COMPOUNDS AND METHODS FOR MODULATING SPLICING

CLAIM OF PRIORITY

This application claims priority to U.S. Application No. 63/255,178, filed on October 13, 2021; U.S. Application No. 63/255,348, filed on October 13, 2021; U.S. Application No. 63/255,079, filed on October 13, 2021; U.S. Application No. 63/393,208, filed on July 28, 2022; and U.S. Application No. 63/393,210, filed on July 28, 2022. 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.

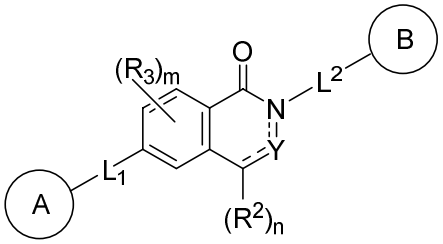
SUMMARY

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 example, the compounds described herein are compounds of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof), and compositions thereof, e.g., to target, and in examples 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 example, the compounds described herein may be used to alter the composition or structure of a nucleic acid (e.g., a pre-mRNA or mRNA (e.g., a pre-mRNA and the mRNA which arises from the pre-mRNA), e.g., by increasing or decreasing splicing at a splice site. In some examples, increasing or decreasing splicing results in modulating the level of a gene product (e.g., an RNA or protein) produced.

In another example, 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 examples, the compounds described herein (e.g., compounds of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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 examples, the compounds described herein (e.g., compounds of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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 examples, the compounds described herein (e.g., compounds of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), 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 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;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^7;

Y is N, C(R^{6a}), or C(R^{6a})(R^{6b}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

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

R^3 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, cycloalkyl, heterocyclyl, –OR^A, –NR^BR^C, –$C(O)R^D$, –$C(O)OR^D$, $C(O)NR^BR^C$, –$NR^BC(O)R^D$, or –$S(O)_xR^D$;

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

each R^5 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, oxo, 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 –$S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

R^{6a} and R^{6b} is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, or halo;

each R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–OR^A$, $–S(O)_xR^D$; 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^9 is independently C_1-C_6-alkyl, halo, or $–OR^{A1}$;

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

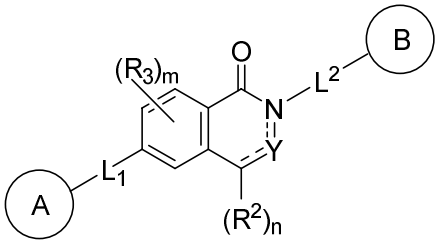
each R^9 and R^{10} is independently C_1-C_6-alkyl, halo, or $–OR^{A1}$;

m is 0, 1, 2, or 3;

n is 0, 1, or 2; and

x is 0, 1, or 2.

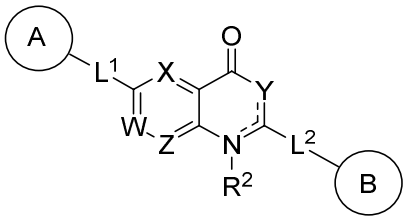
In one example, the present disclosure provides compounds of Formula (I):



(I), or a pharmaceutically acceptable salt, solvate, hydrate,

tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, Y, R^2, R^3, m, n, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure 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;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^8)-, -N(R^8)C(O)-, or -C(O)N(R^8)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^9;

each of W, X, and Z is independently C(R^3) or N;

Y is N, N(R^{4a}), C(R^{4b}), or C(R^{4b})(R^{4c}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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^5; 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^5;

R^2 is absent, hydrogen, or C_1-C_6-alkyl;

R^3 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, –OR^A, –NR^BR^C, –$C(O)R^D$, –$C(O)OR^D$, or –$S(O)_xR^D$;

R^{4a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, or C_1-C_6-haloalkyl;

each of R^{4b} and R^{4c} is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, or $–OR^A$;

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6;

each R^6 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^8 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^9 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

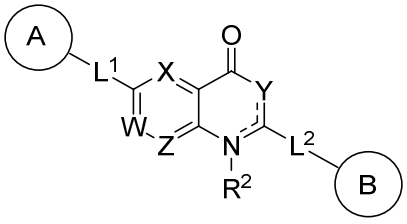
each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–OR^A$, $–S(O)_xR^D$; or R^B and R^C together with the atom to which they 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^{10} is independently C_1-C_6-alkyl or halo; and

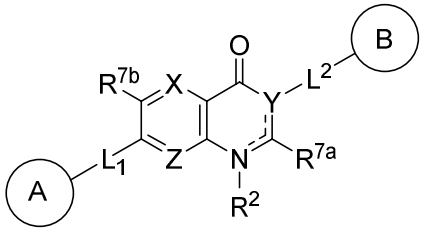
x is 0, 1, or 2.

In another example, the present disclosure features 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, X, Y, Z, R^2, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure provides a compound of Formula (III):



(III)

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 of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^8)-, -N(R^8)C(O)-, or -C(O)N(R^8)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^9;

each of X and Z is independently C(R^3) or N;

Y is N, C, or C(R^{4b}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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^5; 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^5;

R^2 is absent, hydrogen, or C_1-C_6-alkyl;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–S(O)_xR^D$;

R^{4b} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, or C_1-C_6-haloalkyl;

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6;

each R^6 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 $–OR^A$;

R^{7a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, or $–OR^A$;

R^{7b} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or $–OR^A$;

each R^8 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^9 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

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, $–OR^A$; or

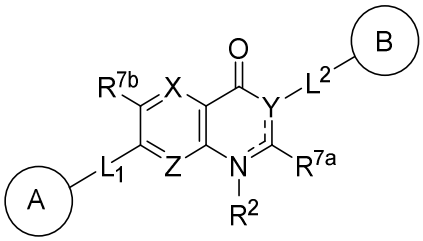
R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^{10};

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

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

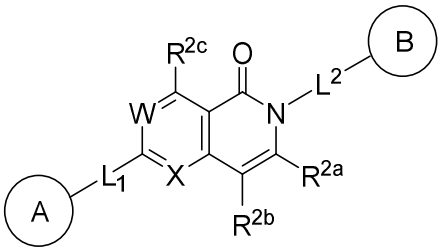
x is 0, 1, or 2.

In another example, the present disclosure provides compounds of Formula (III):



(III), 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^{7a}, R^{7b}, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure provides a compound of Formula (IV):



(IV)

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 X are each independently $C(R^3)$ or N, wherein one of W and X is independently N;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)$-, $-N(R^4)C(O)$-, or $-C(O)N(R^4)$-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

R^{2a}, R^{2b}, and R^{2c} are each independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

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

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

each R^6 and R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

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

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, cycloalkyl, heterocyclyl, $–OR^A$, $–S(O)_xR^D$; or

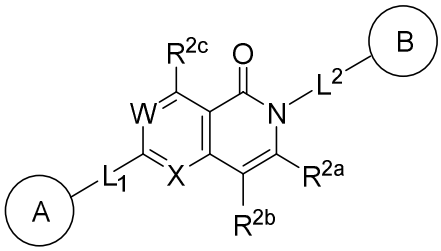
R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^9;

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^9 is independently C_1-C_6-alkyl or halo; and

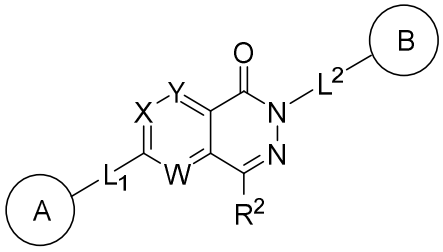
x is 0, 1, or 2.

In another example, the present disclosure provides compounds of Formula (IV):



(IV), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, W, X, R^{2a}, R^{2b}, R^{2c}, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure provides a compound of Formula (V):



(V)

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, X, and Y are each independently $C(R^3)$ or N, wherein at least one of W, X, and Y is independently N;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)-$, $-N(R^4)C(O)-$, or $-C(O)N(R^4)-$, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

R^2 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

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

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

each R^6 and R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

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

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, cycloalkyl, heterocyclyl, $–OR^A$, $–S(O)_xR^D$; or

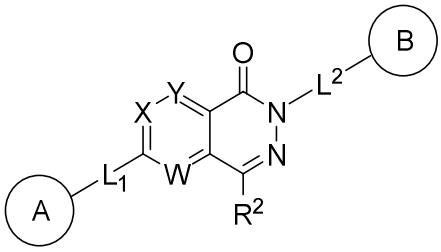
R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^9;

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^9 is independently C_1-C_6-alkyl or halo; and

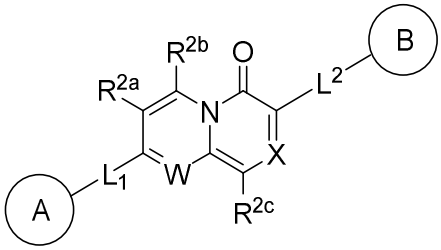
x is 0, 1, or 2.

In another example, the present disclosure provides compounds of Formula (V):



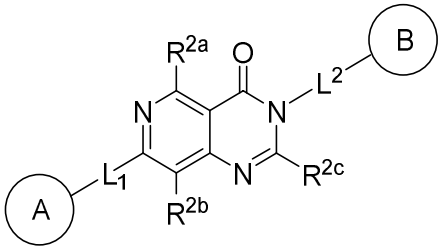
(V), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, W, X, Y, R^2, and subvariables thereof are defined as described herein.

In another example, the present disclosure provides compounds of Formula (VI):



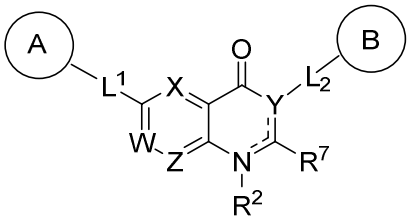
(VI), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, W, X, R^{2a}, R^{2b}, R^{2c}, and subvariables thereof are defined as described herein.

In another example, the present disclosure provides compounds of Formula (VII):



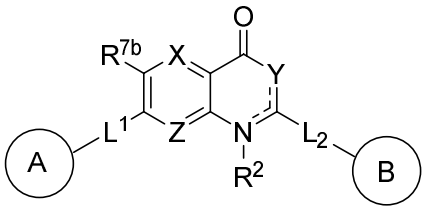
(VII), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, R^{2a}, R^{2b}, R^{2c}, and subvariables thereof are defined as described herein.

In another example, the present disclosure provides compounds of Formula (VIII):



(VIII), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^1, L^2, W, X, Y, Z, R^2, R^7, and subvariables thereof are defined as described herein.

In another example, the present disclosure provides compounds of Formula (IX):



(IX), 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^{7b}, and subvariables thereof are defined as described herein.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable excipient.

In another example, the present disclosure provides pharmaceutical compositions comprising a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In an example, the pharmaceutical compositions described herein include an effective amount (e.g., a therapeutically effective amount) of a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), 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 examples, the compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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 examples, the compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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 examples, the compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), e.g., in a healthy or diseased cell or tissue). In some examples, the presence of a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), e.g., in a healthy or diseased cell or tissue).

In another aspect, the present disclosure provides 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), (II), (III), (IV), or (V), described herein:

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

In another aspect, the present disclosure provides 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), (II), (III), (IV), or (V) or a pharmaceutically acceptable salt or a composition thereof.

In another aspect, the present disclosure provides a use of a compound of Formula (I), (II), (III), (IV), or (V) or a pharmaceutically acceptable salt or a composition thereof in the manufacture of a medicament for treating a disease or disorder.

In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or related compositions. In some examples, the disease or disorder entails unwanted or aberrant splicing. In some examples, the disease or disorder is a proliferative disease, disorder, or condition. Exemplary proliferative diseases include cancer, a benign neoplasm, or angiogenesis. In other examples, the present disclosure provides methods for treating and/or preventing a non-proliferative disease, disorder, or condition. In still other examples, 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 example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another example, the present disclosure provides methods of altering the isoform of a target protein with a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically

acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another exampleof the disclosure relates to methods of inhibiting the activity of a target protein in a biological sample or subject. In some examples, administration of a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) to a biological sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or related compositions. In some examples, the disease or disorder entails unwanted or aberrant splicing. In some examples, the disease or disorder is a proliferative disease, disorder, or condition. Exemplary proliferative diseases include cancer, a benign neoplasm, or angiogenesis. In other examples, the present disclosure provides methods for treating and/or preventing a non-proliferative disease, disorder, or condition. In still other examples, 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 example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another example, 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), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another example, the present disclosure provides compositions for use in altering the isoform of a target protein with a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another exampleof the disclosure relates to compositions for use in inhibiting the activity of a target protein in a biological sample or

subject. In some examples, administration of a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX) to a biological sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

In another example, the present disclosure features kits comprising a container with a compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or a pharmaceutical composition thereof. In certain examples, the kits described herein further include instructions for administering the compound of Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), or (IX), or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof, or the pharmaceutical composition thereof.

In any and all examplesof the present disclosure, in some examples, the compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described herein is a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein other than a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described one of U.S. Patent No. 8,729,263, U.S. Publication No. 2015/0005289, WO 2014/028459, WO 2016/128343, WO 2016/196386, WO 2017/100726, WO 2018/232039, WO 2018/098446, WO 2019/028440, WO 2019/060917, WO 2019/199972, and WO 2020/004594. In some examples, the compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described herein is a compound, target nucleic acid (e.g., DNA, RNA, e.g., pre-mRNA), or target protein described one of U.S. Patent No. 8,729,263, U.S. Publication No. 2015/0005289, WO 2014/028459, WO 2016/128343, WO 2016/196386, WO 2017/100726, WO 2018/232039, WO 2018/098446, WO 2019/028440, WO 2019/060917, WO 2019/199972, and WO 2020/004594, each of which is incorporated herein by reference in its entirety.

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

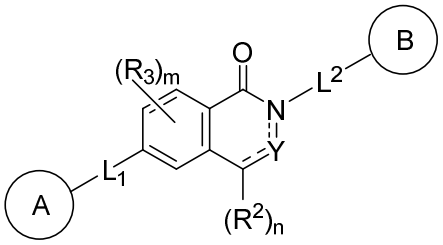
DETAILED DESCRIPTION

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

CLAIMS

1. A compound of Formula (I):



(I)

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

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

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^4)-, -N(R^4)C(O)-, or -C(O)N(R^4)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^7;

Y is N, C(R^{6a}), or C(R^{6a})(R^{6b}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

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

R^3 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, cycloalkyl, heterocyclyl, –OR^A, –NR^BR^C, –$C(O)R^D$, –$C(O)OR^D$, $C(O)NR^BR^C$, –$NR^BC(O)R^D$, or –$S(O)_xR^D$;

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

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

R^{6a} and R^{6b} is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, or halo;

each R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–OR^A$, $–S(O)_xR^D$; 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^9 is independently C_1-C_6-alkyl, halo, or $–OR^{A1}$;

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

each R^9 and R^{10} is independently C_1-C_6-alkyl, halo, or $–OR^{A1}$;

m is 0, 1, 2, or 3;

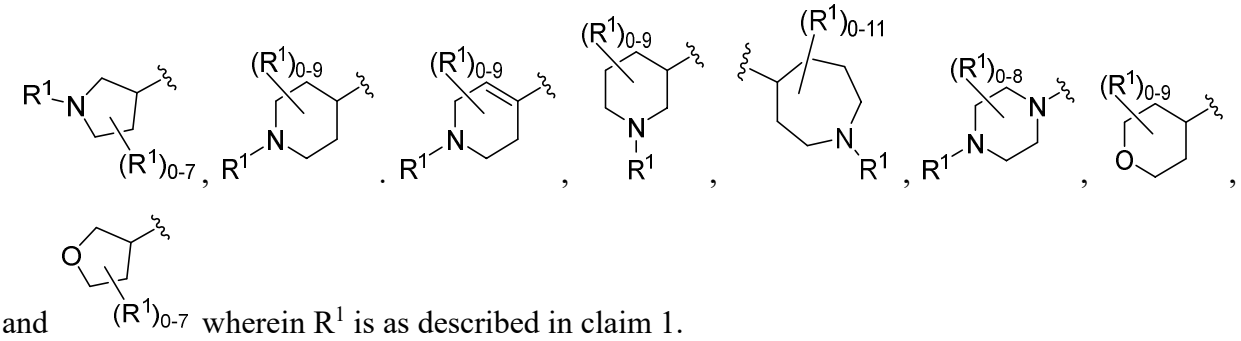
n is 0, 1, or 2; and

x is 0, 1, or 2.

