solid. **LCMS** (ES, *m/z*): 414 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 9.61 (s, 1H), 9.30 (s, 1H), 8.93 (s, 2H), 8.51 (dd, J = 17.4, 7.9 Hz, 2H), 8.31 (dd, J = 15.1, 9.2 Hz, 2H), 8.18 (d, J = 6.6 Hz, 1H), 7.63 (s, 1H), 7.33 (d, J = 9.4 Hz, 1H), 4.24 – 4.05 (m, 2H), 3.89 – 3.72 (m, 2H), 3.65 (d, J = 9.4 Hz, 1H), 2.29 (dd, J = 13.2, 7.3 Hz, 1H), 1.40 (s, 9H).

Example 97: Synthesis of Compound 167

Synthesis of Compound 167

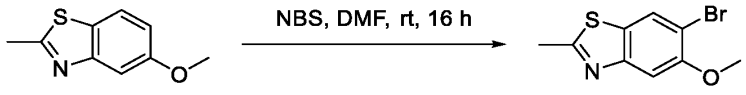


168 **167**

To a stirred solution of 7-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-6-methoxy-3-methylquinazolin-4-one (70 mg, 0.153 mmol, 1.00 equiv) in DCM (0.7 mL, 11.011 mmol, 72.13 equiv) was added BBr_3 (191.21 mg, 0.765 mmol, 5.0 equiv) dropwise at 0 °C. The resulting mixture was stirred for 3 days at room temperature, then quenched with methanol, and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 7, Gradient 2) to afford 7-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-6-hydroxy-3-methylquinazolin-4-one (20.3 mg, 23.81%) as a solid. **LCMS** (ES, *m/z*): 455 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 8.70 – 8.55 (m, 3H), 8.43 (s, 1H), 8.32 (d, J = 9.3 Hz, 1H), 8.26 (s, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.58 (s, 1H), 7.34 (d, J = 9.3 Hz, 1H), 4.20 (s, 2H), 4.08 (d, J = 4.7 Hz, 1H), 3.84 (s, 1H), 3.74 (dd, J = 11.7, 5.5 Hz, 1H), 2.24 (dd, J = 13.3, 7.3 Hz, 1H), 1.39 (s, 9H), 1.24 (s, 1H).

Example 99: Synthesis of Compound 176

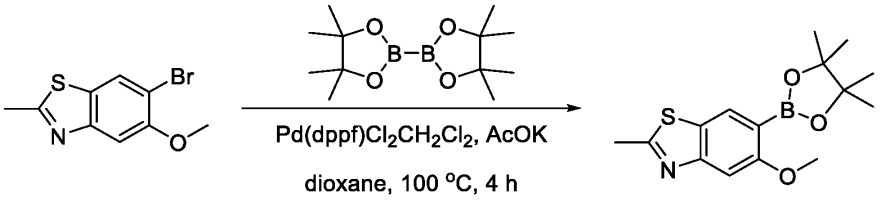
Synthesis of Intermediate B184



B184

To a stirred solution of 5-methoxy-2-methyl-1,3-benzothiazole (1.00 g, 5.579 mmol, 1.0 equiv) in DMF (20 mL) was added N-Bromosuccinimide (1.09 g, 6.137 mmol, 1.1 equiv) at room temperature. The resulting mixture was stirred for 16 h at room temperature, then diluted with water (60 mL) and extracted with ethyl acetate (2x50 mL). The organic layers were combined, washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (3/1) to afford 6-bromo-5-methoxy-2-methyl-1,3-benzothiazole (110 mg, 6.94%) as a solid. **LCMS** (ES, *m/z*): 258.0 $[M+H]^+$.

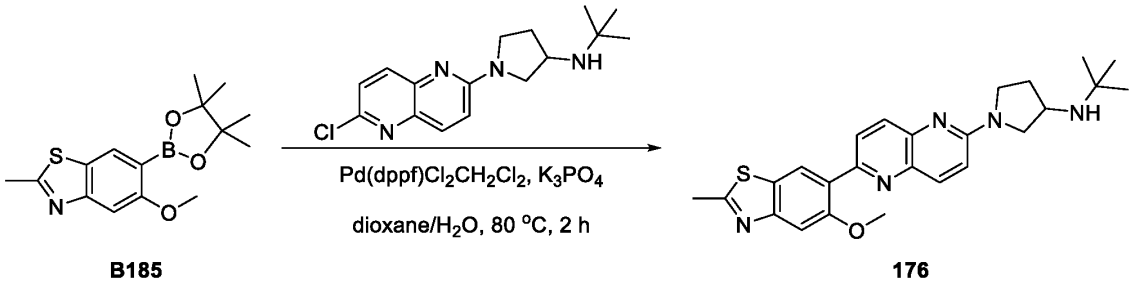
Synthesis of Intermediate B185



B184 **B185**

To a stirred mixture of 6-bromo-5-methoxy-2-methyl-1,3-benzothiazole (110.0 mg, 0.426 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (162.3 mg, 0.639 mmol, 1.5 equiv) in dioxane (2.8 mL) was added AcOK (83.7 mg, 0.852 mmol, 2.0 equiv) and $Pd(dppf)Cl_2.CH_2Cl_2$ (34.7 mg, 0.043 mmol, 0.1 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 4 h at 100 °C under N_2 atmosphere, then concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with PE/EA (1/1) to afford 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazole (140.0 mg, 92.57%) as a oil. **LCMS** (ES, *m/z*): 306.2$[M+H]^+$.

Synthesis of Compound 176



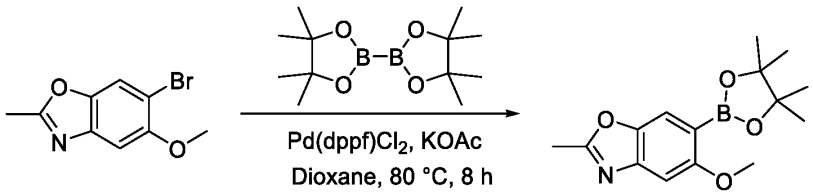
B185 **176**

To a stirred mixture of 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzothiazole (130.0 mg, 0.426 mmol, 1.0 equiv) and N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (129.8 mg, 0.426 mmol, 1.0 equiv) in dioxane (2.5 mL) and water (0.5 mL) was added K_3PO_4 (271.2 mg, 1.278 mmol, 3.0 equiv) and $Pd(dppf)Cl_2CH_2Cl_2$ (34.7 mg, 0.043 mmol, 0.1 equiv) at room temperature under N_2 atmosphere. The resulting mixture was stirred for 2 h at 80 °C under N_2 atmosphere, then concentrated under vacuum to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (10/1),

followed by Prep-HPLC (Condition 6, Gradient 2) to afford N-tert-butyl-1-[6-(5-methoxy-2-methyl-1,3-benzothiazol-6-yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (7.1 mg) as a solid. **LCMS** (ES, *m/z*): 448.2 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.66 (s, 1H), 7.11 (d, J = 9.3 Hz, 1H), 3.93 (s, 3H), 3.87-3.86 (m, 1H), 3.72-3.69 (m, 1H), 3.56-3.45 (m, 2H), 3.30-2.88 (m, 1H), 3.15-3.14 (m, 1H), 2.82 (s, 3H), 2.21-2.20 (m, 1H), 1.78-1.76 (m, 1H), 1.11 (s, 9H).

Example 100: Synthesis of Compound 177

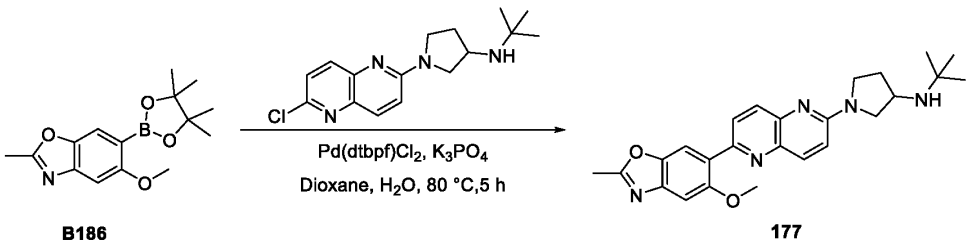
Synthesis of Intermediate B186



B186

A mixture of 6-bromo-5-methoxy-2-methyl-1,3-benzoxazole (200 mg, 0.826 mmol, 1.0 equiv), bis(pinacolato)diboron (251.7 mg, 0.991 mmol, 1.2 equiv), potassium acetate (162.17 mg, 1.652 mmol, 2.0 equiv), dioxane (5 mL) and $Pd(dppf)Cl_2$ (60.4 mg, 0.083 mmol, 0.1 equiv) was stirred for 8 h at 80 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (255 mg, 96.07%) as an oil. **LCMS** (ES, *m/z*): 290 $[M+H]^+$.

Synthesis of Compound 177



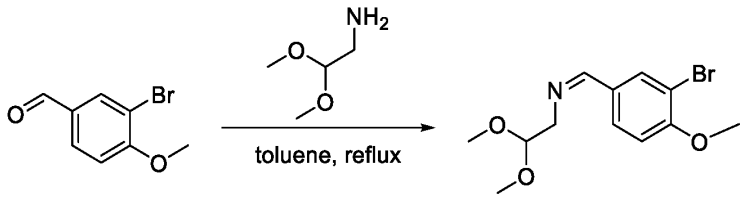
B186 **177**

To a mixture of 5-methoxy-2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzoxazole (100 mg, 0.346 mmol, 1.0 equiv) and N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-

yl)pyrrolidin-3-amine (115.9 mg, 0.381 mmol, 1.1 equiv) in water (0.6 mL) and dioxane (3.0 mL) was added (phosphoperoxy)potassium; dipotassium (146.8 mg, 0.692 mmol, 2.0 equiv), and $Pd(dtbpf)Cl_2$ (45.1 mg, 0.069 mmol, 0.2 equiv). The reaction mixture was stirred for 5 h at 80 °C under a nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with CH_2Cl_2 / MeOH (10:1) to afford a solid. The solid was purified by Prep-HPLC (Condition 6, Gradient 3) to afford N-tert-butyl-1-[6-(5-methoxy-2-methyl-1,3-benzoxazol-6-yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine as a solid. **LCMS** (ES, *m/z*): 432 $[M+H]^+$. **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 9.3 Hz, 1H), 8.02-7.93 (m, 2H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 1H), 7.10 (d, *J* = 9.4 Hz, 1H), 3.90 (s, 3H), 3.89-3.86 (m, 1H), 3.72-3.71 (m, 1H), 3.53-3.47 (m, 2H), 3.15-3.12 (m, 1H), 2.64 (s, 3H), 2.18-2.17 (m, 1H), 1.79-1.72 (m, 2H), 1.10 (s, 9H).

