HETEROCYCLIC AMIDES AND THEIR USE FOR MODULATING SPLICING

CLAIM OF PRIORITY

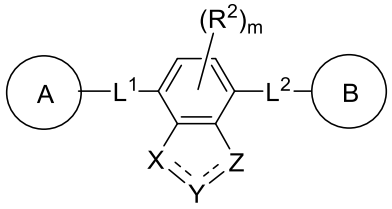
This application claims priority to U.S. Application No. 62/983,541, filed February 28, 2020; U.S. Application No. 63/007,333, filed April 8, 2020; U.S. Application No. 63/040,484, filed June 17, 2020; U.S. Application No. 63/072,790, filed August 31, 2020; and U.S. Application No. 63/126,492, filed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

BACKGROUND

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

SUMMARY

In an aspect, there is provided a compound of Formula (I-a):



(I-a)

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

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

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

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^5;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

m is 0, 1, or 2; and

x is 0, 1, or 2.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable excipient.

e.g., as determined by qPCR %.

In another aspect, there is provided a method of forming a complex comprising a component of a spliceosome, a nucleic acid, and a compound of Formula (I-a) or a composition thereof as defined above:

comprising contacting the nucleic acid with a compound of Formula (I-a).

In another aspect, there is provided a method of altering the conformation of a nucleic acid comprising contacting the nucleic acid with a compound of Formula (I-a) as defined above, or the pharmaceutical composition as defined above.

In another aspect, there is provided the use a compound of Formula (I-a) as defined above or the pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a disease or disorder selected from: proliferative disease, neurological disease or disorder, autoimmune disease or disorder, immunodeficiency disease or disorder, lysosomal storage disease or disorder, cardiovascular disease or disorder, metabolic disease or disorder, respiratory disease or disorder, renal disease or disorder, or infectious disease.

In another aspect, there is provided a compound of Formula (I-a) as defined above or the pharmaceutical composition as defined above for use in therapy.

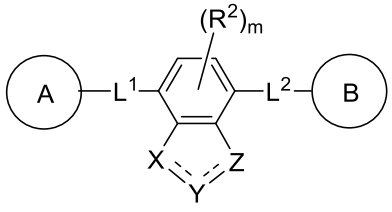
The present disclosure features compounds and related compositions that, *inter alia*, modulate nucleic acid splicing, e.g., splicing of a pre-mRNA, as well as methods of use thereof. In an ~~embodiment~~example, the compounds described herein are compounds of Formula (I) (e.g., a compound of Formulas (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) and pharmaceutically acceptable

salts, solvates, hydrates, tautomers, or stereoisomers thereof. The present disclosure additionally provides methods of using the compounds of the ~~invention~~disclosure (e.g., compounds of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers thereof), and compositions thereof, e.g., to target, and in ~~embodiment~~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 ~~aspect~~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 ~~embodiment~~examples, increasing or decreasing splicing results in modulating the level of a gene product (e.g., an RNA or protein) produced.

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

In another ~~aspect~~example, the present disclosure features a compound of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A and B are each independently cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of

or more R^7; each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl; each R^{A1} is hydrogen or C_1-C_6-alkyl; m is 0, 1, or 2; and x is 0, 1, or 2.

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

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

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

In another ~~aspect~~example, the present disclosure provides methods for preventing and/or treating a disease, disorder, or condition in a subject by administering a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, or related compositions. In some ~~embodiment~~examples, the disease or disorder entails unwanted or aberrant splicing. In some ~~embodiment~~examples, the disease or disorder is a proliferative disease, disorder, or condition. Exemplary proliferative diseases include cancer, a benign neoplasm, or angiogenesis. In other ~~embodiment~~examples, the present disclosure provides methods for treating and/or preventing a non-proliferative disease, disorder, or condition. In still other ~~embodiment~~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 ~~aspect~~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 Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another ~~aspect~~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 Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another ~~aspect~~example, the present disclosure provides methods of altering the isoform of a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h))) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another ~~aspect~~example of the disclosure relates to methods of inhibiting

the activity of a target protein in a biological sample or subject. In some ~~embodiment~~example, administration of a compound of Formula (I) to a biological sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

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

In another ~~aspect~~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 Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another ~~aspect~~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 Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h)) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. In another ~~aspect~~example, the present disclosure provides compositions for use in altering the isoform of a target protein with a compound of Formula (I) (e.g., a compound of Formulas (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), or (I-h))) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof in a biological sample or subject. Another ~~aspect~~example of the disclosure relates to compositions for use in inhibiting the activity of a target protein in a biological sample or subject. In some ~~embodiment~~example, administration of a compound of Formula (I) to a biological

sample, a cell, or a subject comprises inhibition of cell growth or induction of cell death.