2. The compound of claim 1, wherein one of A and B is independently cycloalkyl, heterocyclyl or heteroaryl.

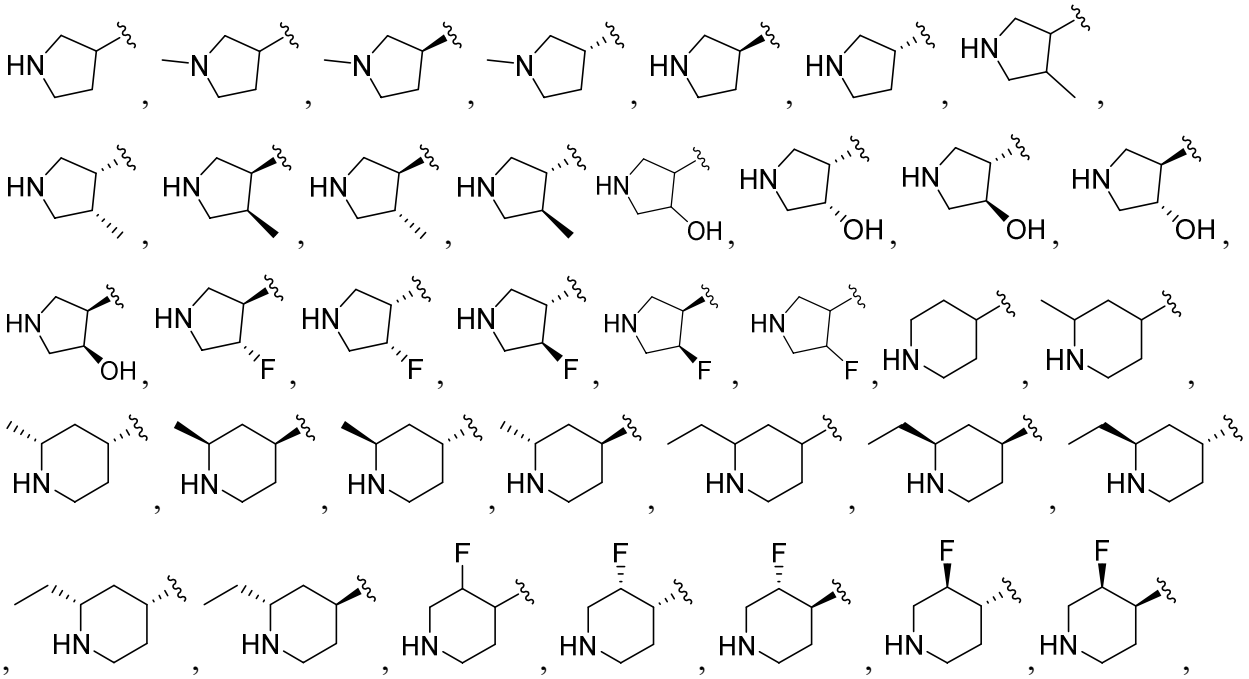
3. The compound of any one of the preceding claims, wherein one of A and B is independently a nitrogen-containing heterocyclyl, oxygen-containing heterocyclyl, or nitrogen-containing heteroaryl.

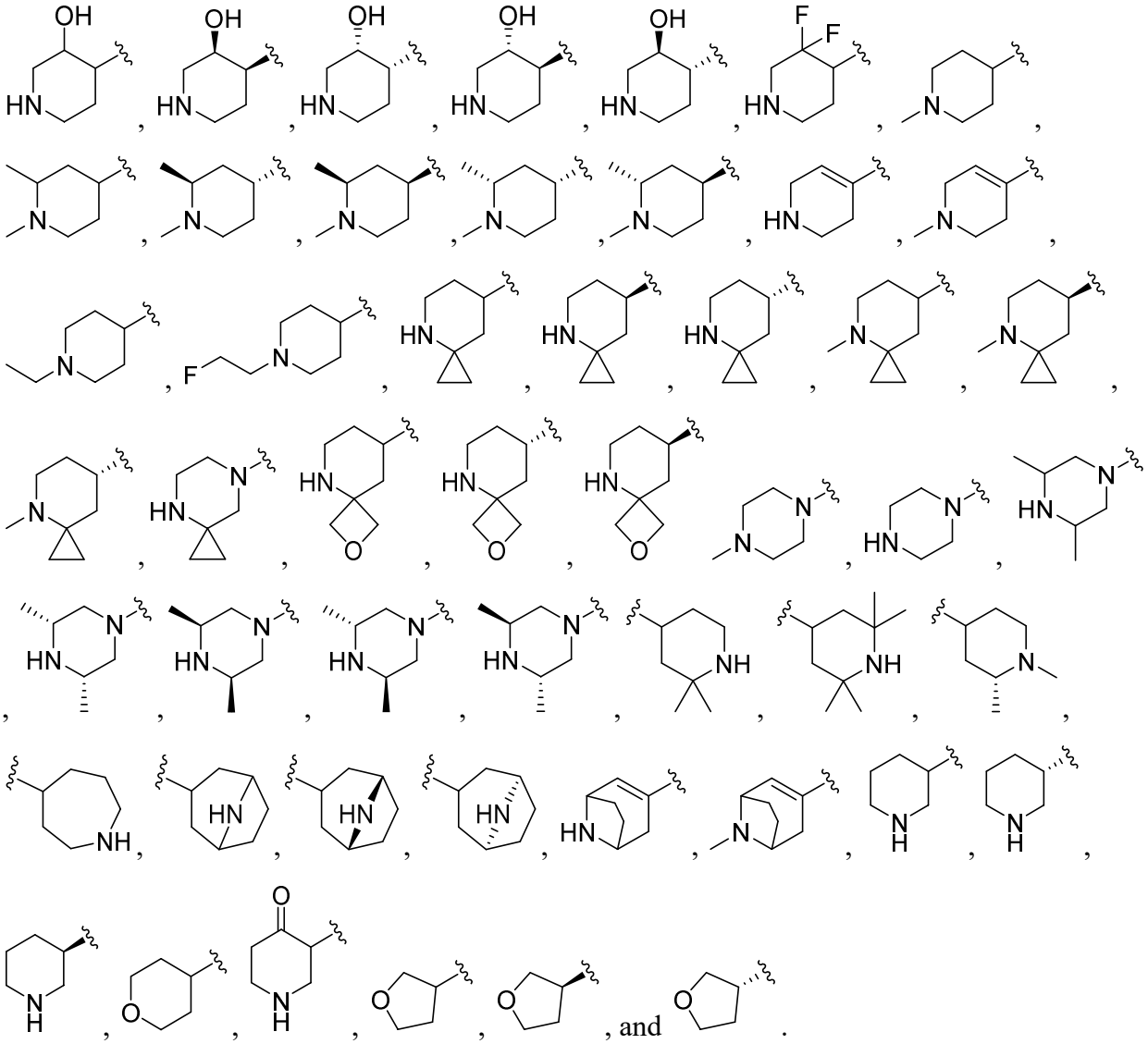
4. The compound of any one of the preceding claims, wherein one of A and B is independently selected from



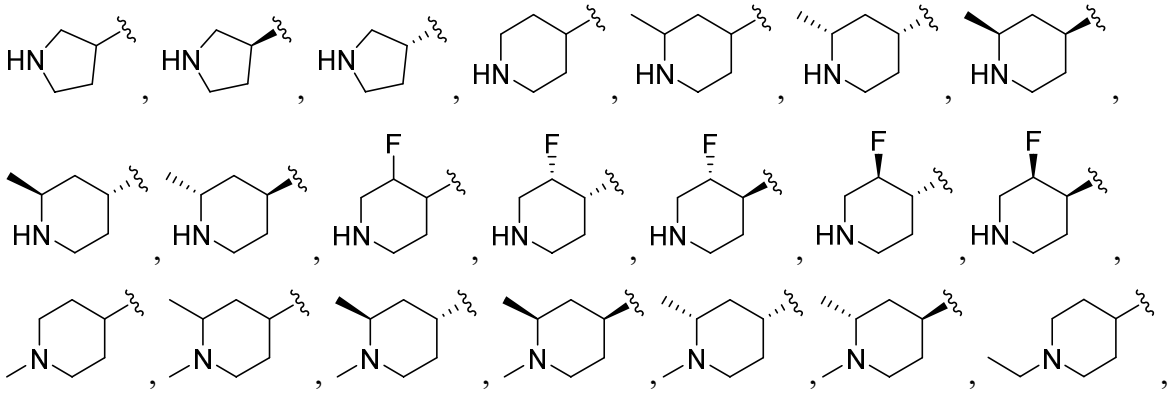
and wherein R^1 is as described in claim 1.

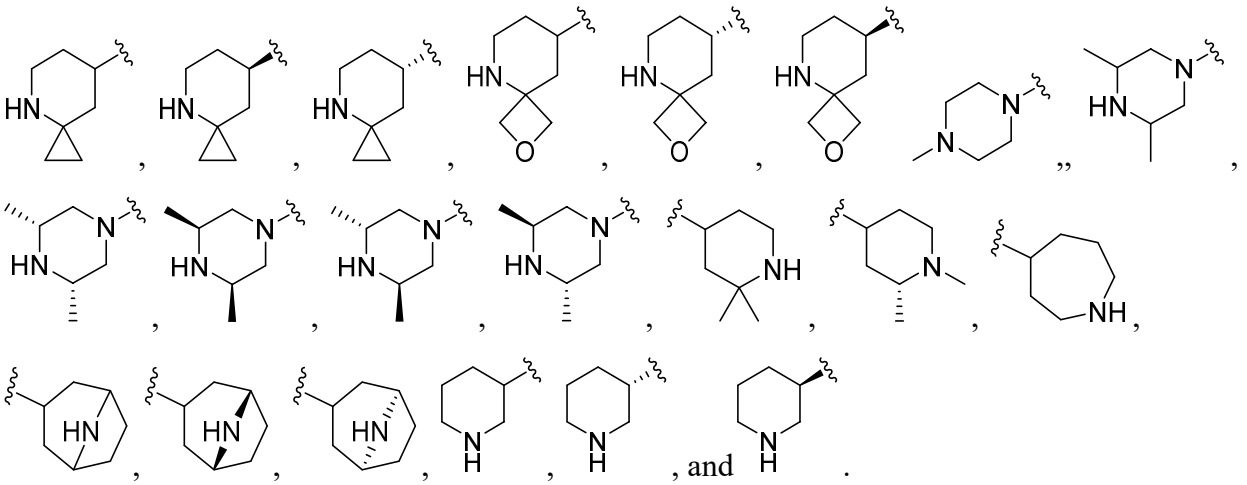
5. The compound of any one of the preceding claims, wherein one of A and B is independently selected from

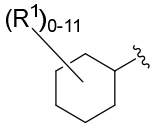


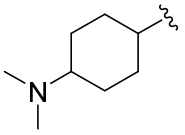


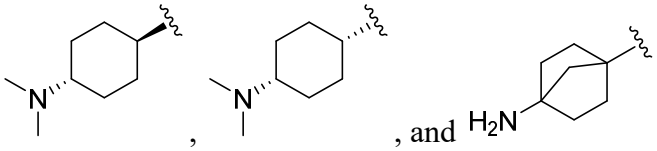
6. The compound of any one of the preceding claims, wherein B is selected from

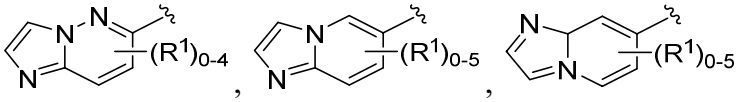


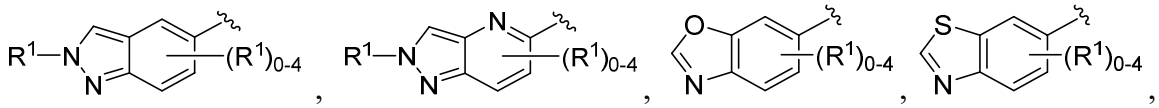


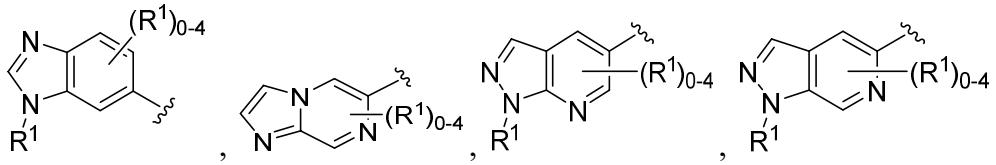
7. The compound of claim 1, wherein one of A and B is .

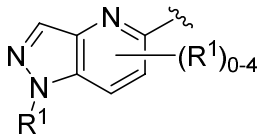
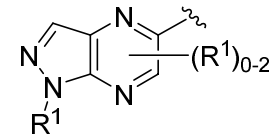
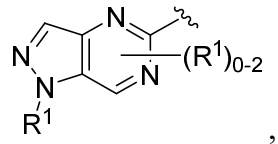
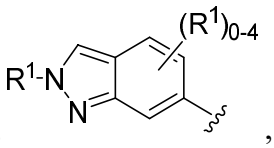
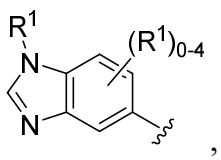
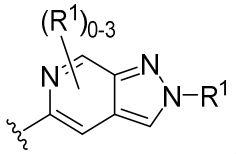
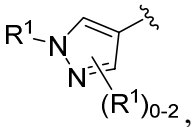
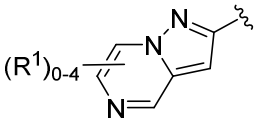
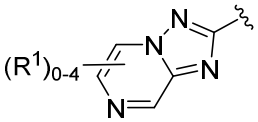
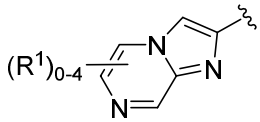
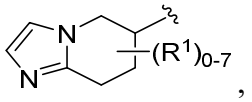
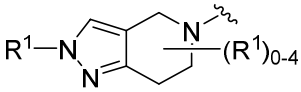
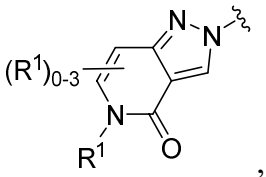
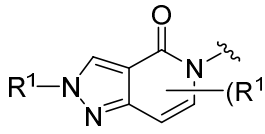
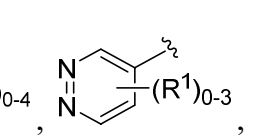
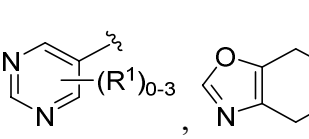
8. The compound of claim 1 or 7 wherein one of A and B is selected from: ,

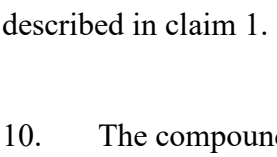
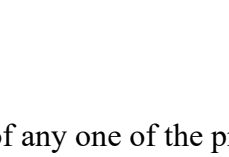
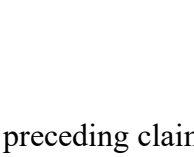
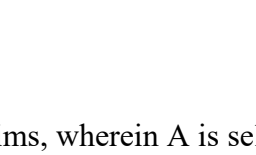