Example 101: Synthesis of Compound 161

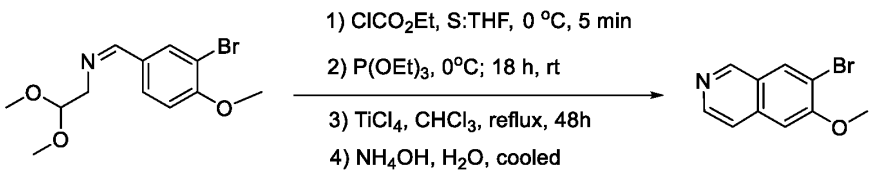
Synthesis of Intermediate B187



B187

A mixture of 3-bromo-4-methoxybenzaldehyde (5 g, 23.251 mmol, 1.00 equiv) and 2,2-dimethoxyethanamine (3.67 g, 34.877 mmol, 1.5 equiv) in toluene (50 mL, 469.945 mmol, 20.21 equiv) were heated to reflux for 6 h, then concentrated under reduced pressure to give a residue. **LCMS** (ES, *m/z*): 302 $[M+H]^+$.

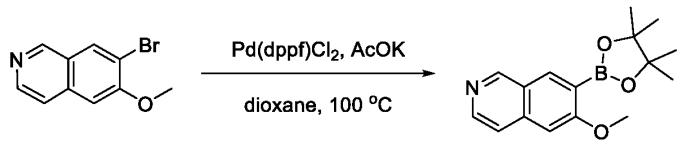
Synthesis of Intermediate B188



B187 B188

To a stirred solution of (Z)-[(3-bromo-4-methoxyphenyl)methylidene](2,2-dimethoxyethyl)amine (9 g, 29.785 mmol, 1.00 equiv) in THF (50 mL) was added ethyl chloroformate (3.23 g, 29.785 mmol, 1.00 equiv) dropwise at 0 °C. The reaction mixture was stirred for 5 min, then triethyl phosphite (5.94 g, 35.742 mmol, 1.2 equiv) was added dropwise. The resulting mixture was stirred for 18 h at room temperature. The solvents were removed *in vacuo*, and excess reagent was removed by forming an azeotrope with toluene (50 mL) and concentrating the resulting mixture under reduced pressure to give a residue. The residue was combined with titanium tetrachloride (22.60 g, 119.140 mmol, 4.0 equiv) and $CHCl_3$ (50 mL). The resulting mixture was heated to reflux for 48 h, then poured on ice and adjusted to pH 9 using aqueous ammonia. The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, washed with brine (1x100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to afford 7-bromo-6-methoxyisoquinoline (3 g, 42.31%) as a solid. **LCMS** (ES, *m/z*): 238 $[M+H]^+$.

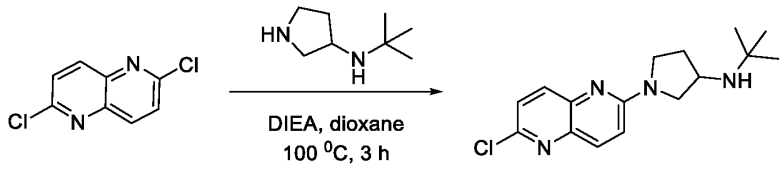
Synthesis of Intermediate B189



B188 **B189**

To a mixture of 7-bromo-6-methoxyisoquinoline (200 mg, 0.840 mmol, 1.00 equiv) and bis(pinacolato)diboron (319.98 mg, 1.260 mmol, 1.5 equiv) in dioxane (4 mL, 47.216 mmol, 56.21 equiv) was added AcOK (82.44 mg, 0.840 mmol, 1.0 equiv) and $Pd(dppf)Cl_2$ (61.47 mg, 0.084 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred for 3 h at 100 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. **LCMS** (ES, *m/z*): 286$[M+H]^+$.

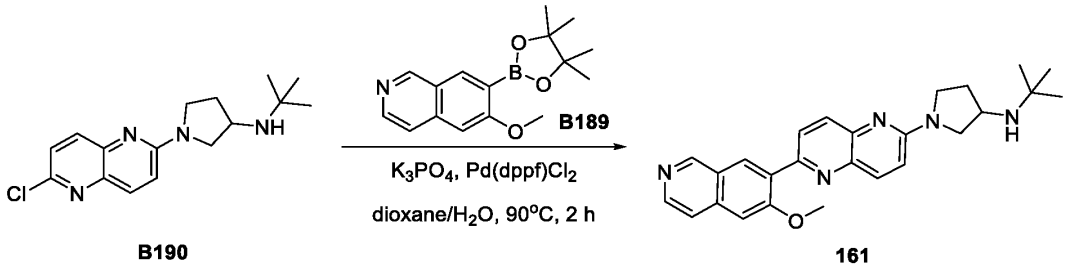
Synthesis of Intermediate B190



B190

To a stirred mixture of N-tert-butylpyrrolidin-3-amine (0.71 g, 5.024 mmol, 1.0 equiv) and 2,6-dichloro-1,5-naphthyridine (1 g, 5.024 mmol, 1 equiv) in dioxane (10 mL) was added DIEA (0.78 g, 6.029 mmol, 1.2 equiv) at room temperature. The resulting mixture was stirred for 3 h at 100 °C. The resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with DCM/MeOH (1/20) to afford N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (550 mg, 35.91%) as a solid. **LCMS** (ES, *m/z*): 305.2[M+H]$^+$.

Synthesis of Compound 161

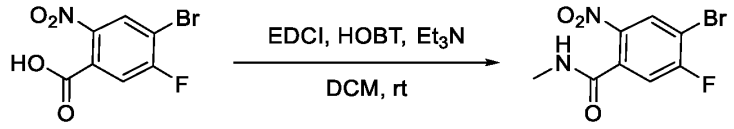


B190 **161**

To a mixture of 6-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (200 mg, 0.701 mmol, 1.00 equiv) and N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (213.80 mg, 0.701 mmol, 1.00 equiv) in 1,4-dioxane (3 mL, 34.050 mmol, 48.55 equiv) and water (0.6 mL, 33.305 mmol, 47.48 equiv) was added K_3PO_4 (446.64 mg, 2.103 mmol, 3.0equiv) and $Pd(dppf)Cl_2$ (45.71 mg, 0.070 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The reaction mixture was stirred 2 h at 90 °C under nitrogen atmosphere, then concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 6, Gradient 4) to afford N-tert-butyl-1-[6-(6-methoxyisoquinolin-7-yl)-1,5-naphthyridin-2-yl]pyrrolidin-3-amine (77 mg, 25.68%) as a solid. **LCMS** (ES, *m/z*): 428[M+H]$^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 9.29 (s, 1H), 8.48 – 8.42 (m, 2H), 8.13 (d, J = 9.3 Hz, 1H), 8.01 – 7.91 (m, 2H), 7.78 (d, J = 5.8 Hz, 1H), 7.54 (s, 1H), 7.13 (d, J = 9.3 Hz, 1H), 4.01 (s, 3H), 3.88 (s, 1H), 3.73 (s, 1H), 3.50 (td, J = 11.5, 9.9, 6.1 Hz, 2H), 3.19 – 3.10 (m, 1H), 2.18 (s, 1H), 1.76 (dd, J = 22.9, 12.4 Hz, 2H), 1.24 (s, 1H), 1.10 (s, 9H).

Example 102: Synthesis of Compound 168

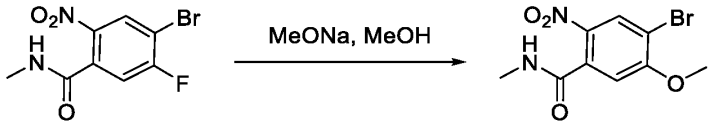
Synthesis of Intermediate B191



B191

To a stirred mixture of 4-bromo-5-fluoro-2-nitrobenzoic acid (10 g, 37.878 mmol, 1.00 equiv) in DCM (100 mL, 1573.005 mmol, 41.53 equiv) was added Et_3N (11.50 g, 113.634 mmol, 3 equiv), HOBT (7.68 g, 56.817 mmol, 1.5 equiv), and EDCI (8.71 g, 45.454 mmol, 1.2 equiv) at room temperature. The reaction mixture was stirred for 5 h at room temperature. The resulting mixture was washed with water (2x100 mL), dried over anhydrous Na_2SO_4, and filtered. After filtration, the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (3:2) to afford 4-bromo-5-fluoro-N-methyl-2-nitrobenzamide (4.7 g, 44.79%) as a solid. **LCMS** (ES, *m/z*): 277 $[M+H]^+$.

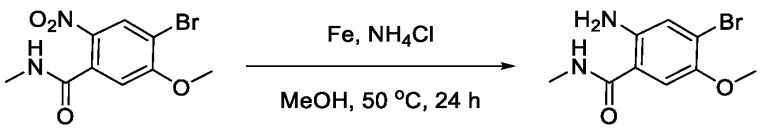
Synthesis of Intermediate B192



B191 **B192**

To a stirred solution of 4-bromo-5-fluoro-N-methyl-2-nitrobenzamide (4.6 g, 16.604 mmol, 1.00 equiv) in methanol (46.00 mL, 1136.212 mmol, 68.43 equiv) was added MeONa (2690.96 mg, 49.812 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for 3 h at room temperature, then diluted with water (50 mL). The reaction mixture was concentrated under reduced pressure to afford a precipitate. The precipitated solid was collected by filtration and washed with water and petroleum ether. The solid was dried to afford 4-bromo-5-methoxy-N-methyl-2-nitrobenzamide (4.4g,91.6%) as a solid. **LCMS** (ES, *m/z*): 289.0 $[M+H]^+$.