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

In any and all ~~aspect~~examples of the present disclosure, in some ~~embodiment~~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, and WO 2019/199972. In some ~~embodiment~~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, and WO 2019/199972, each of which is incorporated herein by reference in its entirety.

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

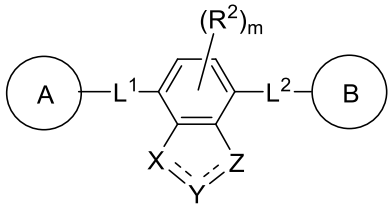
DETAILED DESCRIPTION

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 Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of

CLAIMS

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



(I-a)

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

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

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

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^5;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

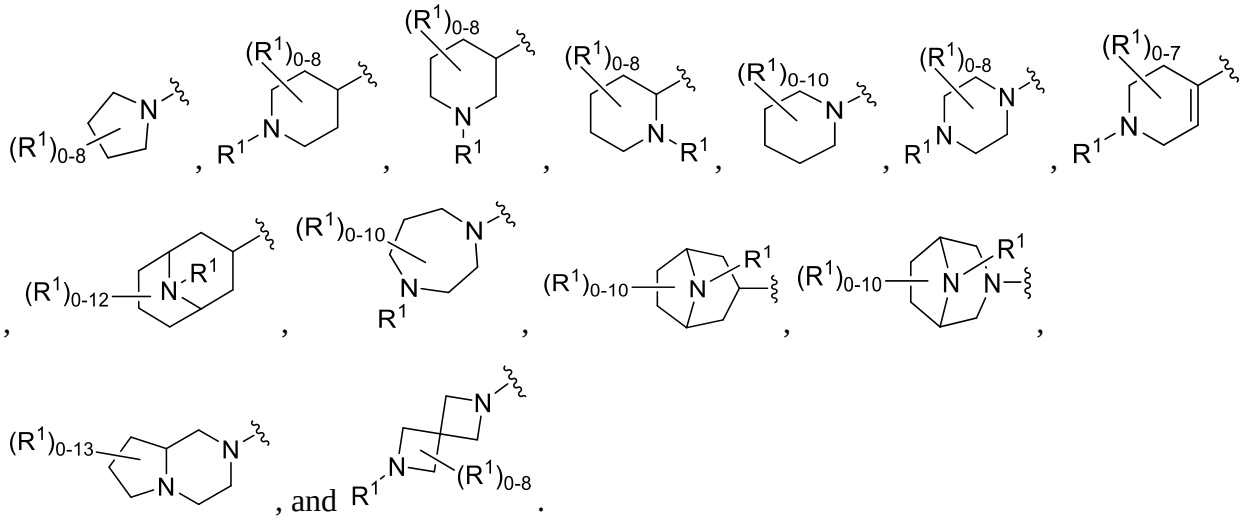
m is 0, 1, or 2; and

x is 0, 1, or 2.

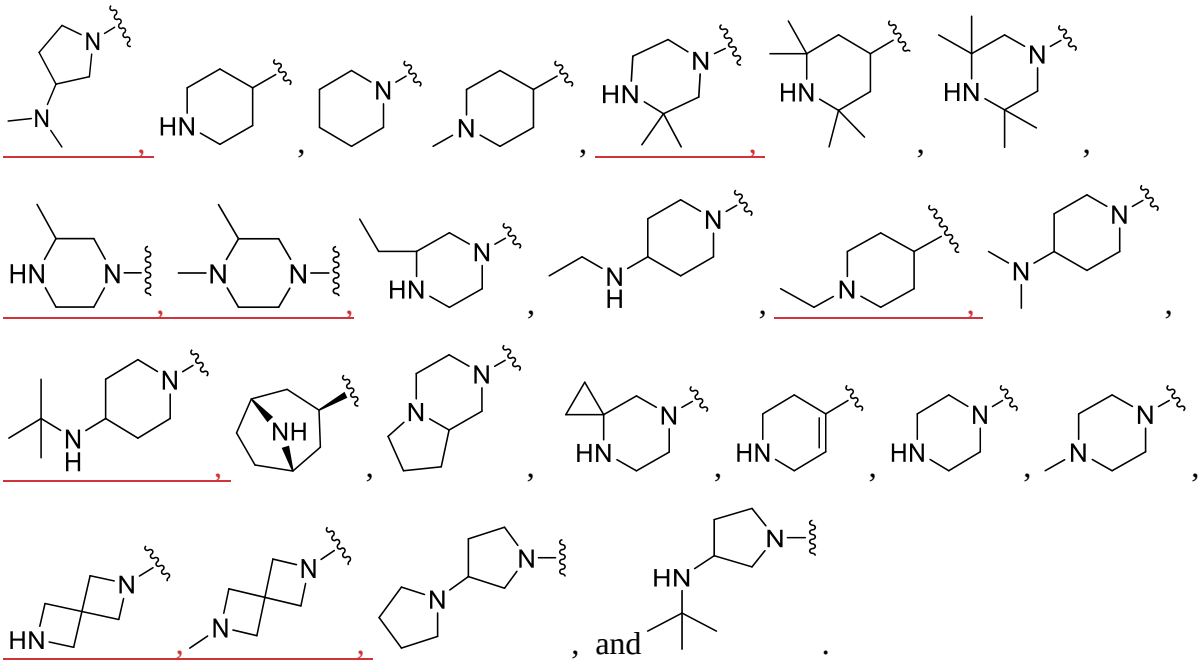
2. The compound of claim 1, wherein A is a monocyclic or bicyclic heterocyclyl.