9. The compound of any one of the preceding claims, wherein one of A and B is independently selected from ,

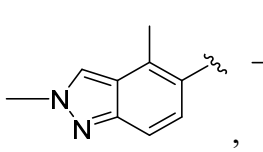
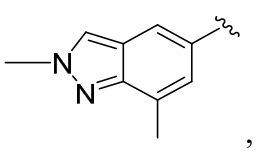


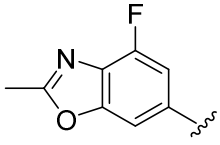
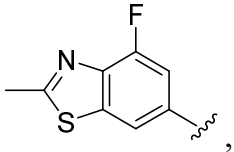
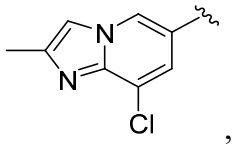
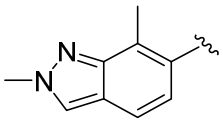
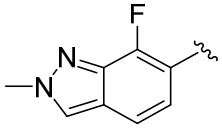
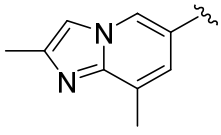
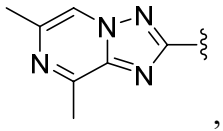
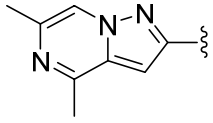
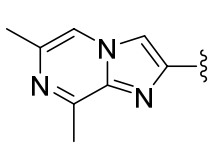
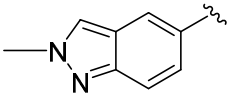
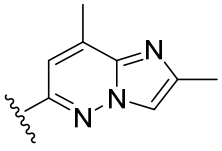
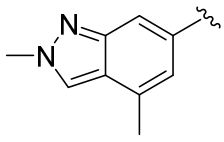
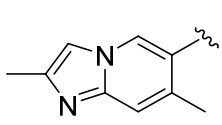
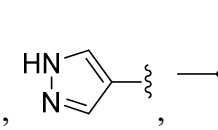
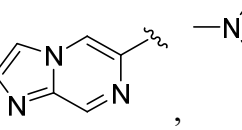
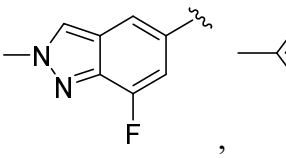


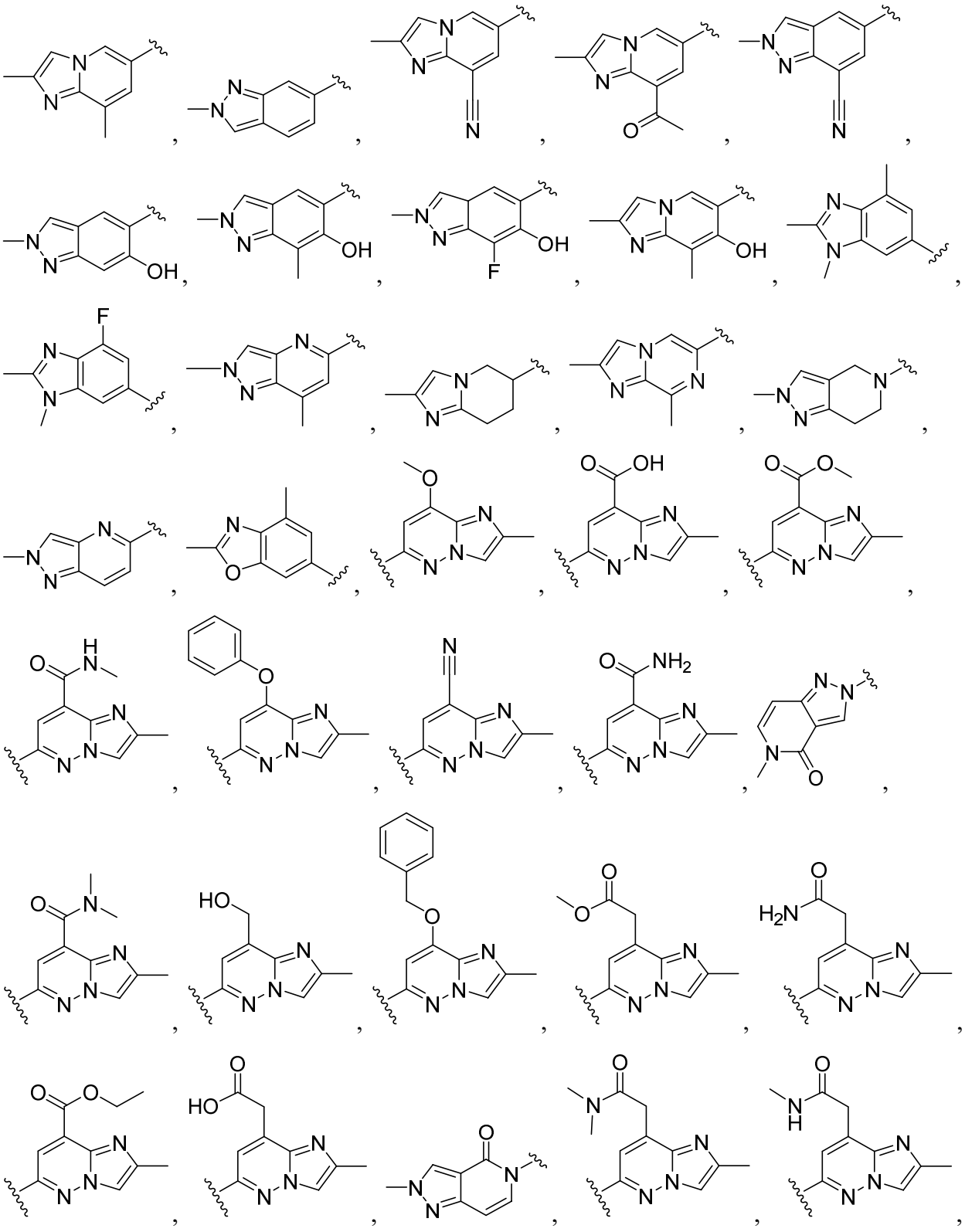

















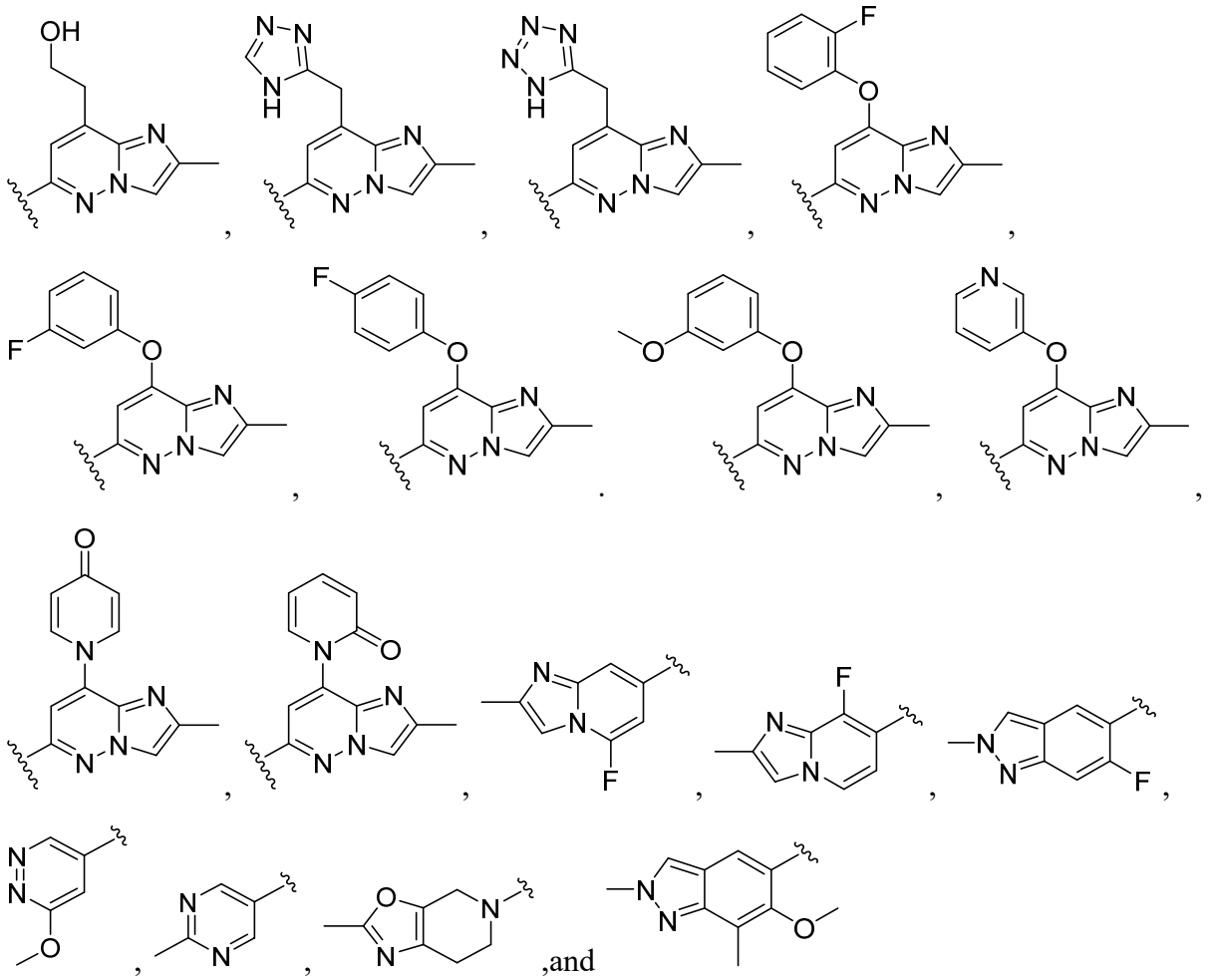




wherein R^1 is as described in claim 1.

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

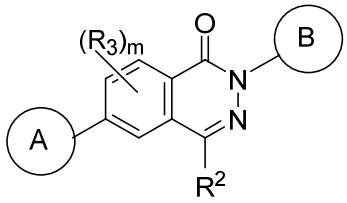




11. The compound of any one of the preceding claims, wherein each of L^1 and L^2 is independently absent.

12. The compound of any one of the preceding claims, wherein Y is $C(R^{6a})$ (e.g., CH) or N.

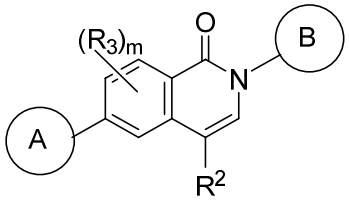
13. The compound of any one of claims 1-12, wherein the compound of Formula (I-i) is a compound of Formula (I-a):



(I-a)

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

14. The compound of any one of claims1-12, wherein the compound of Formula (I-i) is a compound of Formula (I-b):

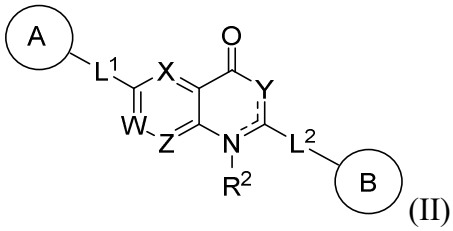


(I-b)

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

15. The compound of any one of claims 1-14, wherein the compound of Formula (I) is a compound listed in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

16. 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;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^8)-, -N(R^8)C(O)-, or -C(O)N(R^8)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^9;

each of W, X, and Z is independently C(R^3) or N;

Y is N, N(R^{4a}), C(R^{4b}), or C(R^{4b})(R^{4c}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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^5; 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^5;

R^2 is absent, hydrogen, or C_1-C_6-alkyl;

R^3 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, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, or $–S(O)_xR^D$;

R^{4a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, or C_1-C_6-haloalkyl;

each of R^{4b} and R^{4c} is independently hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, or $–OR^A$;

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6;

each R^6 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^8 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^9 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each R^A is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^9;

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, $–OR^A$, $–S(O)_xR^D$; 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;

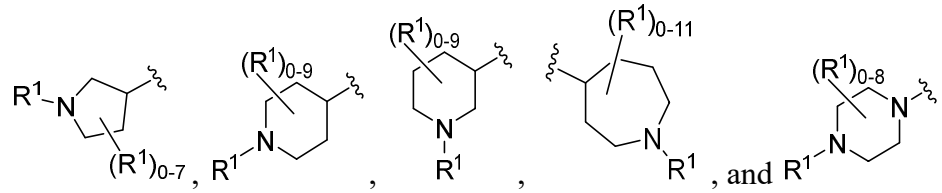
each R^D is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

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

x is 0, 1, or 2.

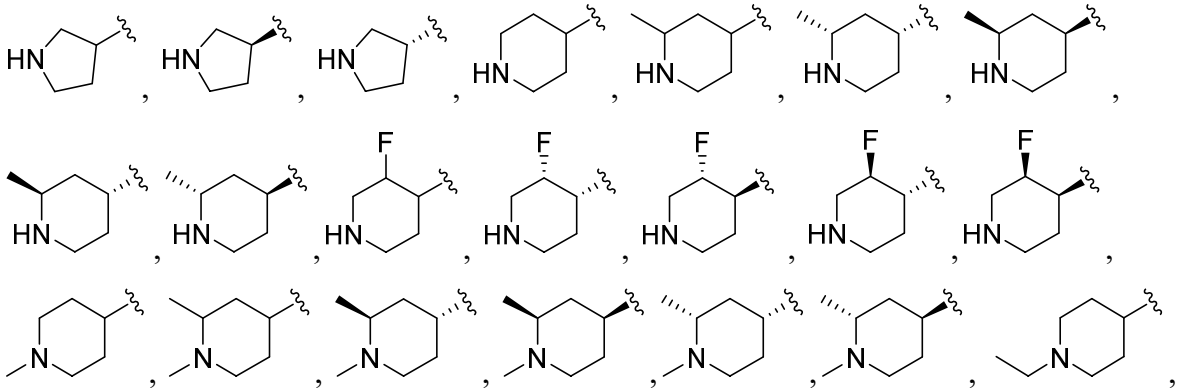
17. The compound of claim 16, wherein one of A and B is independently a nitrogen-containing heterocyclyl or nitrogen-containing heteroaryl.