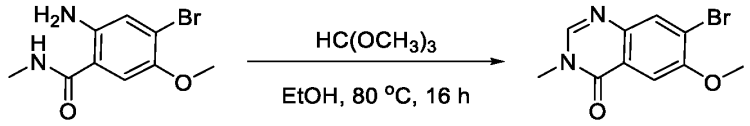
Synthesis of Intermediate B193



B192 **B193**

To a stirred mixture of 4-bromo-5-methoxy-N-methyl-2-nitrobenzamide (4.3 g, 14.875 mmol, 1.00 equiv) and NH_4Cl (7.96 g, 148.750 mmol, 10.00 equiv) in methanol (83.90 mL, 2072.385 mmol, 139.32 equiv) was added Fe (8.31 g, 148.750 mmol, 10.00 equiv) at room temperature. The resulting mixture was stirred for 48 h at 50 °C, then filtered, and the filter cake washed with ethyl acetate (2x50 mL). The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:2) to afford 2-amino-4-bromo-5-methoxy-N-methylbenzamide (3.2 g, 83.03%) as a solid. **LCMS** (ES, *m/z*): 259.1 $[M+H]^+$.

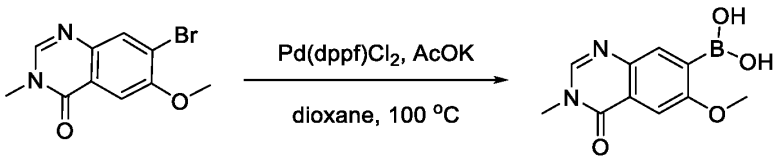
Synthesis of Intermediate B194



B193 **B194**

To a stirred mixture of 2-amino-4-bromo-5-methoxy-N-methylbenzamide (3000 mg, 11.578 mmol, 1.00 equiv) in ethanol (30.00 mL, 516.379 mmol, 44.60 equiv) was added trimethyl orthoformate (14744.55 mg, 138.936 mmol, 12 equiv) at room temperature. The resulting mixture was stirred for 16 h at 80 °C, then concentrated under reduced pressure to give a residue. The residue was purified by silica gel column chromatography, eluted with PE / EA (1:1) to afford 7-bromo-6-methoxy-3-methylquinazolin-4-one (2.5 g, 80.24%) as a solid. **LCMS** (ES, *m/z*): 269.0 $[M+H]^+$.

Synthesis of Intermediate B195

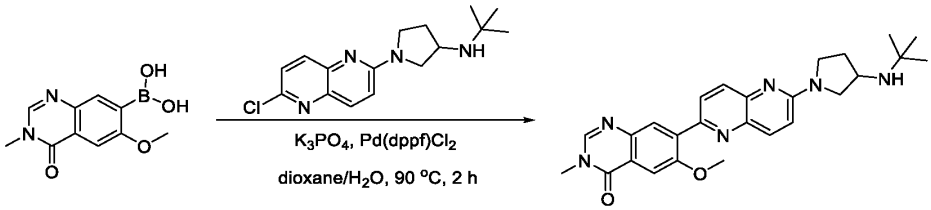


B194 **B195**

To a mixture of 7-bromo-6-methoxy-3-methylquinazolin-4-one (100 mg, 0.372 mmol, 1.00 equiv) and bis(pinacolato)diboron (141.55 mg, 0.558 mmol, 1.5 equiv) in dioxane (1 mL, 11.804 mmol, 31.76 equiv) was added AcOK (109.41 mg, 1.116 mmol, 3 equiv) and $Pd(dppf)Cl_2$ (27.19 mg, 0.037 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. The reaction

mixture was stirred for 3 h at 100°C under nitrogen atmosphere, then concentrated under reduced pressure. **LCMS** (ES, *m/z*): 235.1 $[M+H]^+$.

Synthesis of Compound 168



B195 **168**

To a mixture of 6-methoxy-3-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-4-one (100 mg, 0.316 mmol, 1.00 equiv) and N-tert-butyl-1-(6-chloro-1,5-naphthyridin-2-yl)pyrrolidin-3-amine (96.41 mg, 0.316 mmol, 1.0 equiv) in dioxane (1.5 mL, 17.706 mmol, 55.98 equiv) and water (0.3 mL, 16.653 mmol, 52.65 equiv) was added K_3PO_4 (201.42 mg, 0.948 mmol, 3.0 equiv) and $Pd(dppf)Cl_2$ (23.14 mg, 0.032 mmol, 0.1 equiv) at room temperature under nitrogen atmosphere. After stirring for 2 h at 90°C under nitrogen atmosphere, the resulting mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (Condition 6, Gradient 5) to afford 7-{6-[3-(tert-butylamino)pyrrolidin-1-yl]-1,5-naphthyridin-2-yl}-6-methoxy-3-methylquinazolin-4-one (88 mg, 60.67%) as a solid. **LCMS** (ES, *m/z*): 459.3 $[M+H]^+$. **^{1}H NMR** (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 8.13 – 8.00 (m, 3H), 7.95 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.14 (d, J = 9.3 Hz, 1H), 3.98 (s, 3H), 3.87 (s, 1H), 3.73 (s, 1H), 3.54 (s, 5H), 3.14 (s, 1H), 2.19 (s, 1H), 1.77 (s, 2H), 1.10 (s, 9H).

Example 103: 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) or (II)). 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 3, 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 3: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
100	B	A
101	A	A
102	A	A
103	B	B
104	D	C
105	D	D
106	C	C
107	B	B
108	C	C
109	B	A
110	D	-
111	D	D
112	D	D
115	C	C
116	C	C
117	C	C
118	C	C
119	C	B
120	C	C
121	C	C
122	D	D
123	B	A
124	B	A
125	B	B
126	B	B
127	A	A
129	B	B
130	D	D
131	D	C
132	D	D
133	C	C
134	C	C
135	C	C
136	C	C
137	B	B
138	B	B
139	A	A

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
140	B	A
141	C	C
142	B	B
143	D	D
144	D	D
145	D	D
146	C	C
147	A	A
148	C	C
149	D	D
150	A	A
151	B	B
152	D	D
153	A	A
154	A	A
155	a	A
156	A	A
157	A	A
158	A	A
159	C	C
160	B	B
161	D	D
162	D	D
163	D	D
164	B	B
165	C	C
166	D	D
167	D	D
168	D	D
169	D	D
170	B	A
171	A	A
172	B	A
173	A	A
174	D	D
175	A	A
176	C	C

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
177	C	C
178	B	B
179	A	A
180	B	A
181	-	B
182	D	C
183	-	D
184	B	C
185	C	C
186	A	A
187	A	A
188	B	B
189	B	C
190	D	D
191	A	A
192	D	D
193	C	C
194	A	A
195	A	B
196	D	D
197	A	A
198	A	A
199	B	B
200	C	C
201	B	B
202	A	A
203	A	A
204	C	C
205	C	C
206	C	C
207	C	C
208	D	D
209	A	A
210	A	A
211	A	A

Compound No.	HTT AJ AC_{50} (nM)	HTT CJ IC_{50} (nM)
212	A	A
214	A	A
215	A	A
216	A	A
217	A	A
218	D	D
220	A	A
221	A	A
222	A	A
223	A	A
224	A	A
225	A	A
226	A	A
229	A	A
230	A	A
232	A	A
233	A	A
234	A	B
235	A	A
237	A	A
238	A	A
241	A	A
245	D	D
246	A	A
247	B	A
253	A	A
254	A	A
255	A	A
256	A	A
257	A	A
258	A	A
259	A	A
260	A	A

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 4, 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 4: Modulation of RNA Splicing by Exemplary Compounds

Compound No.	HTT	SMN2	Target C
100	A	A	A
101	A	A	A
102	A	A	A
103	B	D	C
104	C	C	C
105	D	C	C
106	C	B	C
107	B	A	C
108	C	A	C
109	A	A	B
110	D	D	A
111	D	D	D
112	D	D	D
115	C	A	C
116	C	A	C
117	C	A	C
118	C	A	C
119	B	A	C
120	C	A	C
121	C	C	C
122	C	D	D
123	B	A	A
124	A	A	B
125	B	A	B
126	B	A	A

Compound No.	HTT	SMN2	Target C
127	A	A	A
129	B	A	B
130	D	B	D
131	C	A	D
132	D	D	D
133	C	A	C
134	C	A	C
135	C	A	C
136	C	A	B
137	B	A	C
138	B	A	C
139	A	A	B
140	A	A	B
141	C	B	D
142	B	A	B
143	D	D	D
144	D	D	D
145	D	D	D
146	C	B	C
147	A	A	A
148	C	A	C
149	D	B	D
150	A	A	A
151	B	B	B
152	D	C	D

Compound No.	HTT	SMN2	Target C
153	A	A	A
154	A	A	A
155	A	A	B
156	A	A	B
157	A	A	B
158	A	A	A
159	C	B	C
160	B	A	C
161	D	C	D
162	D	C	D
163	D	B	D
164	B	B	B
165	C	C	C
166	D	D	D
167	D	D	D
168	D	D	D
169	D	C	D
170	A	A	B
171	A	A	B
172	A	A	B
173	A	A	A
174	D	D	D
175	A	A	A
176	C	C	C
177	C	C	C
178	B	A	C
179	A	A	B
180	A	A	B
182	C	C	D
184	C	A	B
185	C	B	C
186	A	A	A
187	A	A	A
188	B	A	C
189	C	A	C
190	D	A	D
191	D	D	D
192	D	D	D
193	C	C	C

Compound No.	HTT	SMN2	Target C
194	A	A	A
195	B	A	B
196	D	C	D
197	A	A	B
198	A	A	B
199	B	B	B
200	C	C	C
201	B	A	B
202	A	D	A
203	A	A	A
204	C	B	D
205	C	C	C
206	C	C	C
207	C	C	C
208	D	C	D
209	A	A	A
210	A	A	C
211	A	A	B
212	A	A	B
214	A	A	A
215	A	A	A
216	A	A	A
217	A	A	A
218	D	B	D
220	A	A	A
221	A	A	A
222	A	A	A
223	A	A	A
224	A	A	A
225	A	A	A
226	A	A	A
229	A	A	B
230	A	A	B
232	A	A	A
233	A	A	A
234	B	A	B
235	A	A	A
237	A	A	A
238	A	A	A

Compound No.	HTT	SMN2	Target C
241	A	A	A
245	D	C	D
246	A	A	A
247	A	A	B
253	A	A	A
254	A	A	A