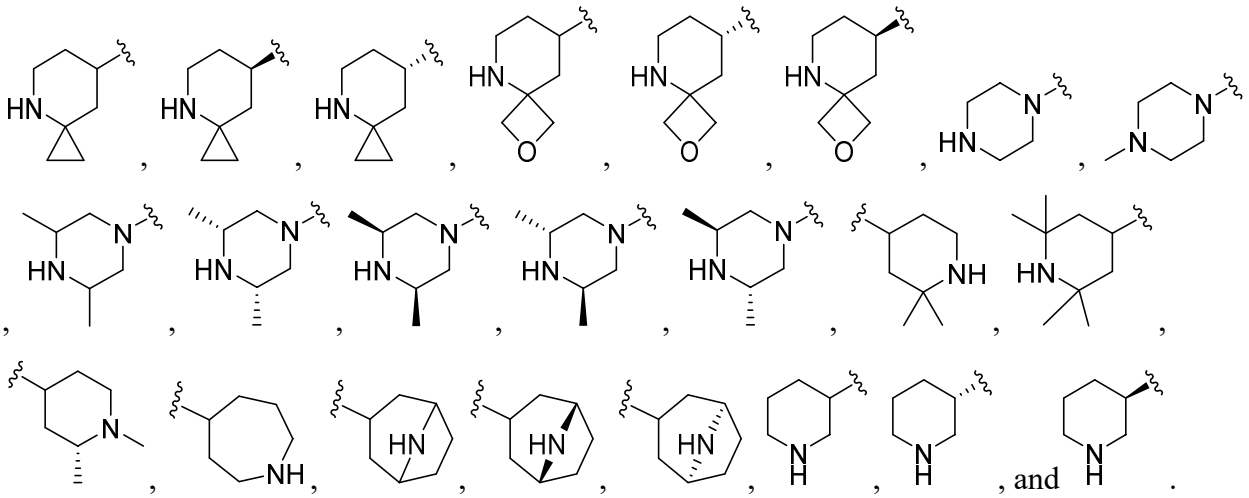
18. The compound of any one of claims 16-17, wherein one of A and B is independently selected from



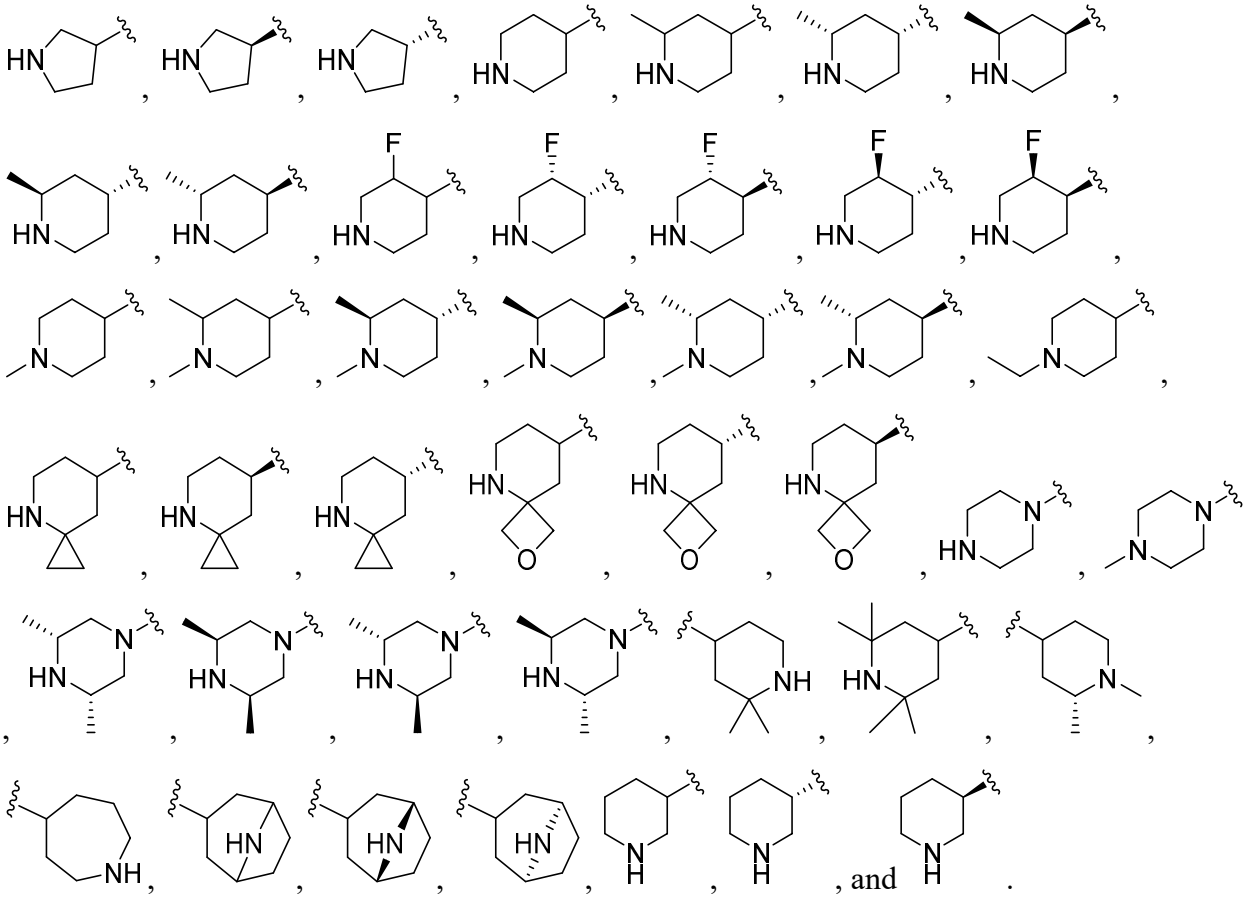
, wherein R^1 is as described in claim 16.

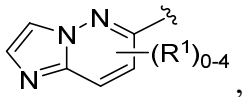
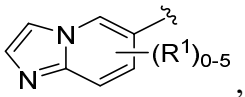
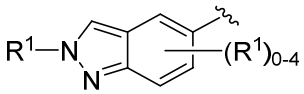
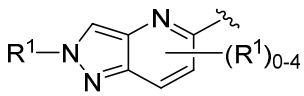
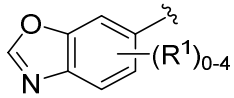
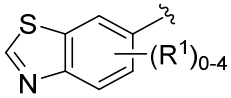
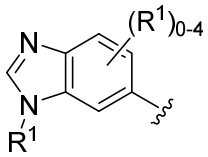
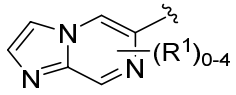
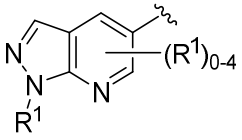
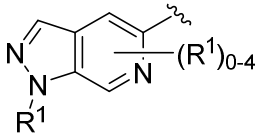
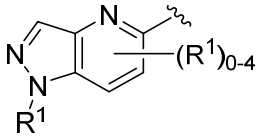
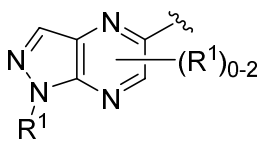
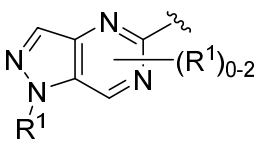
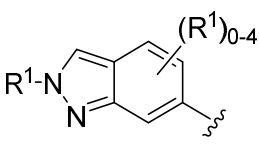
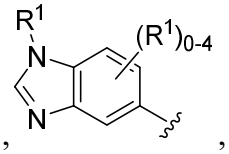
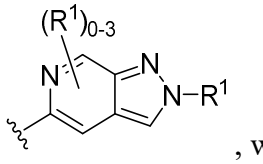
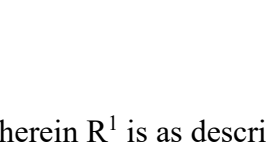
19. The compound of any one of claims 16-18, wherein one of A and B is independently selected from

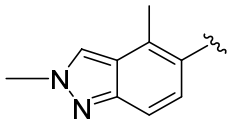
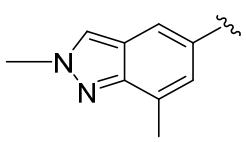
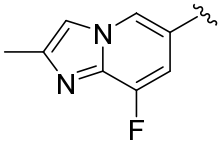
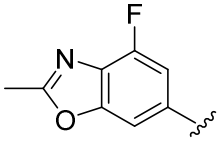
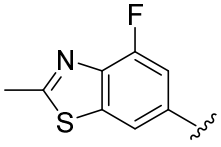
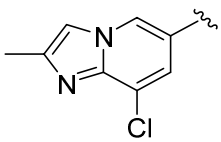
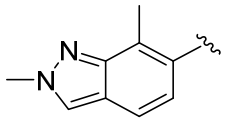
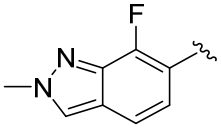
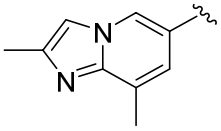
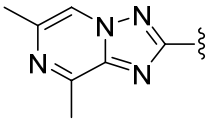
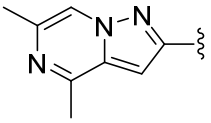
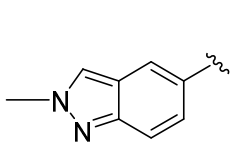
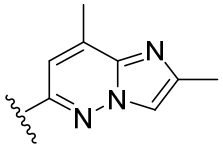
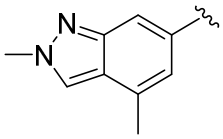




20. The compound of any one of claims 16-19, wherein A is selected from



21. The compound of any one of claims 16-20, wherein one of A and B is independently selected from , , , , , , , , , , , , , , , , , , , , wherein R^1 is as described in claim 16.

22. The compound of any one of claims 16-21, wherein B is selected from , , , , , , , , , , , , , and .

23. The compound of any one of claims 16-22, wherein each of L^1 and L^2 is independently absent.

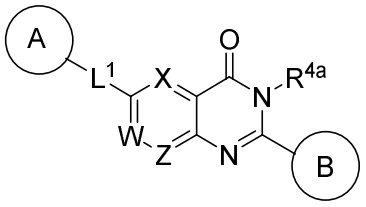
24. The compound of any one of claims 16-23, wherein W is $C(R^3)$ (e.g., CH).

25. The compound of any one of claims 16-24, wherein X is $C(R^3)$ (e.g., CH).

26. The compound of any one of claims 16-25, wherein Z is $C(R^3)$ (e.g., CH).

27. The compound of any one of claims 16-26, wherein Y is $N(R^{4a})$ or $C(R^{4b})$, (e.g., NH).

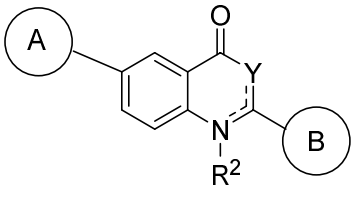
28. The compound of any one of claims 16-21, wherein the compound of Formula (II) is a compound of Formula (II-a):



(II-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, W, X, Z, R^{4a}, and subvariables thereof are as defined in claim 16.

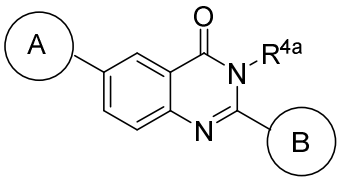
29. The compound of any one of claims 16-27, wherein the compound of Formula (II) is a compound of Formula (II-b):



(II-b),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, Y, R^2, and subvariables thereof are as defined in claim 16.

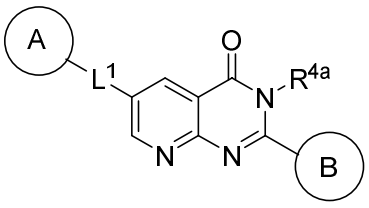
30. The compound of any one of claims 16-27, wherein the compound of Formula (II) is a compound of Formula (II-c):



(II-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, Y, R^{4a}, and subvariables thereof are as defined in claim 16.

31. The compound of any one of claims 16-27, wherein the compound of Formula (II) is a compound of Formula (II-d):

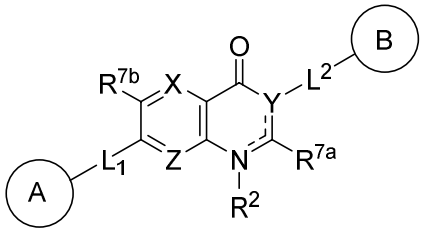


(II-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, R^{4a}, and subvariables thereof are as defined in claim 16.

32. The compound of any one of claims 16-31, wherein the compound of Formula (II) is a compound listed in Table 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

33. A compound of Formula (III):



(III)

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 of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, -N(R^8)-, -N(R^8)C(O)-, or -C(O)N(R^8)-, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^9;

each of X and Z is independently C(R^3) or N;

Y is N, C, or C(R^{4b}), wherein the dashed lines in the ring comprising Y may be single or double bonds as valency permits;

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^5; 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^5;

R^2 is absent, hydrogen, or C_1-C_6-alkyl;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, –OR^A, –NR^BR^C, –$C(O)R^D$, –$C(O)OR^D$, –$S(O)_xR^D$;

R^{4b} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, or C_1-C_6-haloalkyl;

each R^5 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, oxo, 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 –$S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^6;

each R^6 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;

R^{7a} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, oxo, or –OR^A;

R^{7b} is hydrogen, C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, or –OR^A;

each R^8 is independently hydrogen, C_1-C_6-alkyl, or C_1-C_6-haloalkyl;

each R^9 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

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, $–OR^A$; or

R^B and R^C together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more R^{10};

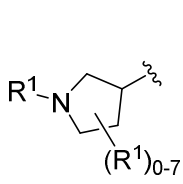
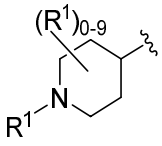
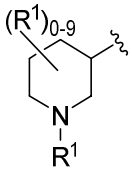
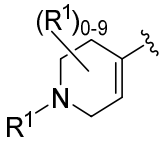
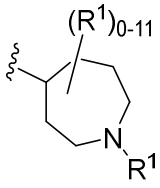
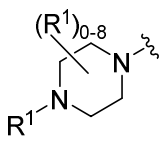
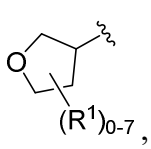
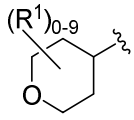
each R^D is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

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

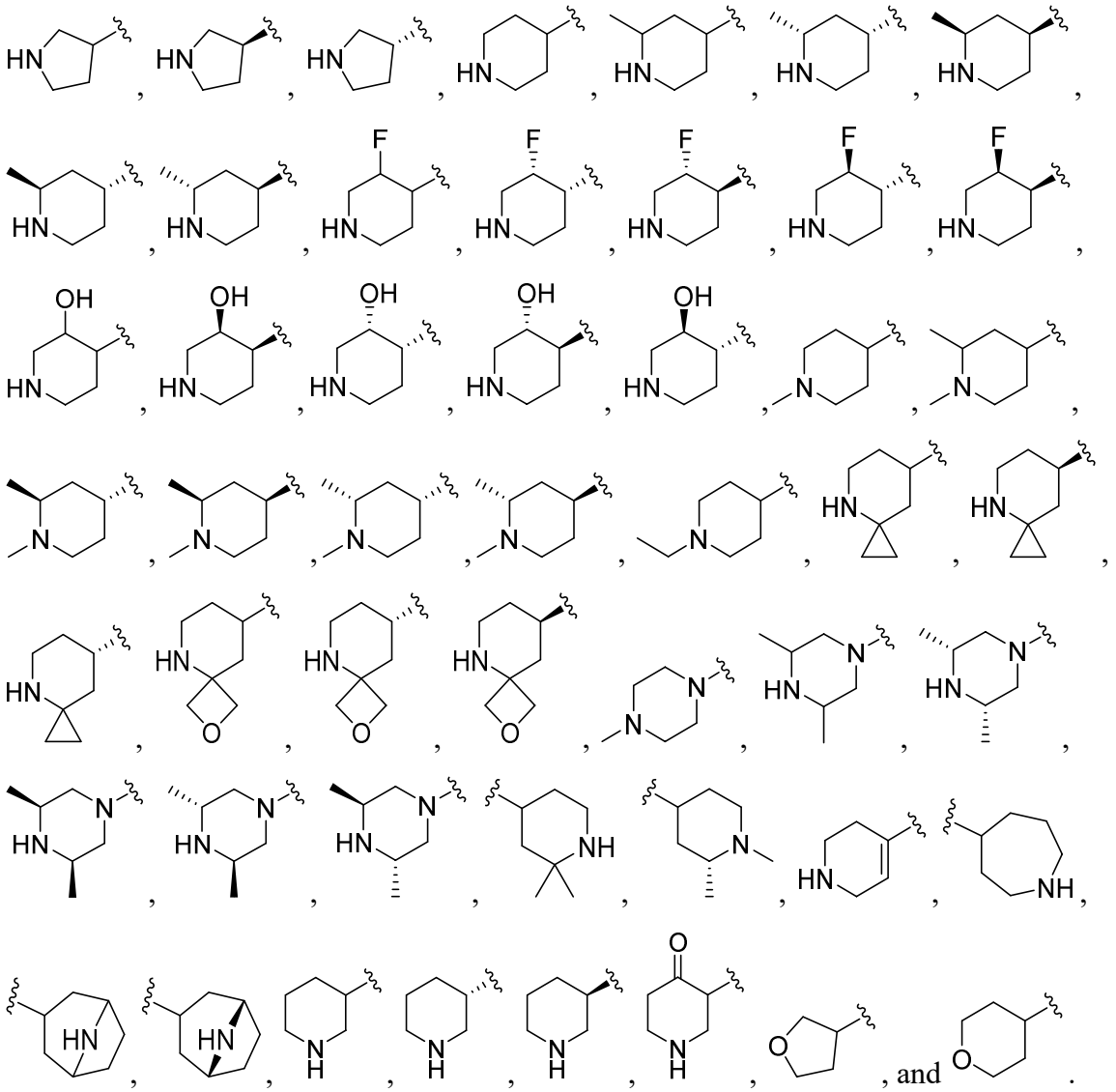
x is 0, 1, or 2.