Compound No.	HTT	SMN2	Target C
255	A	A	A
256	A	A	A
257	A	A	A
258	A	A	B
259	A	A	A
260	A	A	A

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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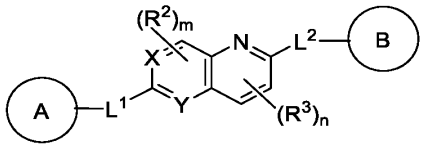
CLAIMS

1. A compound of Formula (I-a):



(I-a)

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

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

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

X and Y are each N or C(R^6);

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, heteroaryl, aryl, C_1-C_6 alkylene-aryl, C_2-C_6 alkenylene-aryl, C_1-C_6 alkylene-heteroaryl, halo, cyano, oxo, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, 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^7; 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^7;

each R^2 and R^3 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, –OR^A, –NR^BR^C, –$NR^BC(O)R^D$, –NO_2, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, or –$S(O)_xR^D$;

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

each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, –OR^A, or –NR^BR^C;

each R^6 is independently hydrogen, halo, cyano, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or –OR^A;

each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^8;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, 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, $–OR^A$, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9; 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^9;

each R^D 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, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^9;

each R^8 is independently C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, halo, cyano, oxo, or $–OR^A$;

each R^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $–OR^{A1}$;

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

n is 0, 1, or 2;

m is 0 or 1; and

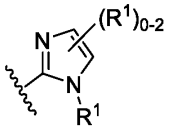
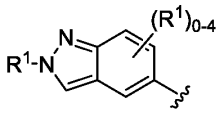
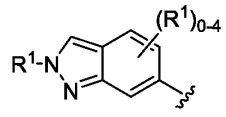
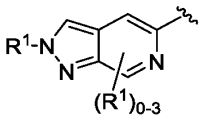
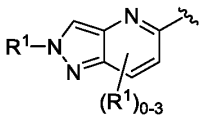
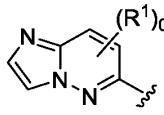
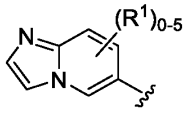
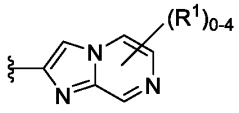
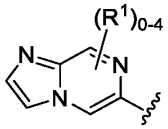
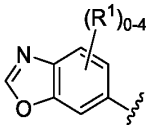
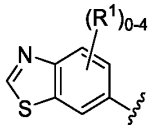
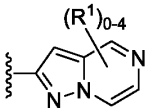
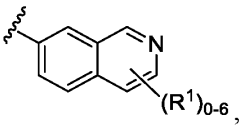
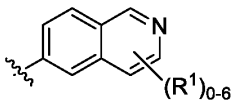
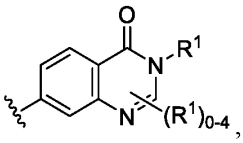
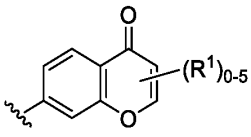
x is 0, 1, or 2.

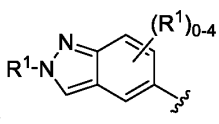
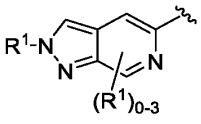
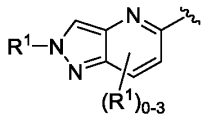
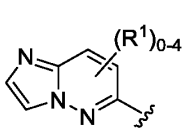
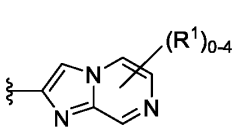
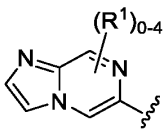
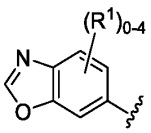
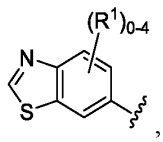
2. The compound of claim 1, wherein one of A and B is independently a monocyclic heteroaryl or bicyclic heteroaryl, each of which is optionally substituted with one or more R^1.

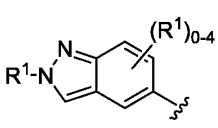
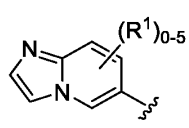
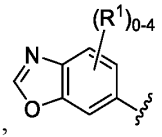
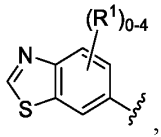
3. The compound of any one of the preceding claims, wherein one of A and B is independently a bicyclic heteroaryl optionally substituted with one or more R^1.

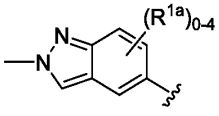
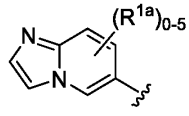
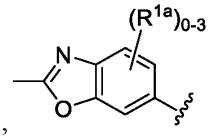
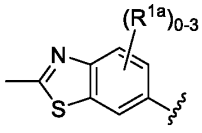
4. The compound of any one of the preceding claims, wherein one of A and B is independently a nitrogen-containing heteroaryl optionally substituted with one or more R^1.

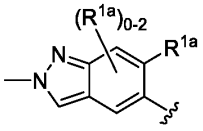
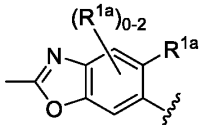
5. The compound of any one of the preceding claims, wherein one of A and B is a 5-10 membered heteroaryl optionally substituted with one or more R^1.

6. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described in claim 1.

7. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , , , , , ,  and , wherein R^1 is as described in claim 1.

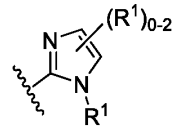
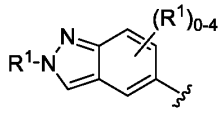
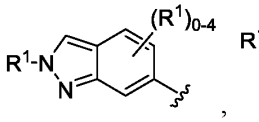
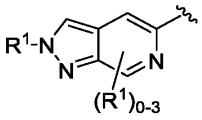
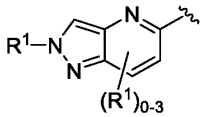
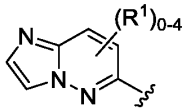
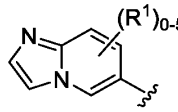
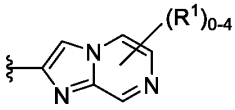
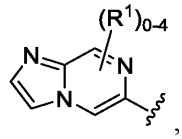
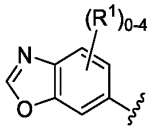
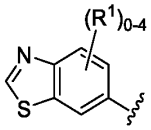
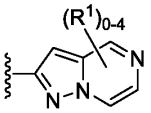
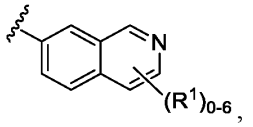
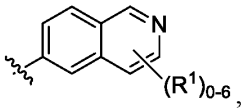
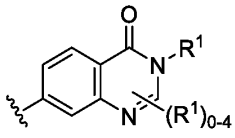
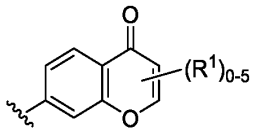
8. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , , , , wherein R^1 is as described in claim 1.

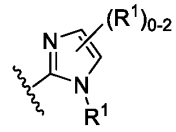
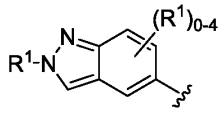
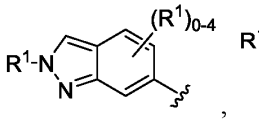
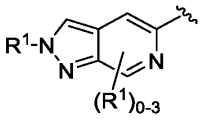
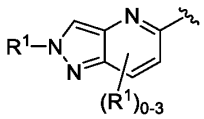
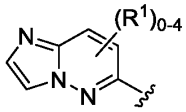
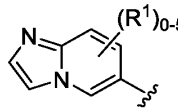
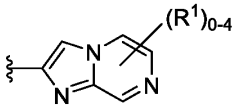
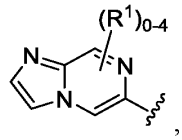
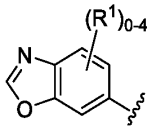
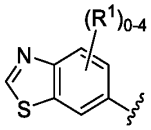
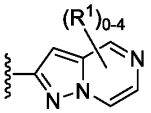
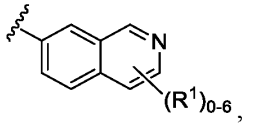
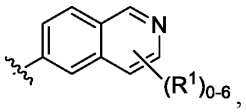
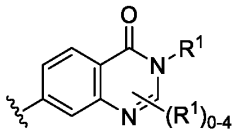
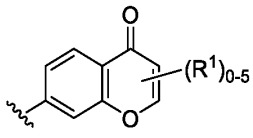
9. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , ,  and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7.

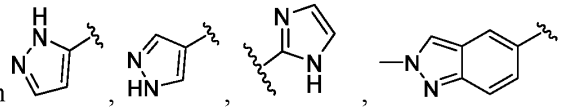
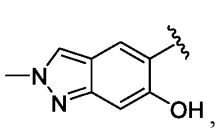
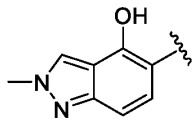
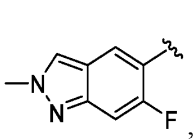
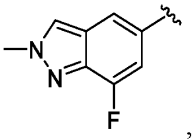
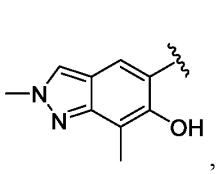
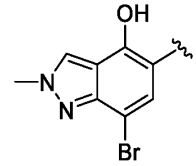
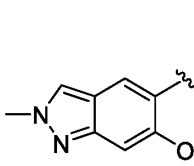
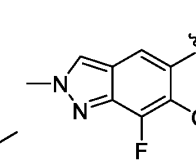
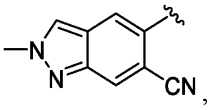
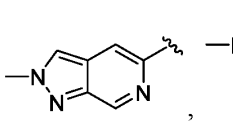
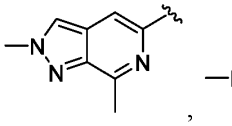
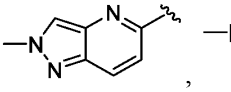
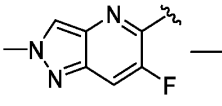
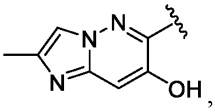
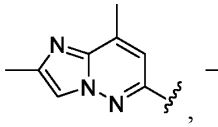
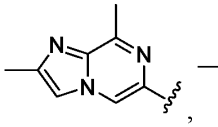
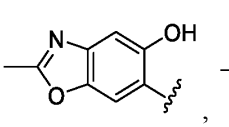
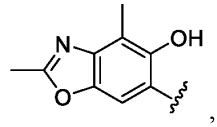
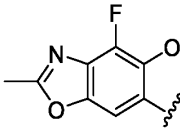
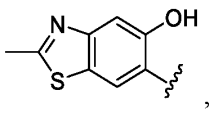
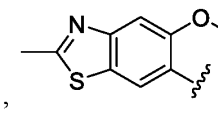
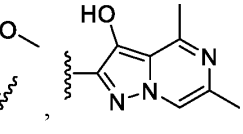
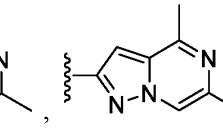
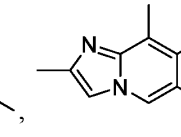
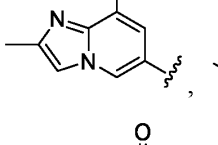
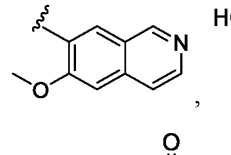
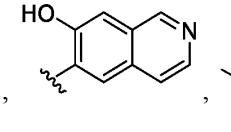
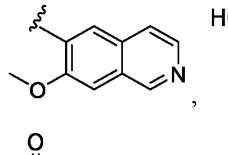
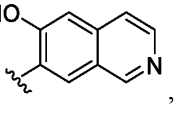
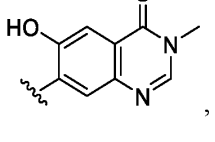
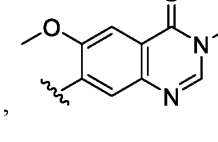
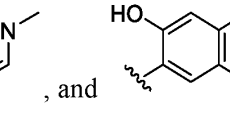
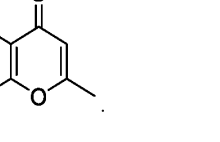
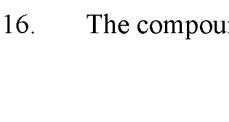
10. The compound of any one of the preceding claims, wherein one of A and B is independently selected from  and , wherein each R^{1a} is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $-OR^A$, and each alkyl, heteroalkyl, and haloalkyl is optionally substituted with one or more R^7.

11. The compound of claim 10, wherein at least one of R^{1a} is C_1-C_6-alkyl, halo, or $-OR^A$.

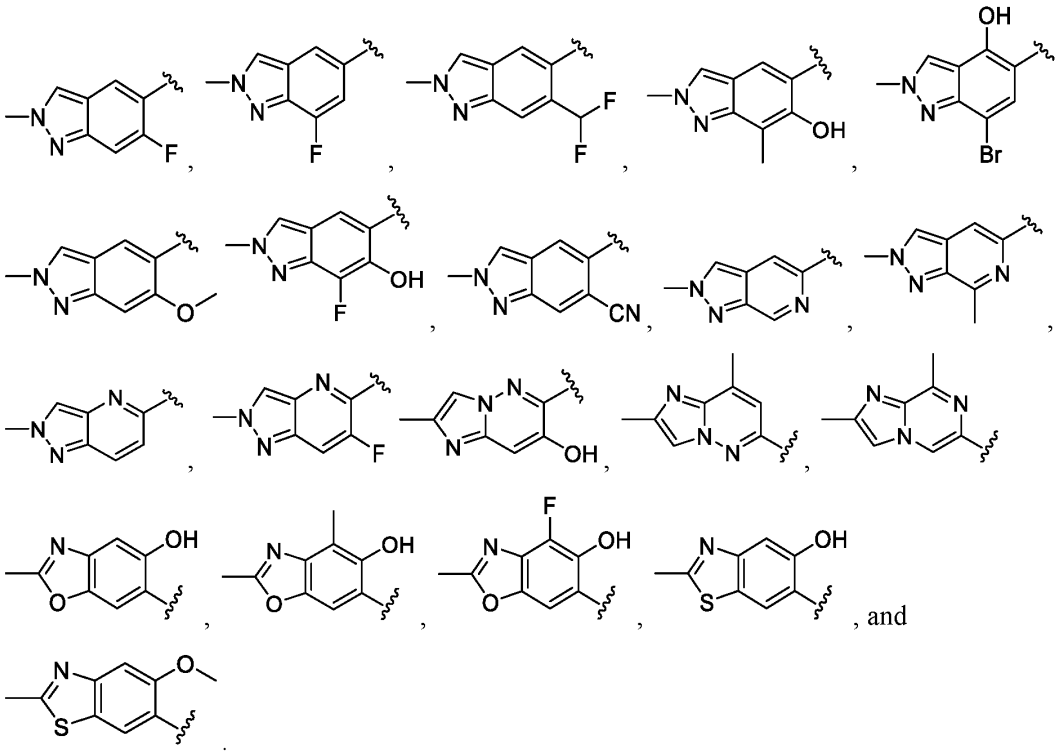
12. The compound of any one of claims 10-11, wherein R^{1a} is $-OR^A$ and R^A is H.

13. The compound of any one of the preceding claims, wherein A is independently selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described in claim 1.

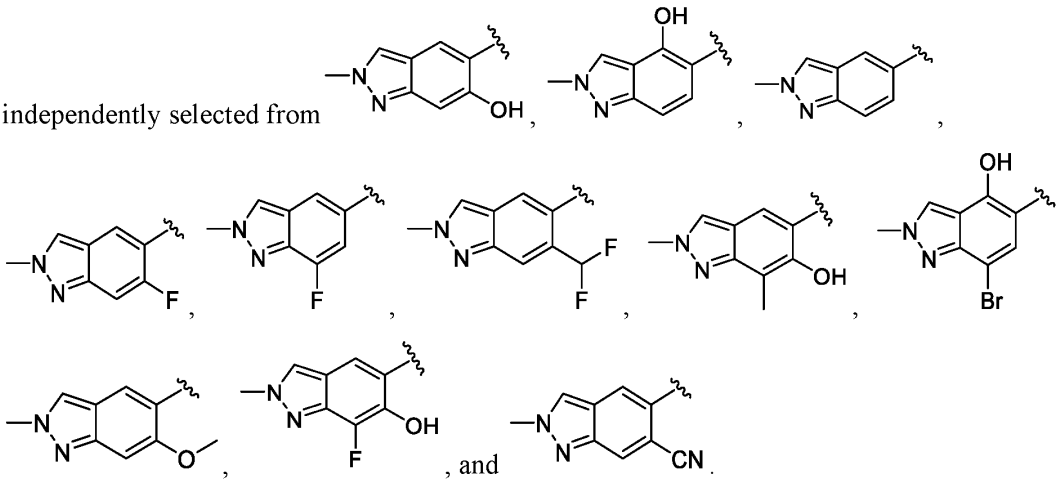
14. The compound of any one of the preceding claims, wherein B is independently selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described in claim 1.

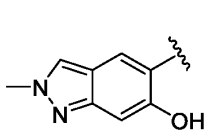
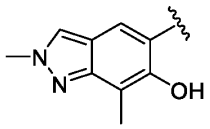
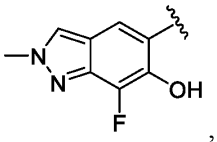
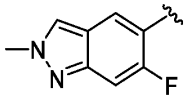
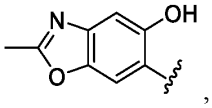
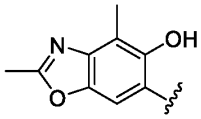
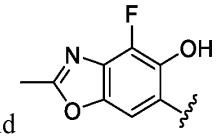
15. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , and .

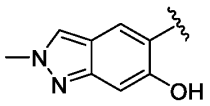
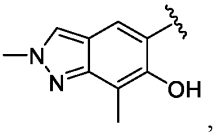
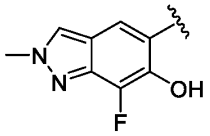
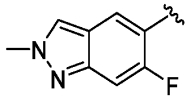
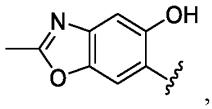
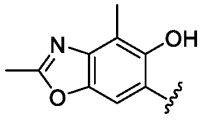
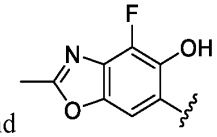
16. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , , .

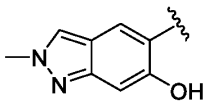
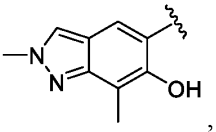
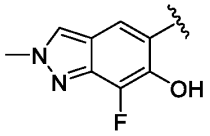
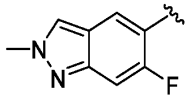
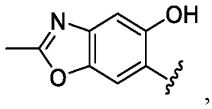
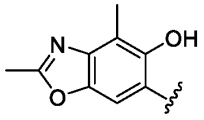
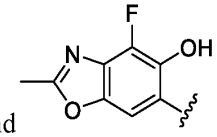