34. The compound of claim 33, wherein one of A and B is independently a nitrogen-containing heterocyclyl, oxygen-containing heterocyclyl, or nitrogen-containing heteroaryl.

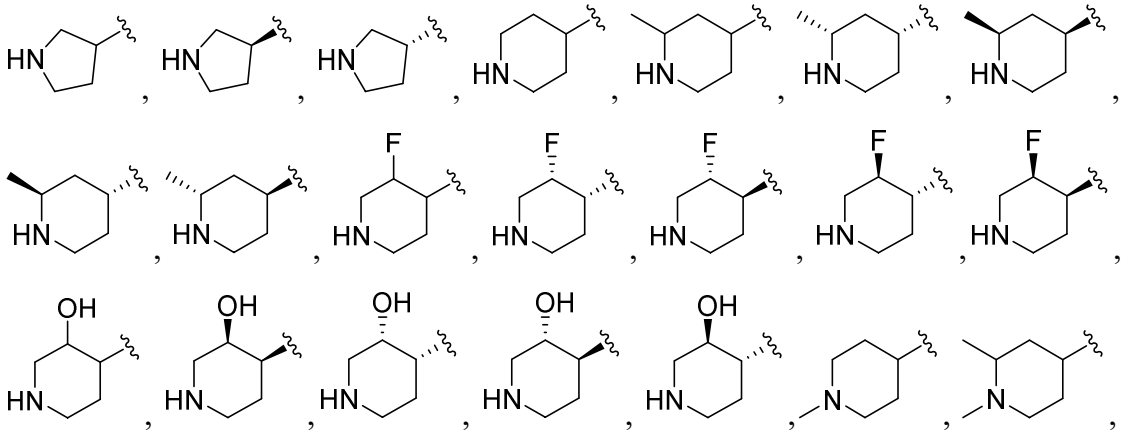
35. The compound of any one of claims 33-34, wherein one of A and B is independently selected from

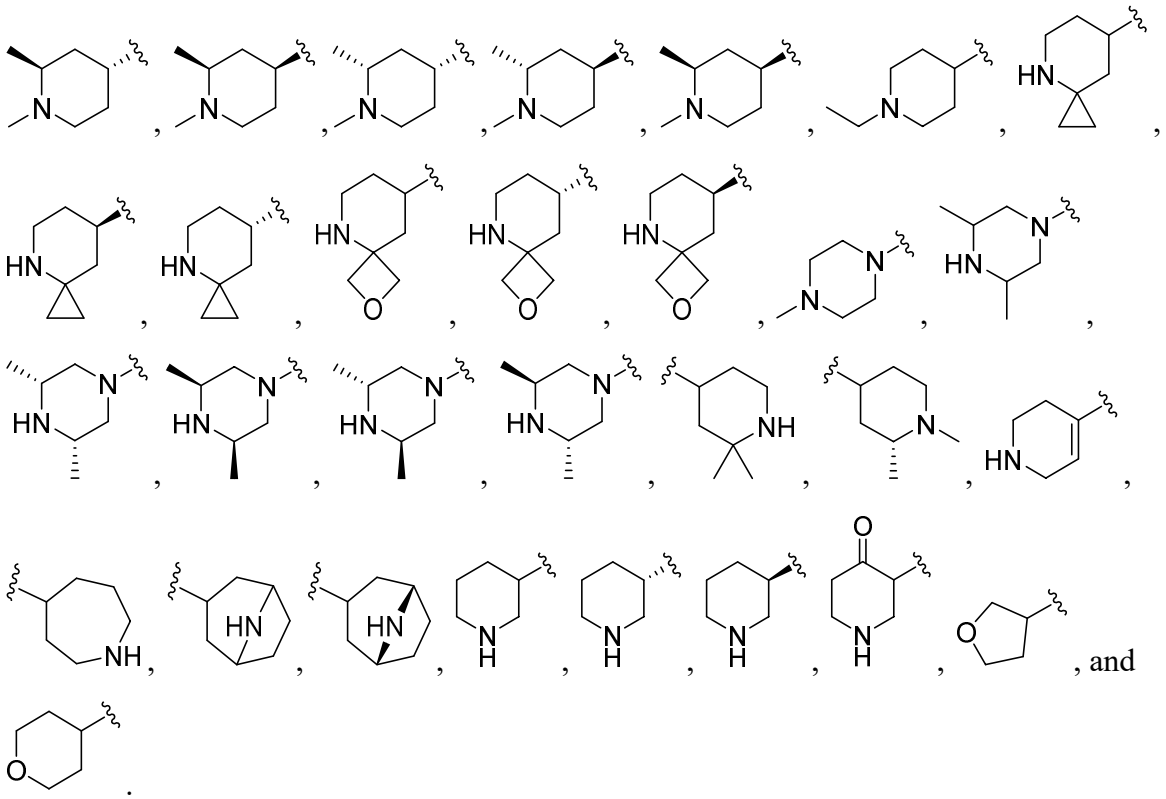

, 
, 
, 
, 
, 
, 
, and 
, wherein R^1 is as described in claim 33.

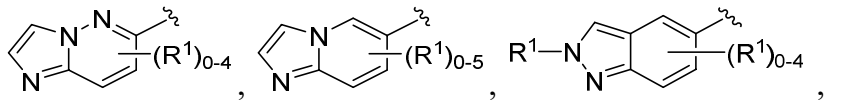
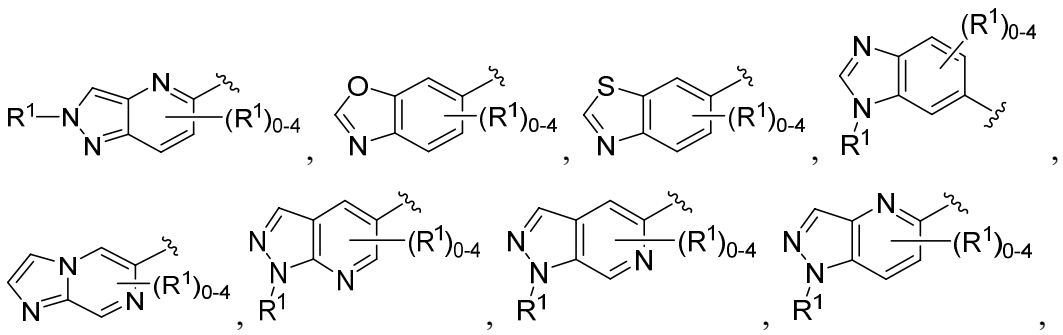
36. The compound of any one of claims 33-35, wherein one of A and B is independently selected from

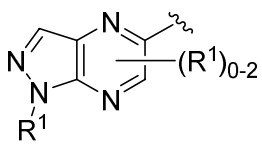
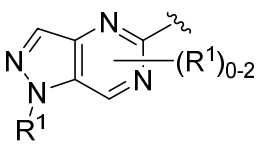
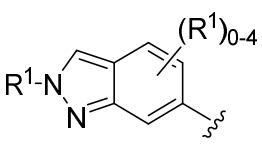
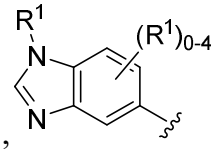
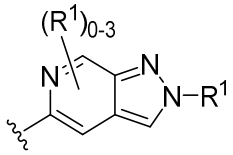


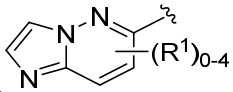
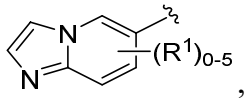
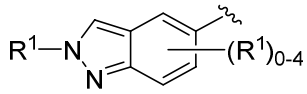
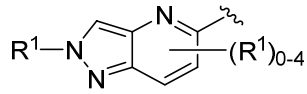
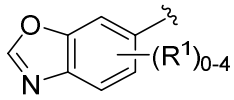
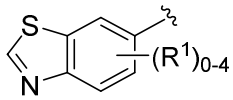
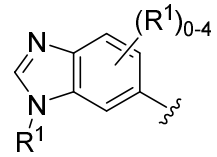
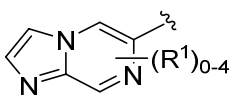
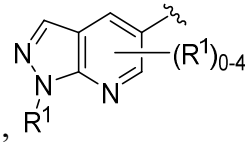
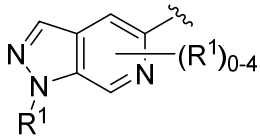
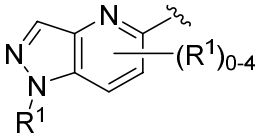
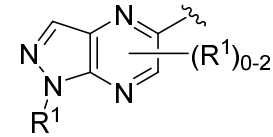
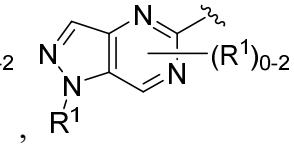
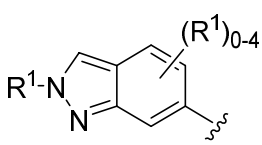
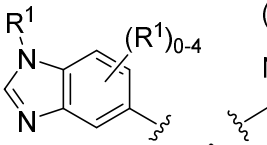
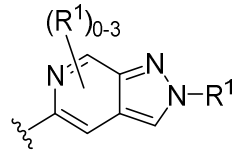
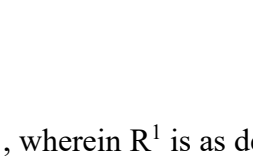
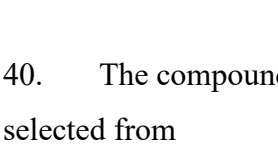
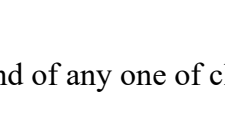
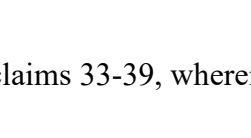
37. The compound of any one of claims 33-36, wherein B is selected from



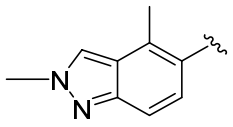
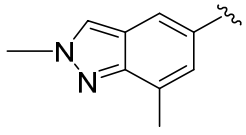
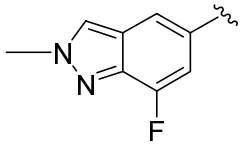
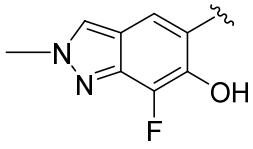
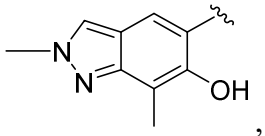
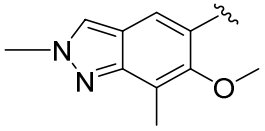


38. The compound of any one of claims 33-37, wherein one of A and B is independently selected from , .

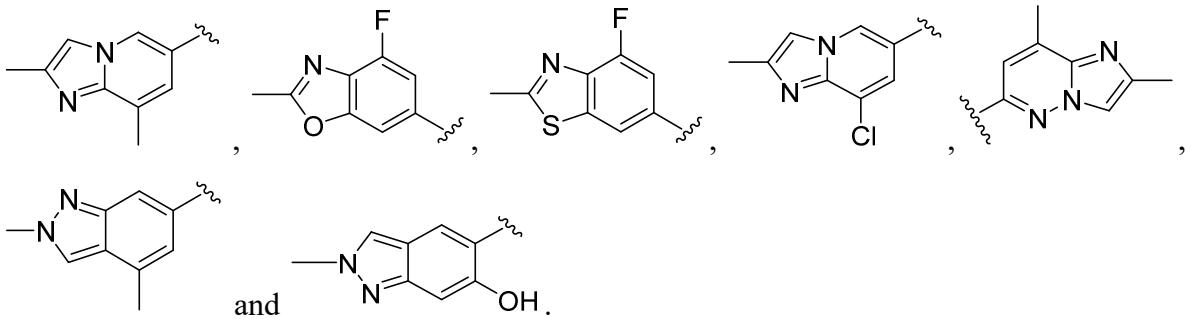





, wherein R^1 is as described in claim 33.

39. The compound of any one of claims 33-38, wherein A is selected from ,



















, wherein R^1 is as described in claim 33.

40. The compound of any one of claims 33-39, wherein one of A and B is independently selected from





and .

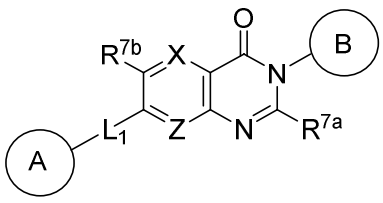
41. The compound of any one of claims 33-40, wherein each of L^1 and L^2 is independently absent.

42. The compound of any one of claims 33-41, wherein X is $C(R^3)$ (e.g., CH).

43. The compound of any one of claims 33-42, wherein Z is $C(R^3)$ (e.g., CH).

44. The compound of any one of claims 33-43, wherein Y is N.

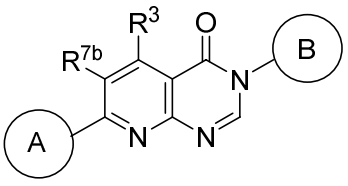
45. The compound of any one of claims 33-44, wherein the compound of Formula (III) is a compound of Formula (III-a):



(III-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, X, Z, R^{7b}, and subvariables thereof are as defined in claim 33.

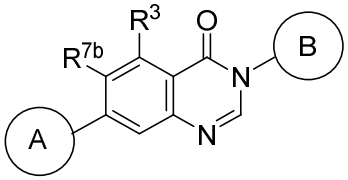
46. The compound of any one of claims 33-44, wherein the compound of Formula (III) is a compound of Formula (III-b):



(III-b),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, R^3, R^{7b}, and subvariables thereof are as defined in claim 33.

47. The compound of any one of claims 33-44, wherein the compound of Formula (III) is a compound of Formula (III-c):

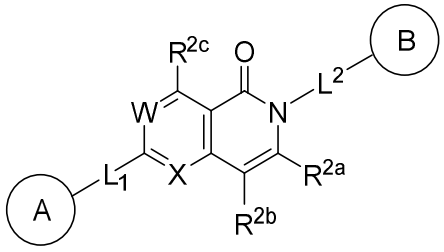


(III-c),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, R^3, R^{7b}, and subvariables thereof are as defined in claim 33.

48. The compound of any one of claims 33-47, wherein the compound of Formula (III) is a compound listed in Table 3 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

49. A compound of Formula (IV):



(IV)

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 X are each independently $C(R^3)$ or N, wherein one of W and X is independently N;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)-$, $-N(R^4)C(O)-$, or $-C(O)N(R^4)-$, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

R^{2a}, R^{2b}, and R^{2c} are each independently hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

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

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

each R^6 and R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

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

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, cycloalkyl, heterocyclyl, $–OR^A$, $–S(O)_xR^D$; 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;

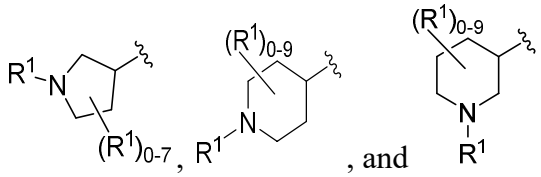
each R^9 is independently C_1-C_6-alkyl or halo; and

x is 0, 1, or 2.

50. The compound of claim 49, wherein one of A and B is independently cycloalkyl, heterocyclyl or heteroaryl.

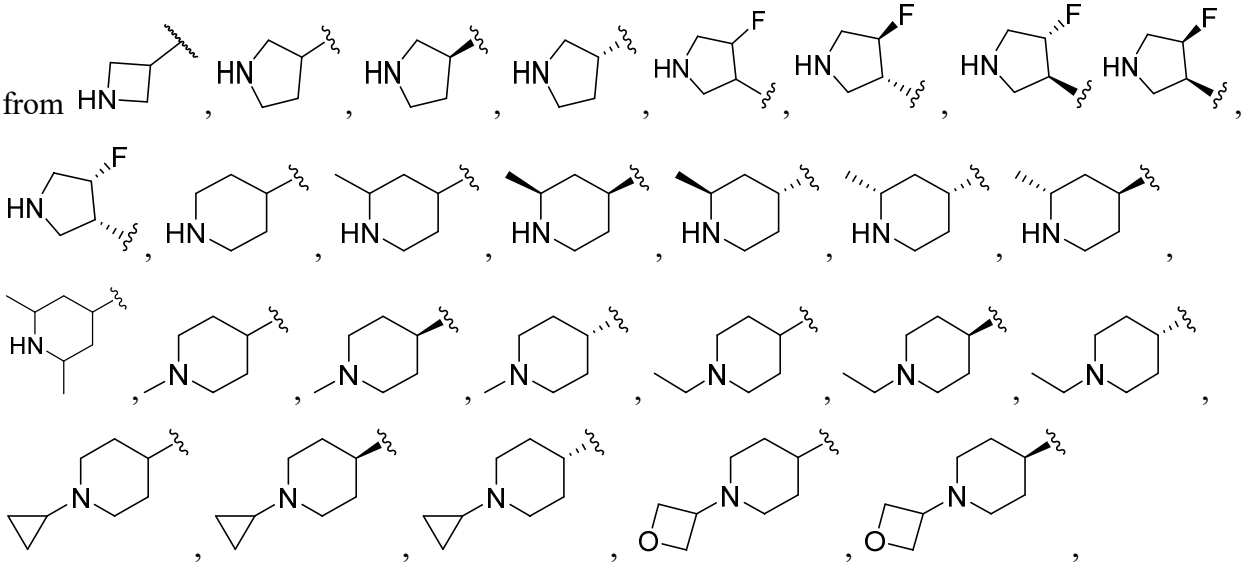
51. The compound of any one of claims 49-50, wherein one of A and B is independently a nitrogen-containing heterocyclyl or nitrogen-containing heteroaryl.

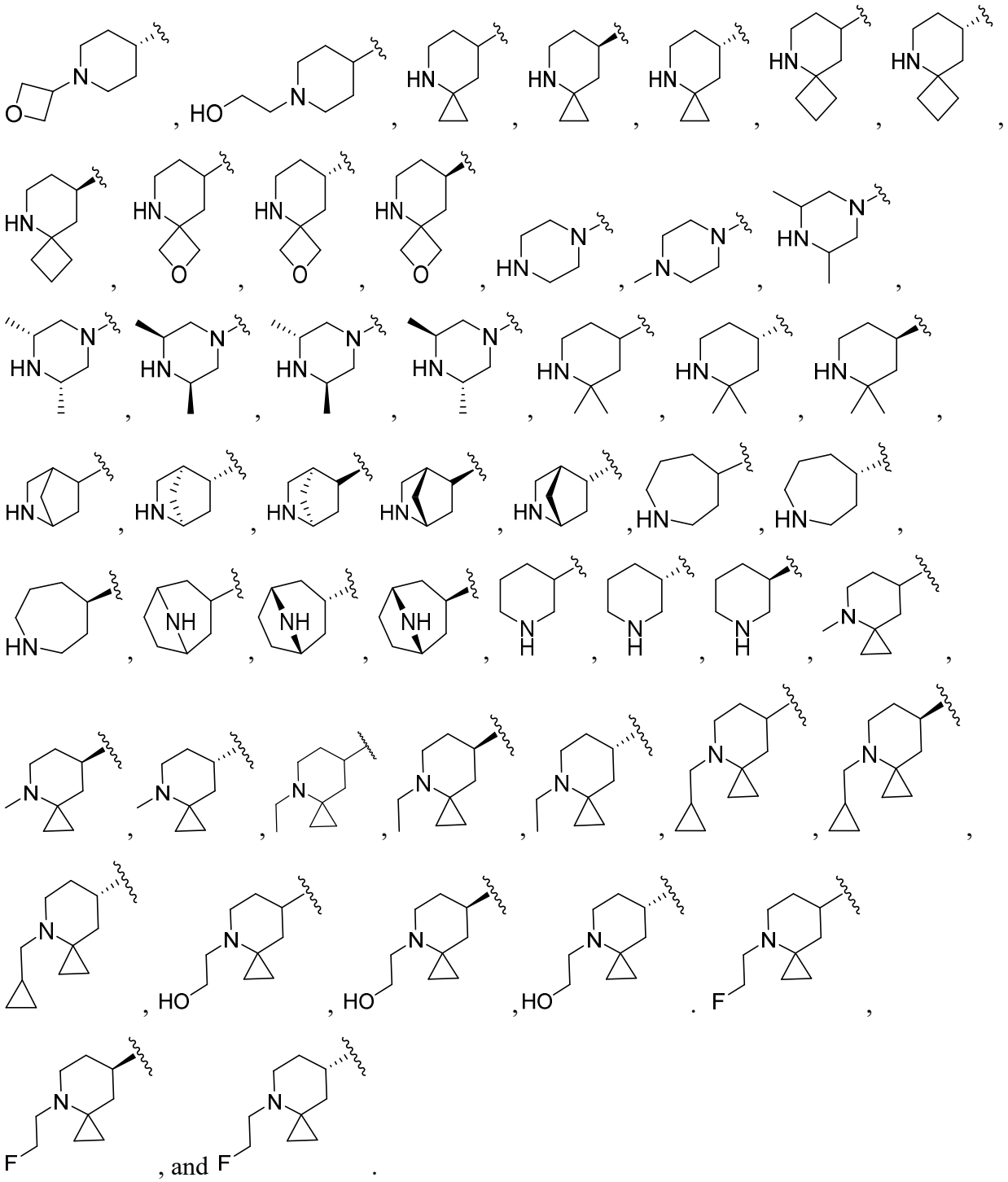
52. The compound of any one of claims 49-51, wherein one of A and B is independently selected from


, and

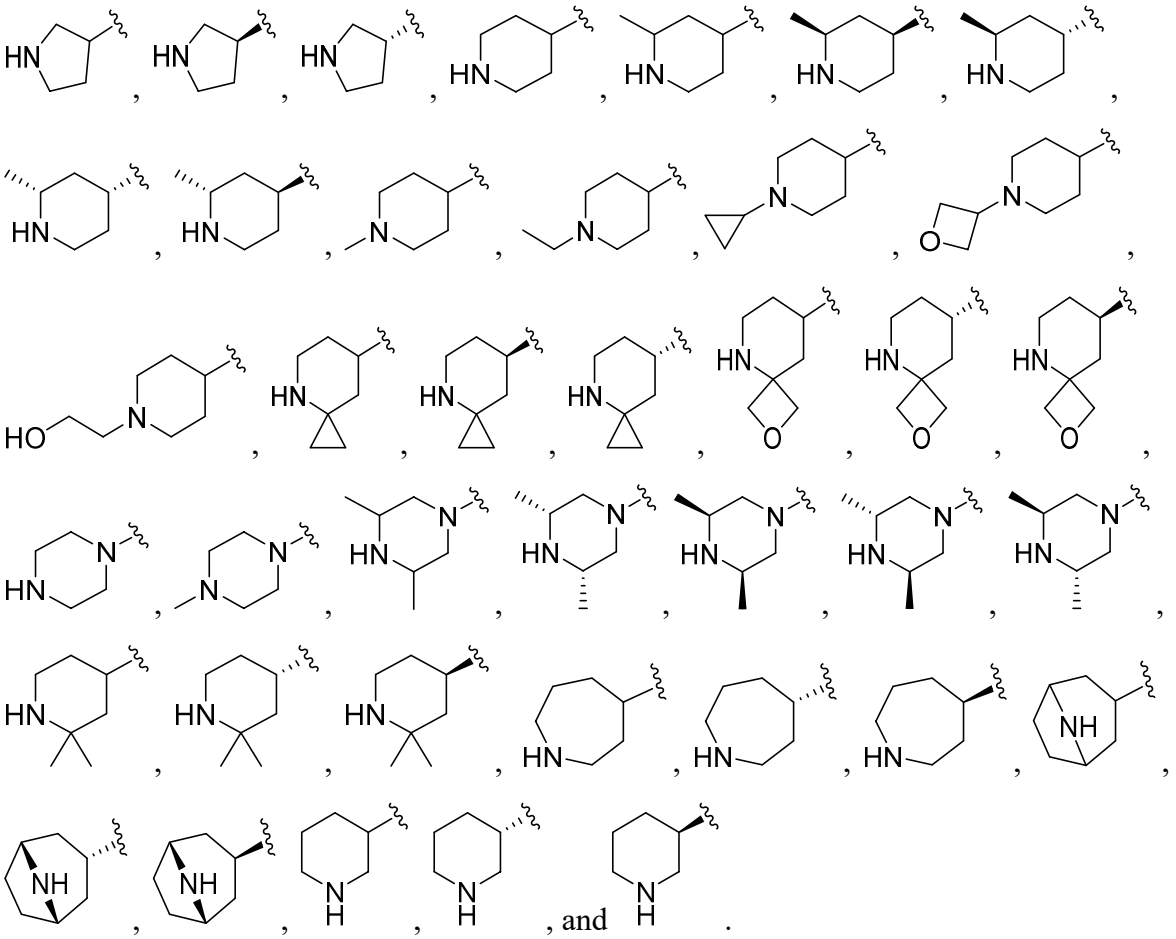
, wherein R^1 is as described in claim 49.

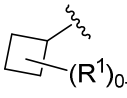
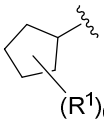
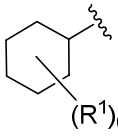
53. The compound of any one of the preceding claims, wherein one of A and B is independently selected from

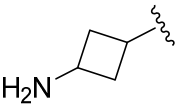
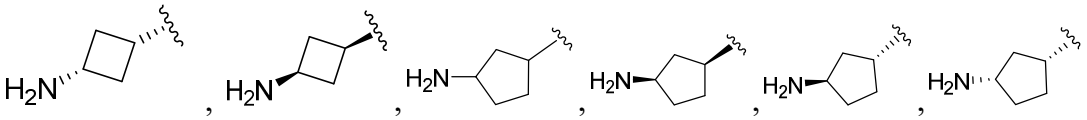
from


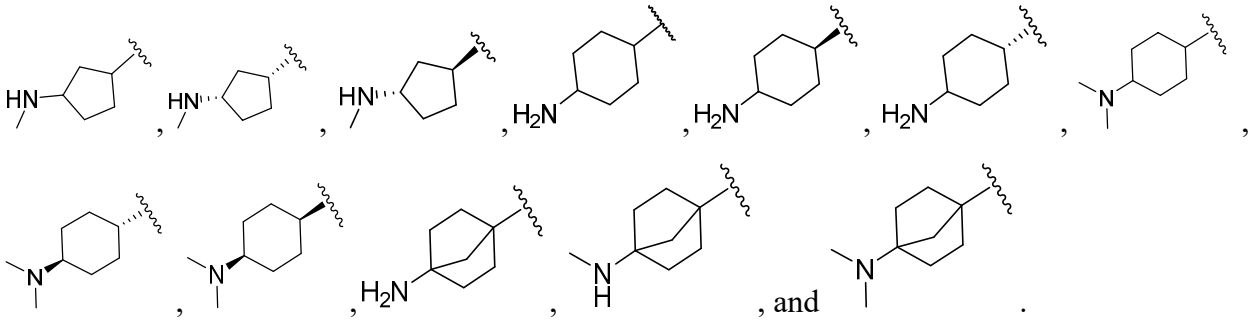


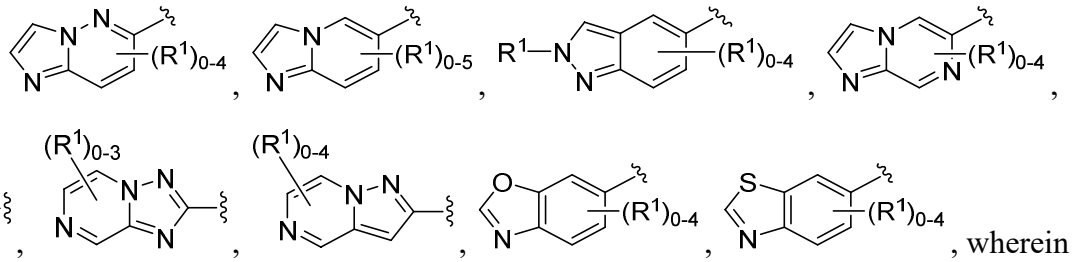
54. The compound of any one of claims 49-53, wherein B is selected from



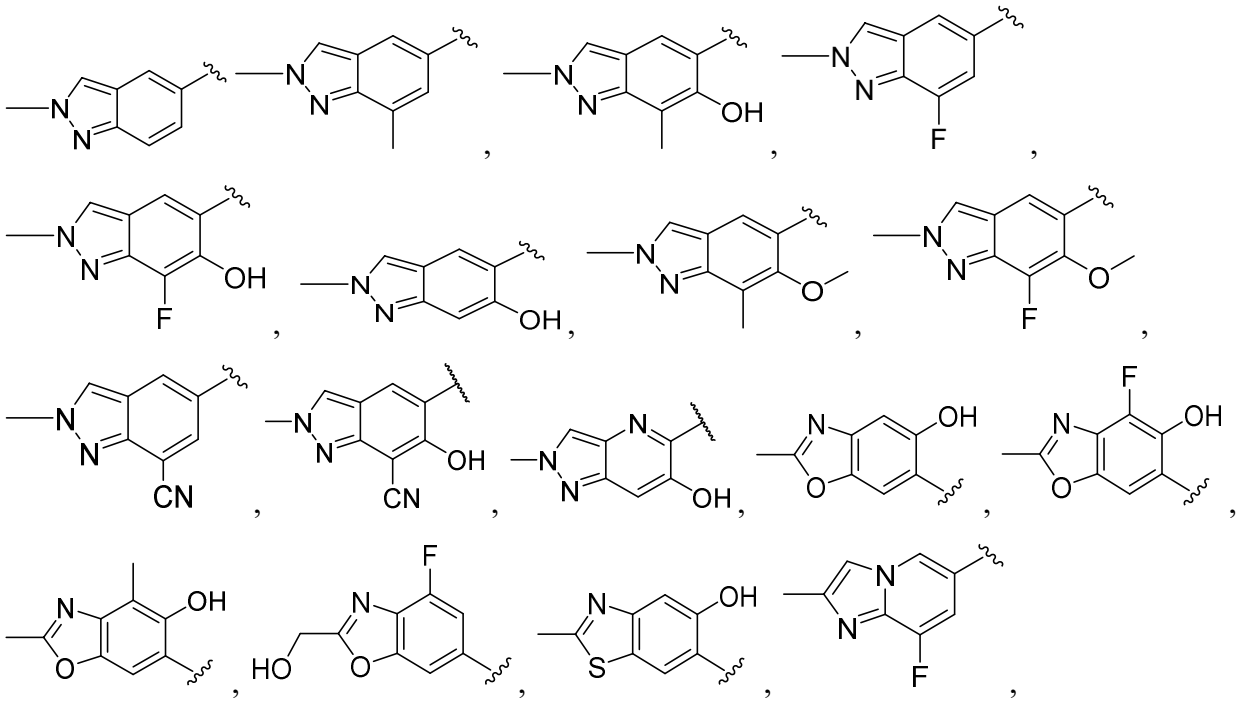
55. The compound of claim 54 , wherein one of A and B is selected from , , and , wherein R^1 is as defined in claim 49.