17. The compound of any one of the preceding claims, wherein one of A and B is independently selected from



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

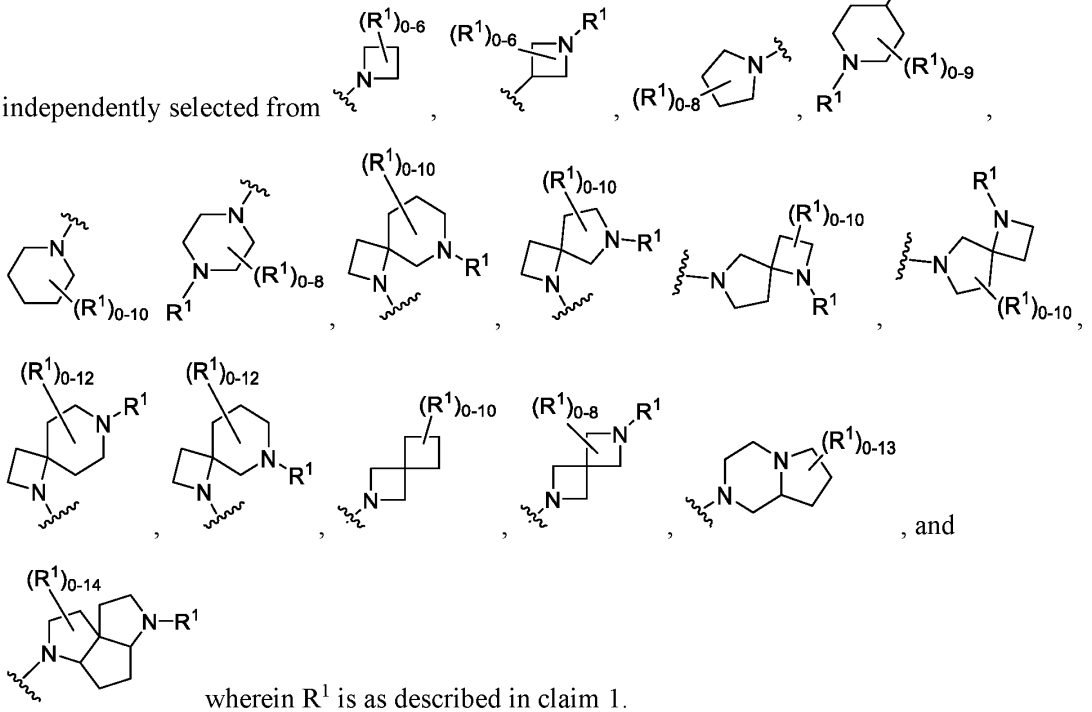
19. The compound of any one of the preceding claims, wherein A is selected from , , , , , , and .

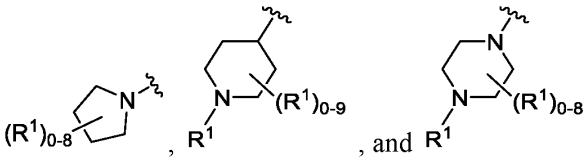
20. The compound of any one of the preceding claims, wherein B is selected from , , , , , , and .

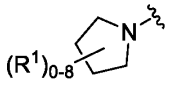
21. The compound of any one of the preceding claims, wherein one of A and B is independently a monocyclic heterocyclyl or bicyclic heterocyclyl, each of which is optionally substituted with one or more R^1.

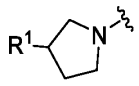
22. The compound of any one of the preceding claims, wherein one of A and B is independently a nitrogen-containing heterocyclyl optionally substituted with one or more R^1.

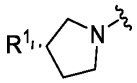
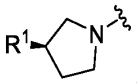
23. The compound of any one of the preceding claims, wherein one of A and B is independently a 4-8 membered heterocyclyl optionally substituted with one or more R^1.

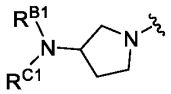
24. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , wherein R^1 is as described in claim 1.

25. The compound of any one of the preceding claims, wherein one of A and B is independently selected from , wherein R^1 is as described in claim 1.

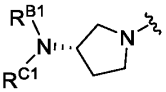
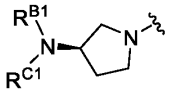
26. The compound of any one of the preceding claims, wherein one of A and B is independently  and R^1 is as described in claim 1.

27. The compound of any one of the preceding claims, wherein one of A and B is independently  and R^1 is as described in claim 1.

28. The compound of any one of the preceding claims, wherein one of A and B is independently selected from  and , and R^1 is as described in claim 1.

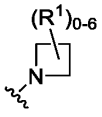
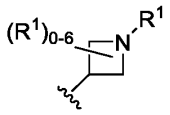
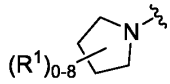
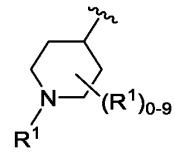
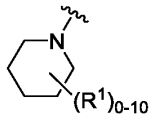
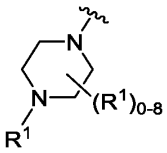
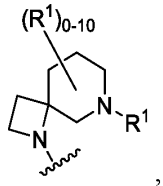
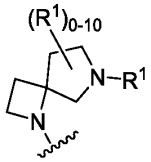
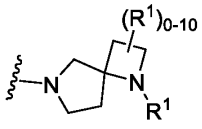
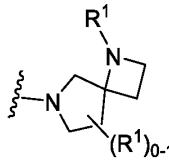
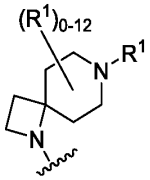
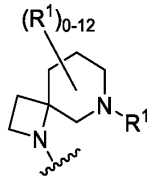
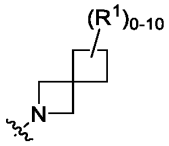
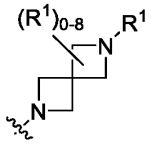
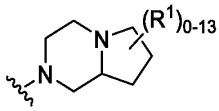
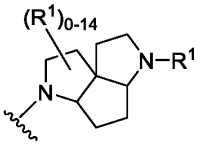
29. The compound of any one of the preceding claims, wherein one of A and B is independently , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

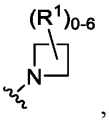
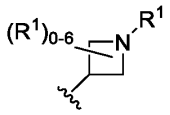
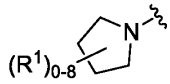
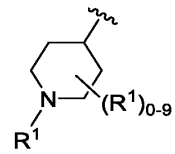
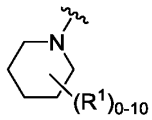
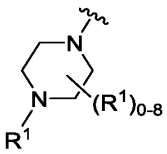
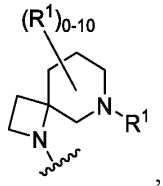
30. The compound of claim 29, wherein R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

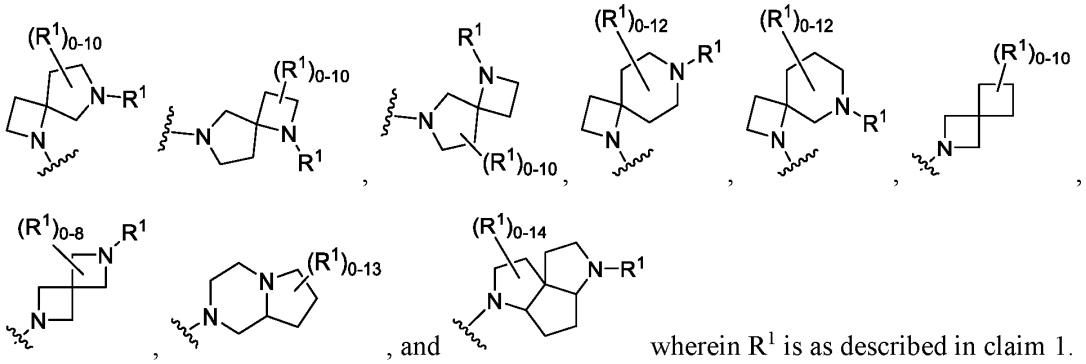
31. The compound of any one of the preceding claims, wherein one of A and B is independently selected from  and , and each of R^{B1} and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

32. The compound of claim 31, wherein R^{B1} is hydrogen and R^{C1} is selected from hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, C_1-C_6 alkylene-

cycloalkyl, and C_1-C_6 alkylene-heterocyclyl, wherein each alkyl, alkylene, heteroalkyl, haloalkyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more R^9.

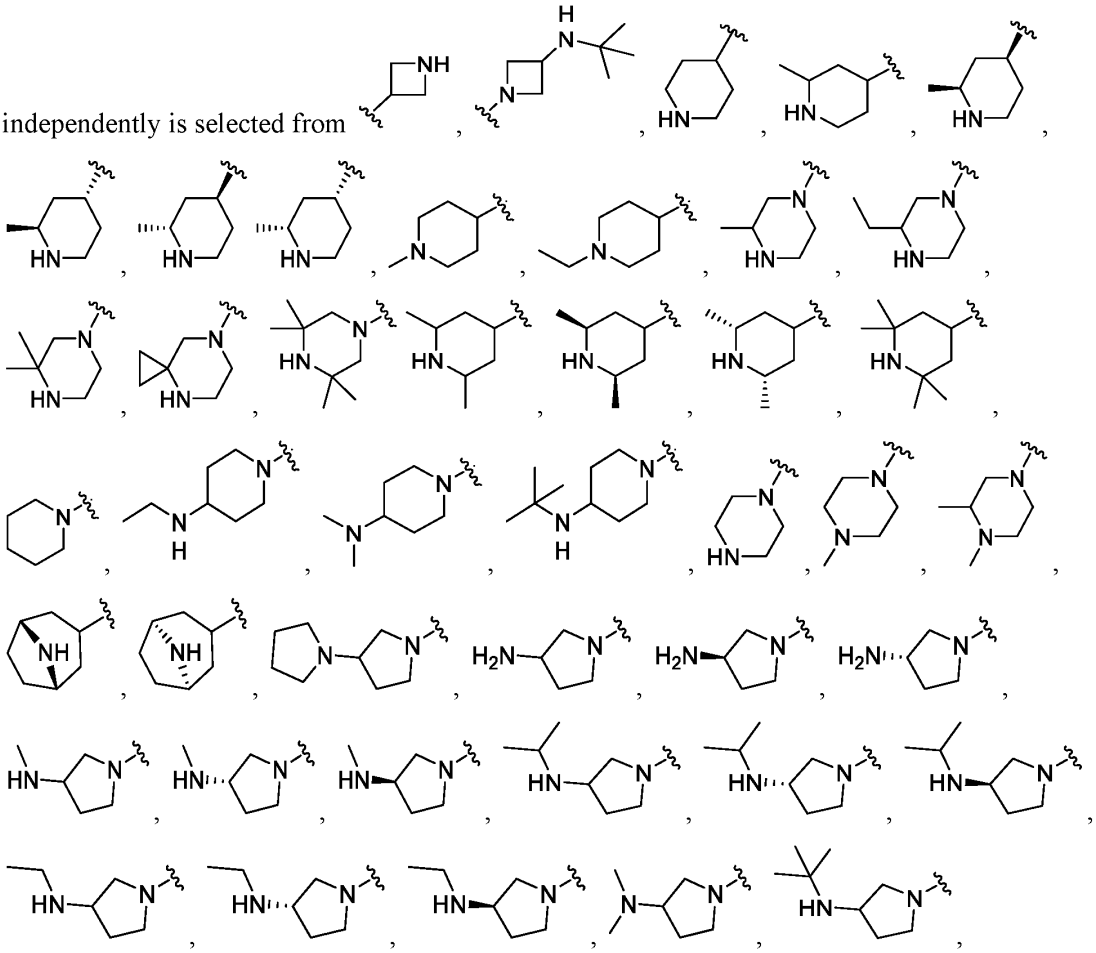
33. The compound of any one of the preceding claims, wherein A is selected from , , , , , , , , , , , , , , , and  wherein R^1 is as described in claim 1.