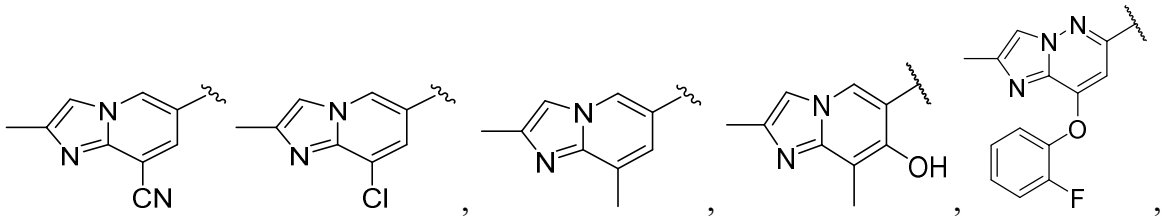
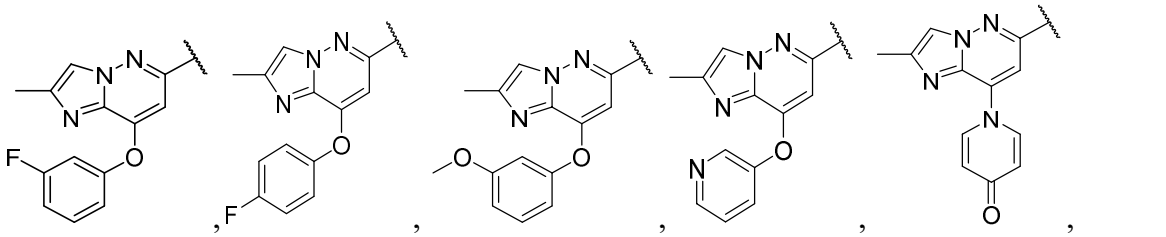
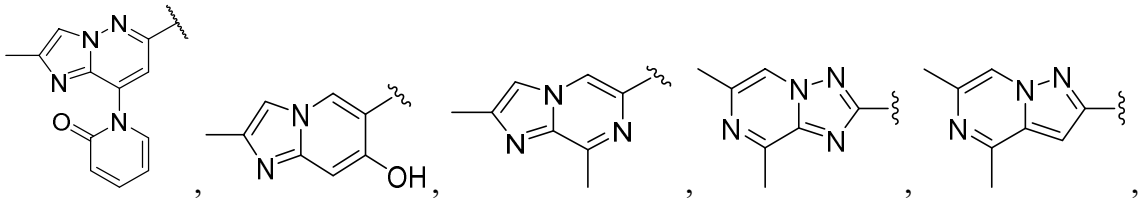
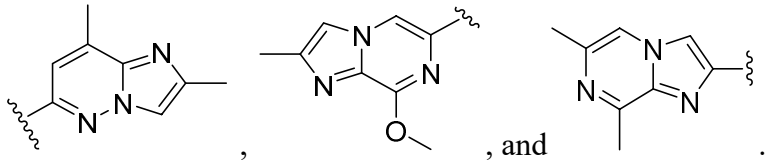
56. The compound of claim 55, wherein one of A and B is selected from , .

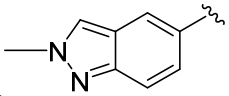


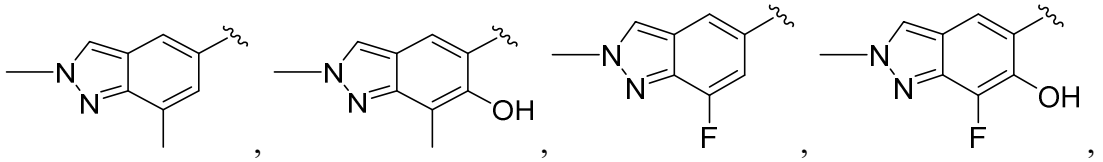
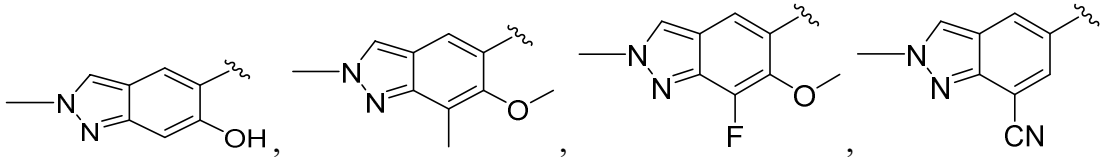
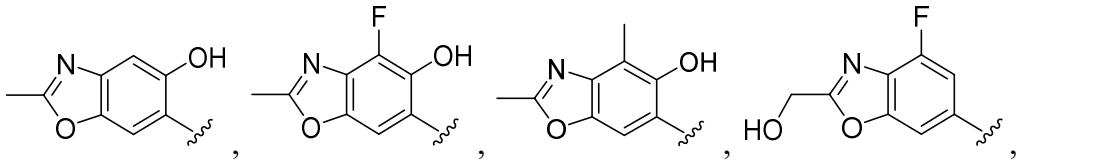
57. The compound of any one of claims 49-56, wherein one of A and B is independently selected from , wherein R^1 is as described in claim 49.

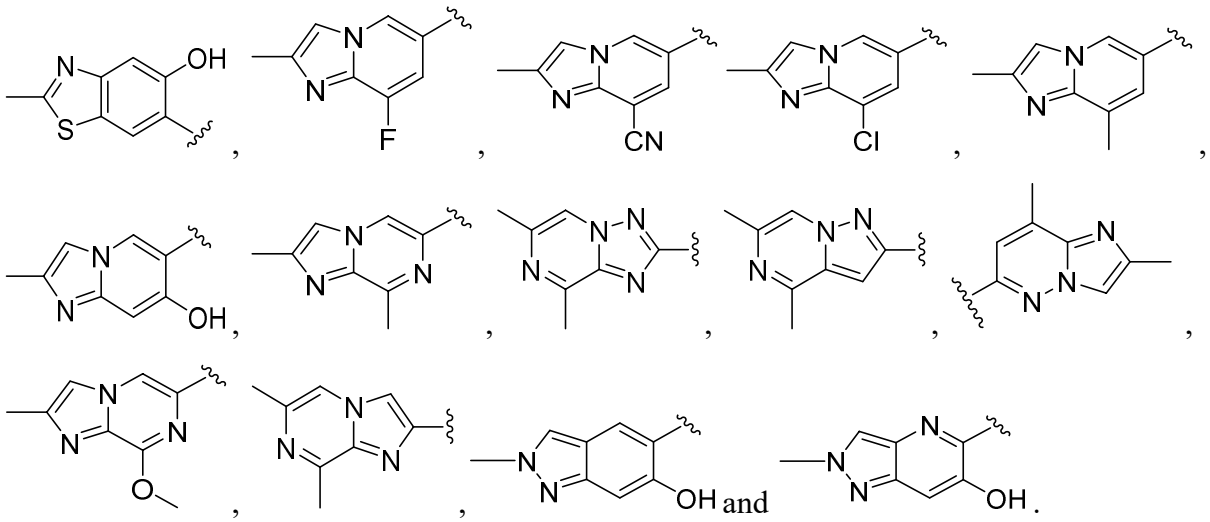
58. The compound of any one of claims 49-57, wherein one of A and B is independently selected from







, and .

59. The compound of any one of claims 49-58, wherein A is selected from 



60. The compound of any one of claims 49-59, wherein each of L^1 and L^2 is independently absent.

61. The compound of any one of claims 49-60, wherein W is $C(R^3)$ (e.g., CH).

62. The compound of any one of claims 49-60, wherein W is N.

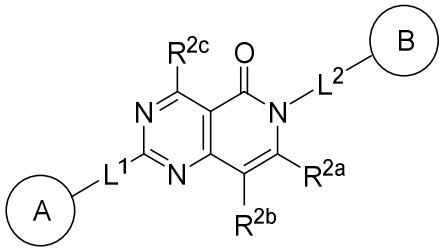
63. The compound of any one of claims 49-62, wherein X is N.

64. The compound of any one of claims 49-60, wherein each of W and X is N.

65. The compound of any one of claims 49-60, wherein W is $C(R^3)$ (e.g., CH) and X is N.

66. The compound of any one of claims 49-65, wherein each of R^{2a}, R^{2b}, and R^{2c} is independently hydrogen or alkyl (e.g., CH_3).

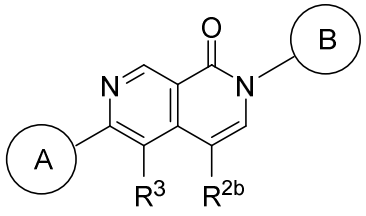
67. The compound of any one of claims 49-66, wherein the compound of Formula (IV) is a compound of Formula (IV-a):



(IV-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, L^2, R^{2a}, R^{2b}, R^{2c}, and subvariables thereof are as defined in claim 49.

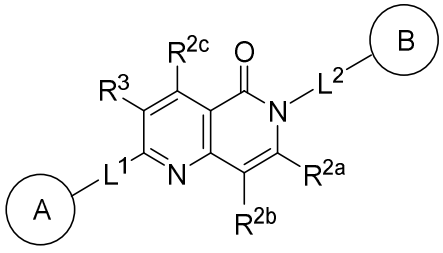
68. The compound of any one of claims 49-66, wherein the compound of Formula (IV) is a compound of Formula (IV-d):



(IV-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, R^{2b}, R^3, and subvariables thereof are as defined in claim 49.

69. The compound of any one of claims 49-66, wherein the compound of Formula (IV) is a compound of Formula (IV-e):

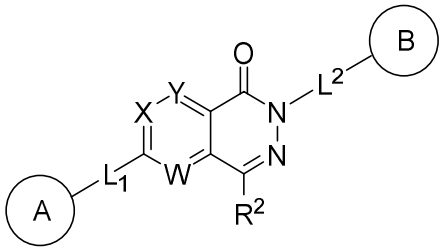


(IV-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, L^2, R^{2a}, R^{2b}, R^{2c}, R^3, and subvariables thereof are as defined in claim 49.

70. The compound of any one of claims 49-69, wherein the compound of Formula (IV) is a compound listed in Table 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

71. A compound of Formula (V):



(V)

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, X, and Y are each independently $C(R^3)$ or N, wherein at least one of W, X, and Y is independently N;

each of L^1 and L^2 is independently absent, C_1-C_6-alkylene, C_1-C_6-heteroalkylene, -O-, -C(O)-, $-N(R^4)-$, $-N(R^4)C(O)-$, or $-C(O)N(R^4)-$, wherein each alkylene and heteroalkylene is optionally substituted with one or more R^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_2-C_6 alkenylene-aryl, heteroaryl, 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^5; 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^5;

R^2 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

R^3 is hydrogen, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, halo, cyano, cycloalkyl, heterocyclyl, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–C(O)NR^BR^C$, or $–S(O)_xR^D$;

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

each R^5 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, oxo, 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 $–S(O)_xR^D$, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more R^7;

each R^6 and R^7 is independently C_1-C_6-alkyl, C_1-C_6-heteroalkyl, C_1-C_6-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$;

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

each R^B and R^C is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, C_1-C_6 alkylene-heteroaryl, cycloalkyl, heterocyclyl, $–OR^A$, $–S(O)_xR^D$; 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;

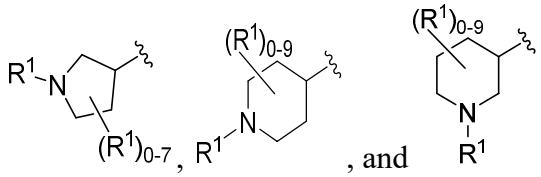
each R^D is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

each R^9 is independently C_1-C_6-alkyl or halo; and

x is 0, 1, or 2.

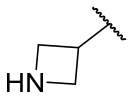
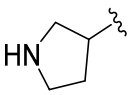
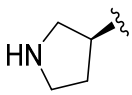
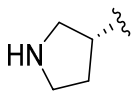
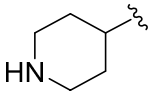
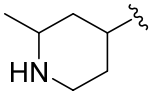
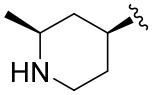
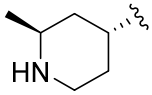
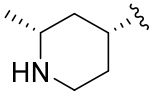
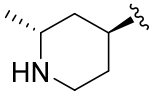
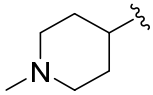
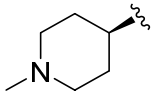
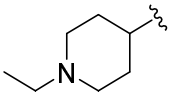
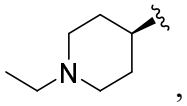
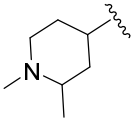
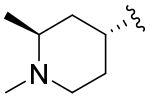
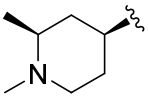
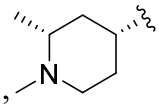
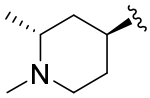
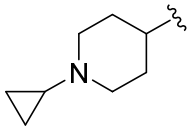
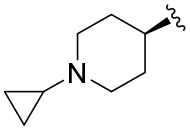
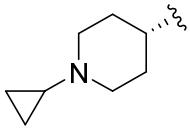
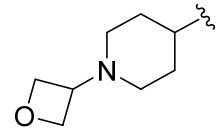
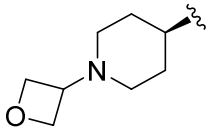
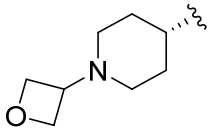
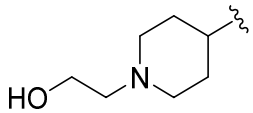
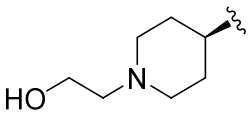
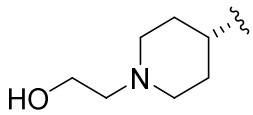
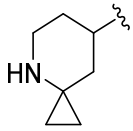
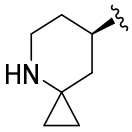
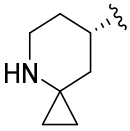
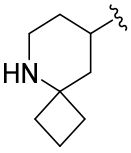
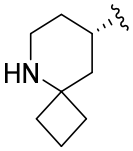
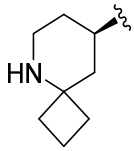
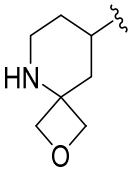
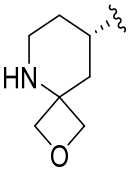
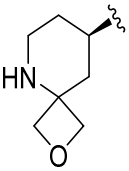
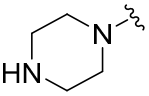
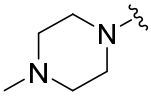
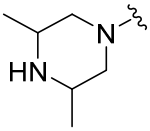
72. The compound of claim 71, wherein one of A and B is independently a nitrogen-containing heterocyclyl or nitrogen-containing heteroaryl.