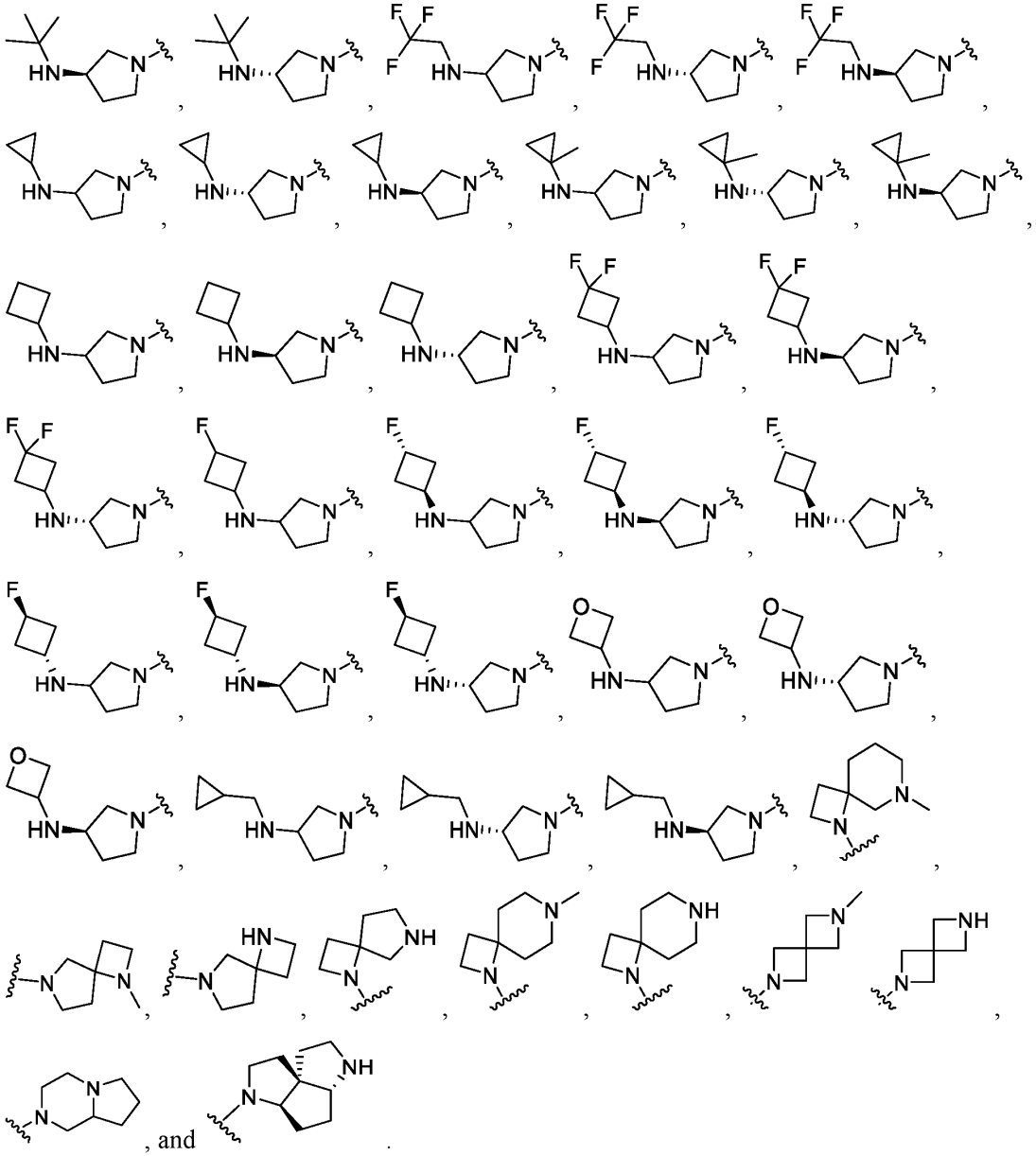
34. The compound of any one of the preceding claims, wherein B is selected from , , , , , , ,

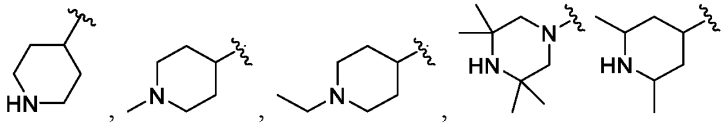


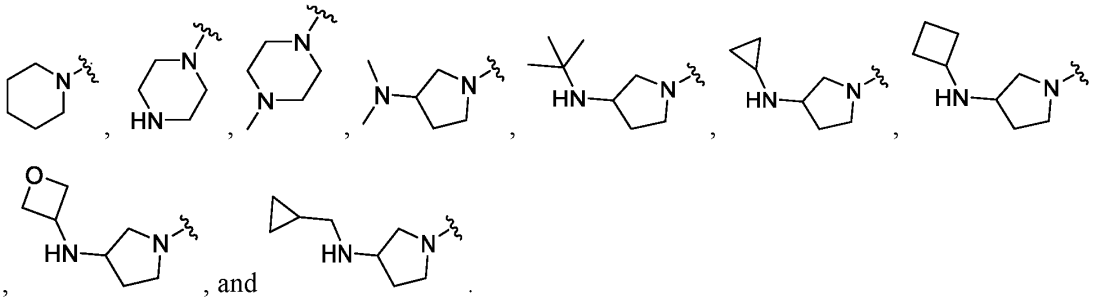
wherein R^1 is as described in claim 1.

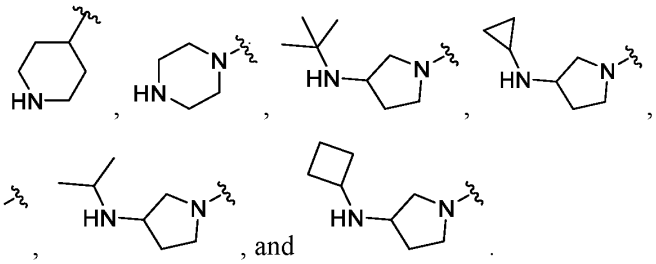
35. The compound of any one of the preceding claims, wherein one of A and B is independently is selected from

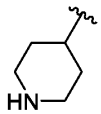
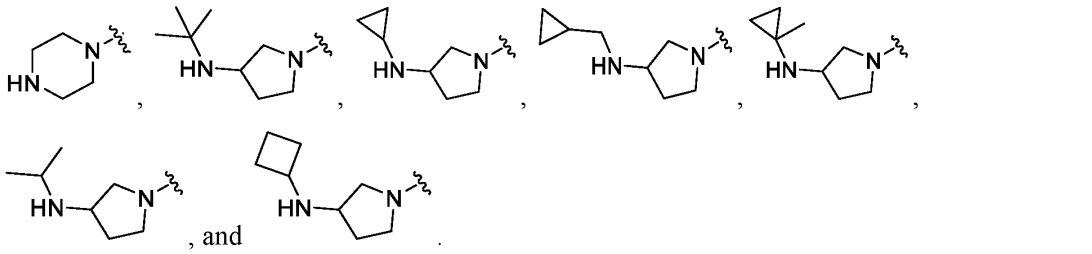


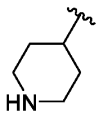
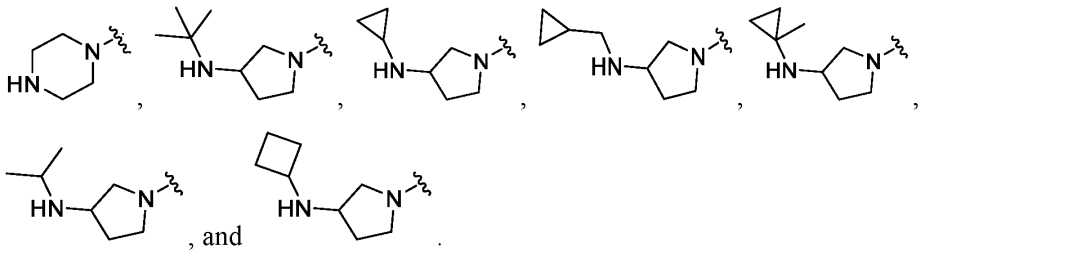


36. The compound of any one of the preceding claims, wherein one of A and B is independently is selected from ,



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

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

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

40. The compound of any one of the preceding claims, wherein each of A and B are not independently heteroaryl.

41. The compound of any one of the preceding claims, wherein each of A and B are not independently heterocyclyl.

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

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

44. The compound of any one of claims 1-42, wherein one of L^1 and L^2 is independently absent and the other of L^1 and L^2 is independently -O- or -N(R^4)-.

45. The compound of any one of the preceding claims, wherein X is N.

46. The compound of any one of the preceding claims, wherein Y is N.

47. The compound of any one of claims 1-44 and 46, wherein X is CH.

48. The compound of any one of claims 1-45 and 47, wherein Y is CH.

49. The compound of any one of claims 1-44, wherein one of X and Y is independently N.

50. The compound of any one of claims 1-44, wherein each of X and Y is independently N.

51. The compound of any one of claims 1-44, wherein one of X and Y is independently CH.

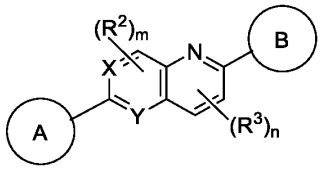
52. The compound of any one of the preceding claims, wherein m is 0 or 1.