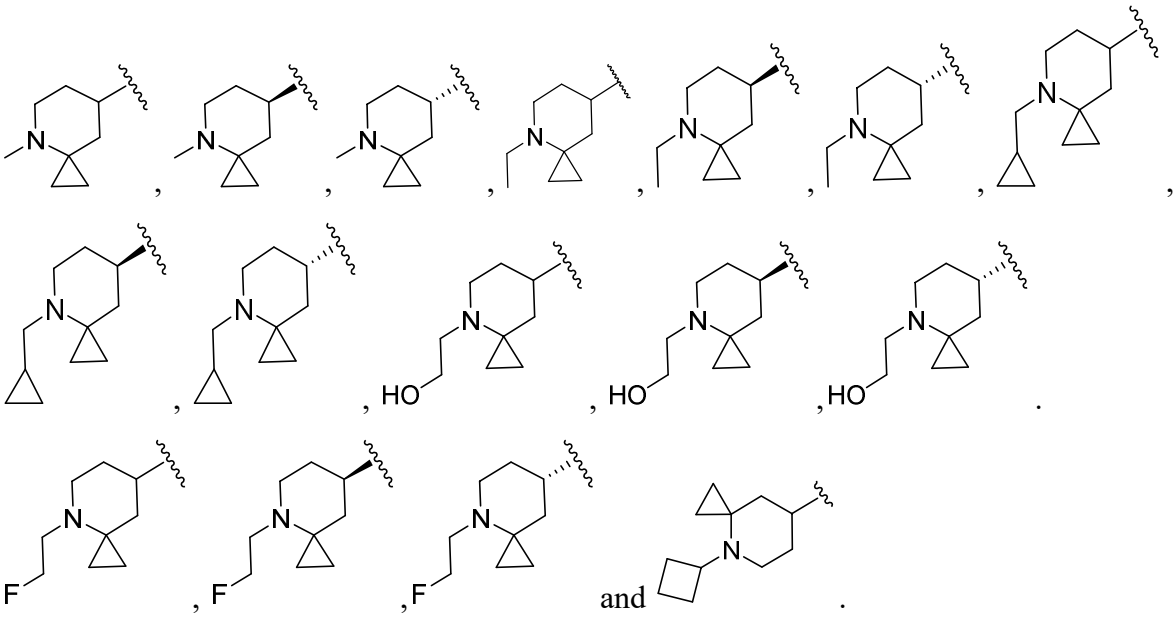
73. The compound of any one of claims 71-72, wherein one of A and B is independently selected from



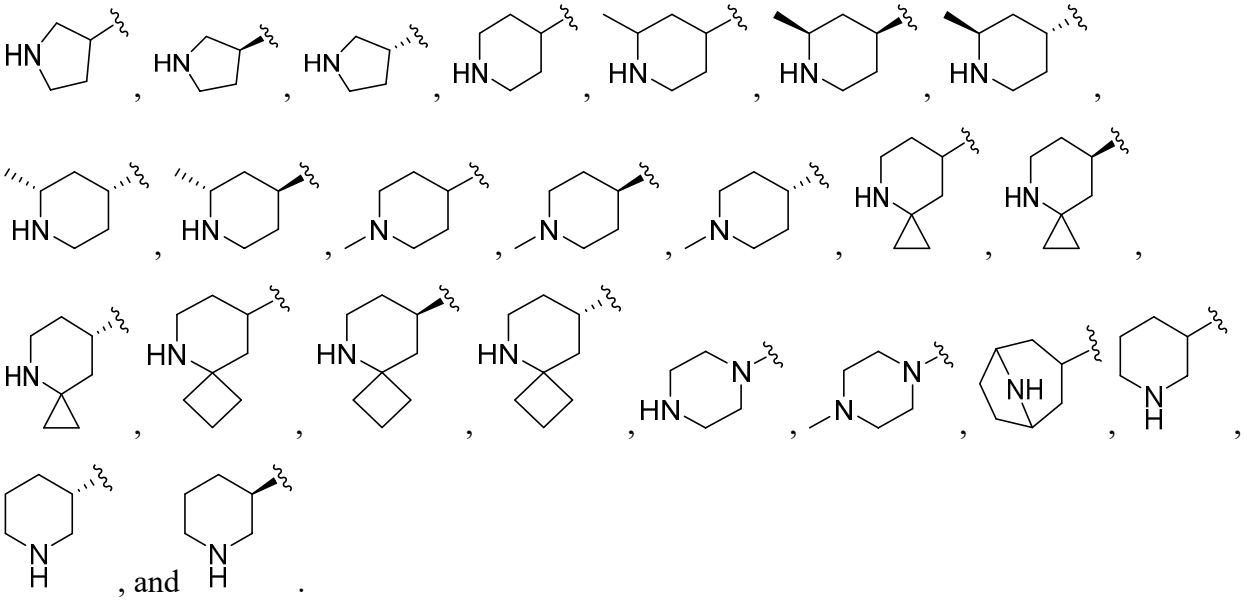
, and , wherein R^1 is as described in claim 71.

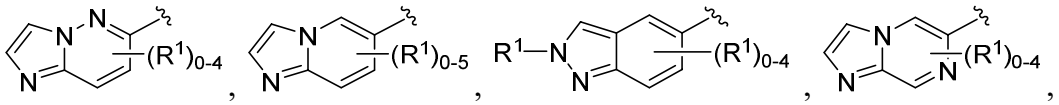
74. The compound of any one of claims 71-73, wherein one of A and B is independently selected from

from , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , , .

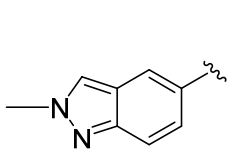
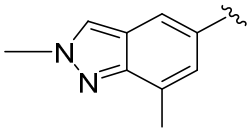
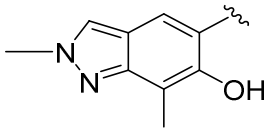
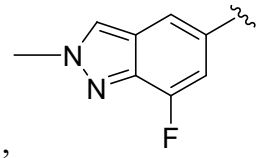
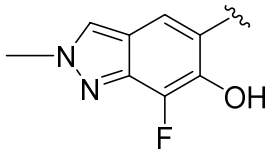
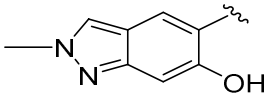
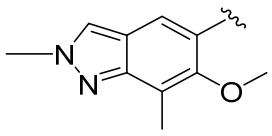
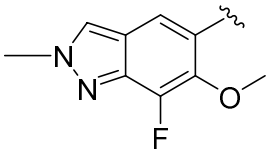
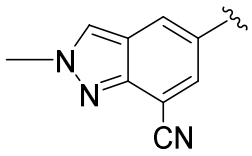
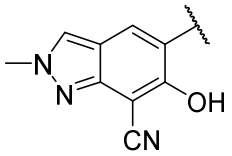
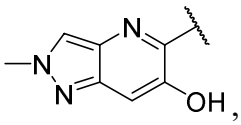
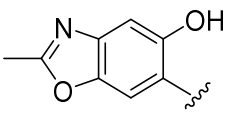
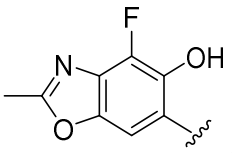
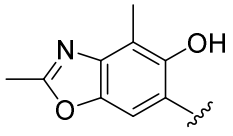
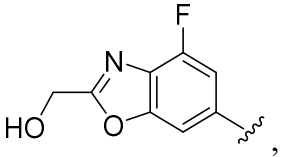
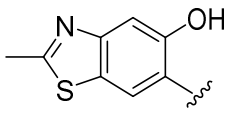
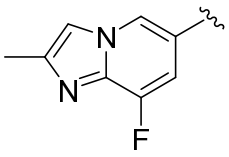
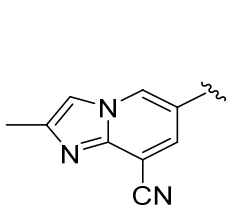
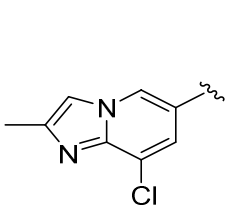
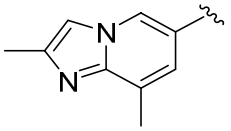
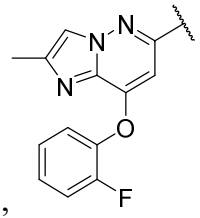
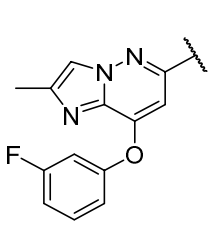
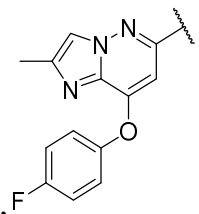
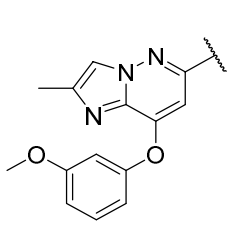
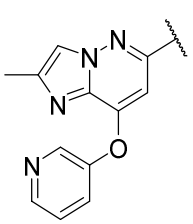
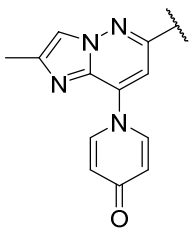
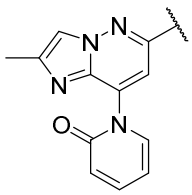
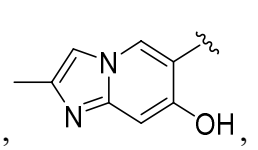
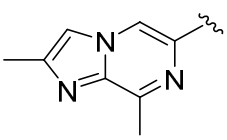
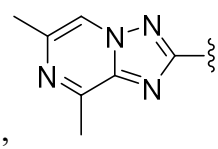
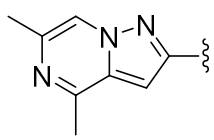
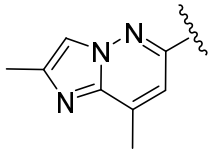
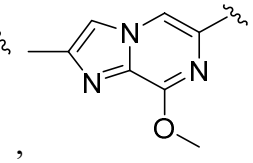
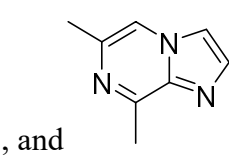
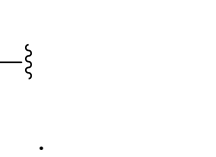


75. The compound of any one of claims 71-74, wherein B is selected from



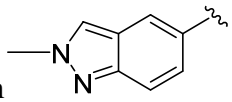
76. The compound of any one of claims 71-75, wherein one of A and B is independently selected from , wherein R^1 is as described in claim 71.

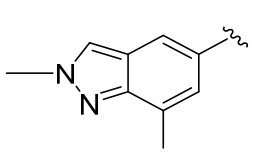
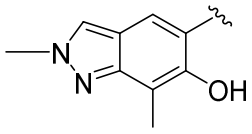
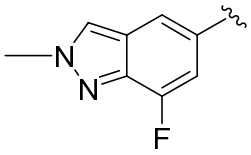
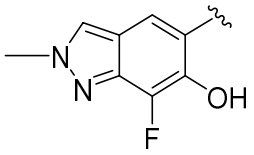
77. The compound of any one of claims 71-76, wherein one of A and B is independently selected from

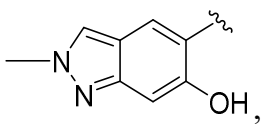
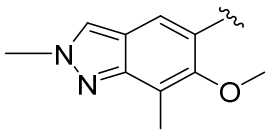
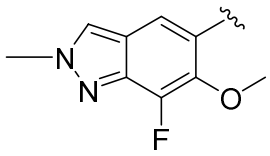
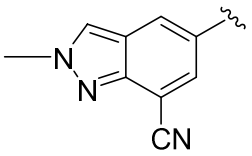




































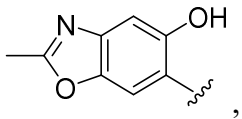
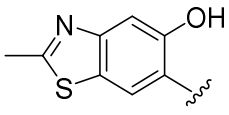
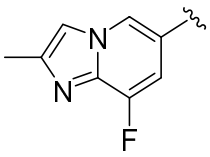
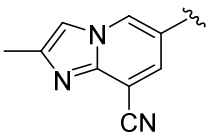
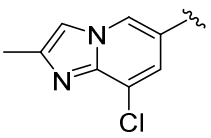


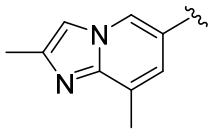
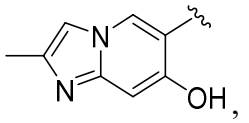
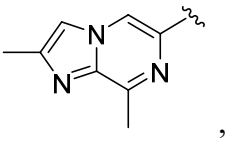
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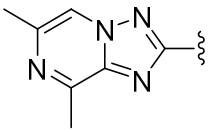
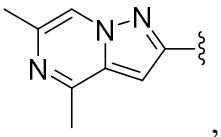
78. The compound of any one of claims 71-77, wherein A is selected from 

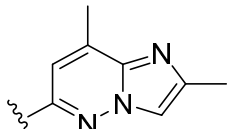
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79. The compound of any one of claims 71-78, wherein each of L^1 and L^2 is both absent.

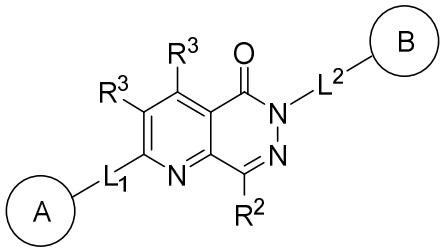
80. The compound of any one of claims 71-79, wherein W is $C(R^3)$ (e.g., CH).

81. The compound of any one of claims 71-80, wherein W is N.

82. The compound of any one of claims 71-81, wherein X is $C(R^3)$ (e.g., CH).

83. The compound of any one of claims 71-82, wherein Y is $C(R^3)$ (e.g., CH).

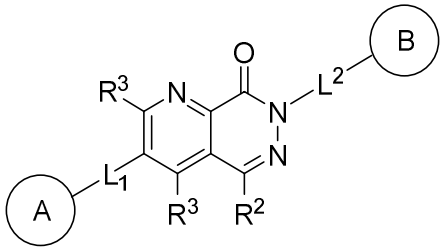
84. The compound of any one of claims 71-83, wherein the compound of Formula (V) is a compound of Formula (V-a):



(V-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, L^2, R^2, R^3, and subvariables thereof are as defined in claim 71.

85. The compound of any one of claims 71-83, wherein the compound of Formula (V) is a compound of Formula (V-e):



(V-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L^1, L^2, R^{2a}, R^{2b}, R^{2c}, R^3, and subvariables thereof are as defined in claim 71.

86. The compound of any one of claims 71-85, wherein the compound of Formula (V) is a compound listed in Table 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

87. A pharmaceutical composition comprising a compound of any one of the preceding claims 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:

(i) alters a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA);

(ii) binds to a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA); or

(iii) stabilizes 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:

(i) 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. ; or

(ii) 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.

90. 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), (II), (III), (IV), or (V), described herein:

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

91. The method of claim 90, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I), (II), (III), (IV), or (V) or a pharmaceutically acceptable salt or a composition thereof.

92. 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), (II), (III), (IV), or (V) or a pharmaceutically acceptable salt or a composition thereof.

93. The method of claim 92, wherein the altering comprises:

(i) forming a bulge in the nucleic acid;

(ii) stabilizing a bulge in the nucleic acid; or

(iii) reducing a bulge in the nucleic acid.

94. Use of a compound of Formula (I), (II), (III), (IV), or (V) or a pharmaceutically acceptable salt or a composition thereof in the manufacture of a medicament for treating a disease or disorder.

95. The use of claim 94, wherein the disease or disorder comprises a proliferative disease (e.g., cancer, a benign neoplasm, or angiogenesis).

96. The use of any one of claims 94-95, wherein the proliferative disease is cancer.

97. The use of any one of claims 94-95, wherein the proliferative disease comprises adenoid cystic carcinoma, colorectal cancer, leukemia, lung cancer, prostate cancer, breast cancer, or ovarian cancer.

98. The use of claim 94, 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.

99. The use of claim 94, wherein the disease or disorder comprises neurological disease or disorder.

100. The use of claim 94, wherein the disease or disorder comprises Huntington's disease.