53. The compound of any one of the preceding claims, wherein n is 0 or 1.

54. The compound of any one of the preceding claims, wherein each of m and n is independently 0.

55. The compound of any one of the preceding claims, wherein one of R^2 and R^3 is independently halo (e.g., fluoro).

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



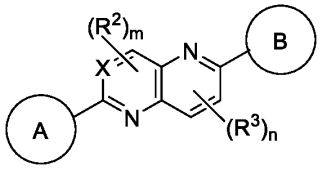
(I-c)

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

57. The compound of claim 56, wherein A is bicyclic, nitrogen-containing heteroaryl (e.g., 6-5 bicyclic nitrogen-containing heteroaryl) optionally substituted with R^1.

58. The compound of claim 56, wherein B is bicyclic, nitrogen-containing heteroaryl (e.g., 6-5 bicyclic nitrogen-containing heteroaryl) optionally substituted with R^1.

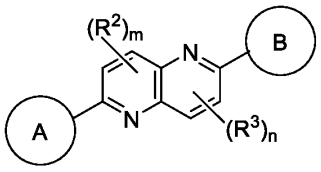
59. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-e):



(I-e),

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

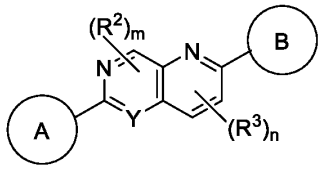
60. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-f):



(I-f),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein m is 0, 1 or 2; and A, B, R^2, R^3, m, n, and subvariables thereof are as defined in claim 1.

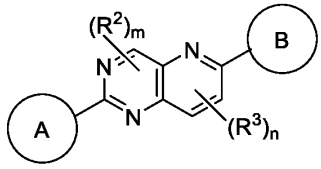
61. The compound of any one of claims 1-58, wherein the compound of Formula (I) is a compound of Formula (I-g):



(I-g),

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

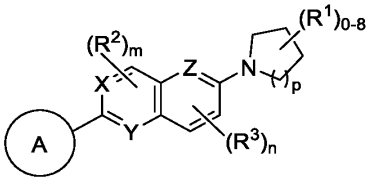
62. The compound of any one of the preceding claims, wherein the compound of Formula (I) is a compound of Formula (I-h):



(I-h),

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

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

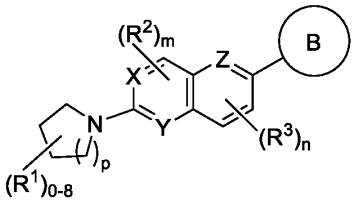


(I-k),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein p is 0, 1, 2 or 3, and A, X, Y, Z, R^2, R^3, m, n, and subvariables thereof are as defined in claim 1.

64. The compound of claim 63, wherein A is bicyclic, nitrogen-containing heteroaryl (e.g., 6-5 bicyclic nitrogen-containing heteroaryl) optionally substituted with R^1.

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



(I-l),

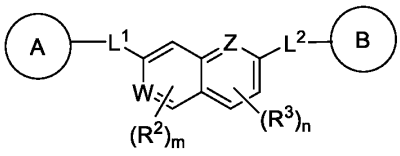
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein p is 0, 1, 2 or 3, and B, X, Y, Z, R^2, R^3, m, n, and subvariables thereof are as defined in claim 1.

66. The compound of claim 65, wherein B is bicyclic, nitrogen-containing heteroaryl (e.g., 6-5 bicyclic nitrogen-containing heteroaryl) optionally substituted with R^1.

67. The compound of any one of claims 63-66, wherein R^1 is OR^A.

68. 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.

69. A compound of Formula (II):



(II)

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

W and Z are each N or C(R^6), wherein at least one of W and Z is 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, 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^7; 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^7;

each R^2 and R^3 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–S(O)_xR^D$;

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

each R^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, $-OR^A$, or $-NR^BR^C$;

each R^6 is independently hydrogen, halo, C_1-C_6-alkyl, C_1-C_6-haloalkyl, or $-OR^A$;

each R^7 is independently C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $-OR^A$, $-NR^BR^C$, $-NR^BC(O)R^D$, $-NO_2$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-C(O)OR^D$, 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^8;

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 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^9;

each R^D 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^8 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^9 is C_1-C_6-alkyl, halo, cyano, oxo, or $-OR^{A1}$;

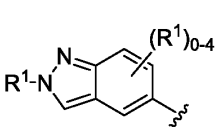
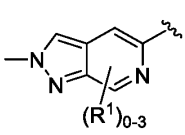
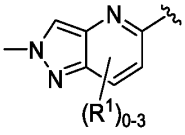
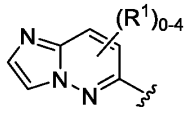
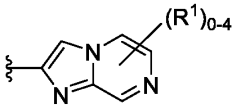
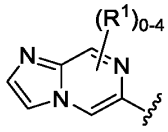
each R^{A1} is hydrogen or C_1-C_6-alkyl;

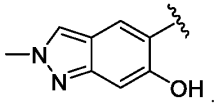
m and n are each independently 0, 1, or 2; and

x is 0, 1, or 2.

70. The compound of claim 69, wherein one of A and B is independently a monocyclic heteroaryl or bicyclic heteroaryl, each of which is optionally substituted with one or more R^1.

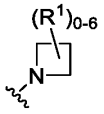
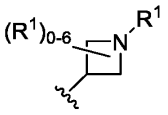
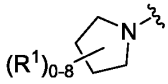
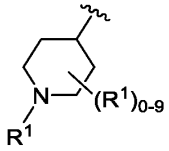
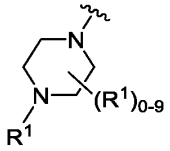
71. The compound of any one of claims 69-70, wherein one of A and B is independently a bicyclic heteroaryl optionally substituted with one or more R^1.

72. The compound of any one of claims 69-71, wherein one of A and B is independently selected from , , , , , and , wherein R^1 is as described in claim 69.

73. The compound of any one of claims 69-72, wherein one of A and B is independently is .

74. The compound of any one of claims 69-73, wherein one of A and B is independently a nitrogen-containing heterocyclyl optionally substituted with one or more R^1.

75. The compound of any one of claims 69-74, wherein one of A and B is independently a 4-8 membered heterocyclyl optionally substituted with one or more R^1.

76. The compound of any one of claims 69-75, wherein one of A and B is independently selected from , , , , and , wherein R^1 is as described in claim 69.

77. The compound of any one of claims 69-76, wherein one of L^1 and L^2 is independently absent.

78. The compound of any one of claims 69-77, wherein each of L^1 and L^2 is independently absent.

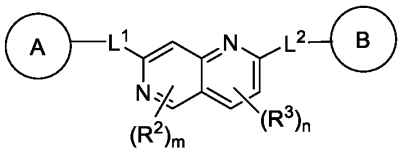
79. The compound of any one of claims 69-78, wherein each of L^1 and L^2 is absent, -$N(R^4)C(O)N(R^4)$-, or C_1-C_6-alkylene-$N(R^4)C(O)N(R^4)$-.

80. The compound of any one of claims 69-79, wherein W is N.

81. The compound of any one of claims 69-80, wherein Z is N.

82. The compound of any one of claims 69-81, wherein each of W and Z is independently N.

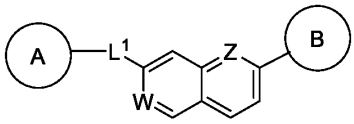
83. The compound of any one of claims 69-82, wherein the compound of Formula (II) is a compound of Formula (II-a):



(II-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, L^2, R^2, R^3, m, n, and subvariables thereof are as defined in claim 69.

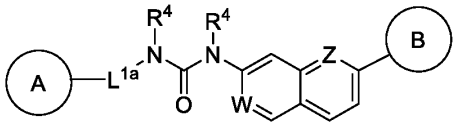
84. The compound of any one of claims 69-83, wherein the compound of Formula (II) is a compound of Formula (II-b):



(II-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, W, Z, and subvariables thereof are as defined in claim 69.

85. The compound of any one of claims 69-84, wherein the compound of Formula (II) is a compound of Formula (II-c):



(II-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein L^{1a} is absent or C_1-C_6-alkylene, and A, B, L^{1a}, W, Z, R^4, and subvariables thereof are as defined in claim 69.

86. The compound of any one of claims 69-85, wherein the compound is selected from any one of the compounds shown in Table 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

87. A pharmaceutical composition comprising a compound of any one of claims 1-86 and a pharmaceutically acceptable excipient.

88. The compound of any one of claims 1-86 or the pharmaceutical composition of claim 87, wherein the compound alters a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

89. The compound of any one of claims 1-86 or the pharmaceutical composition of claim 87, wherein the compound binds to a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

90. The compound of any one of claims 1-86 or the pharmaceutical composition of claim 87, wherein the compound stabilizes a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA).

91. The compound of any one of claims 1-86 or the pharmaceutical composition of claim 87, 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.

92. The compound of any one of claims 1-86 or the pharmaceutical composition of claim 87, 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 %.

93. 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) or (II) as described in any one of claims 1-86 or a pharmaceutical composition of claim 87.

94. The method of claim 93, 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.

95. The method of claim 93, 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.

96. 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 Formula (II):

comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I) or (II), according to any one of claims 1-86 or the pharmaceutical composition of claim 87.

97. The method of claim 96, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I) or (II).

98. 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) or (II), according to any one of claims 1-86 or the pharmaceutical composition of claim 87.

99. The method of claim 98, wherein the altering comprises forming a bulge in the nucleic acid.

100. The method of claim 98, wherein the altering comprises stabilizing a bulge in the nucleic acid.

101. The method of claim 98, wherein the altering comprises reducing a bulge in the nucleic acid.

102. The method of any one of claims 98-101, wherein the nucleic acid comprises a splice site.

103. A composition for use in treating a disease or disorder in a subject comprising administering to the subject a compound of Formula (I) or (II), according to any one of claims 1-86 or the pharmaceutical composition of claim 87.

104. The composition for use of claim 103, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

105. The composition for use of claim 103, 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.

106. The composition for use of claim 103, wherein the disease or disorder comprises neurological disease or disorder.

107. The composition for use of claim 103, wherein the disease or disorder comprises Huntington's disease.

108. A method for treating a disease or disorder in a subject comprising administering to the subject a compound of Formula (I) or (II), according to any one of claims 1-88 or the pharmaceutical composition of claim 87.

109. The method of claim 108, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

110. The method of claim 108, 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.

111. The method of claim 108, wherein the disease or disorder comprises neurological disease or disorder.

112. The method of claim 108, wherein the disease or disorder comprises Huntington's disease.