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

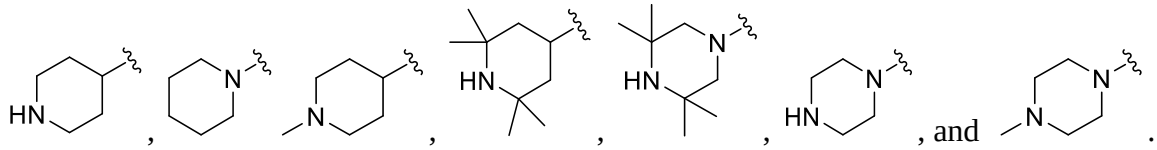
4. The compound of any one of the preceding claims, wherein A is selected from

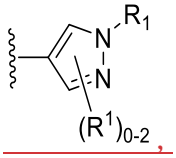
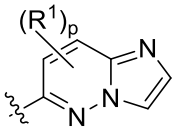
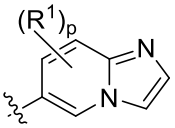
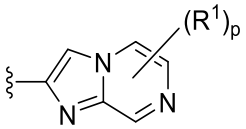
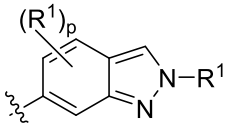
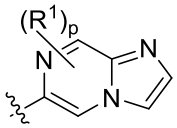
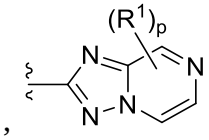
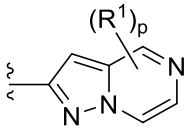
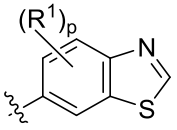
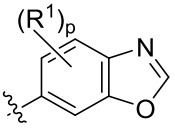


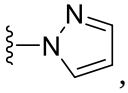
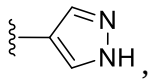
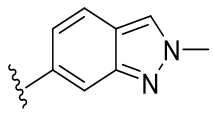
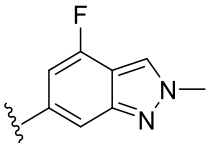
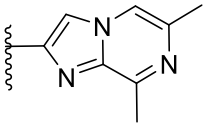
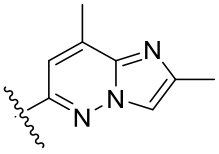
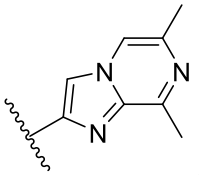
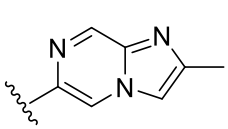
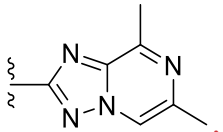
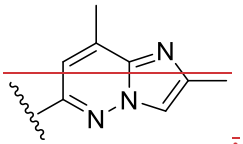
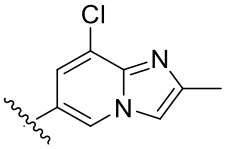
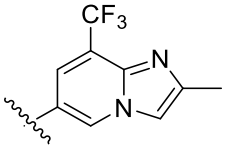
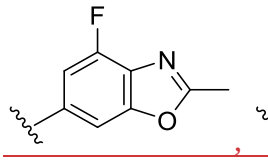
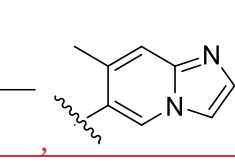
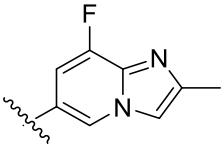
5. The compound of any one of the preceding claims, wherein A is selected from

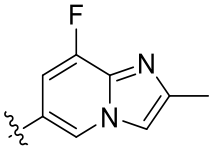


6. The compound of any one of the preceding claims, wherein A is selected from



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

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

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

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

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

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

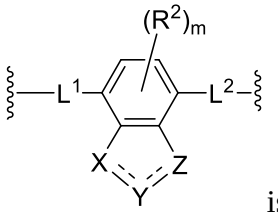
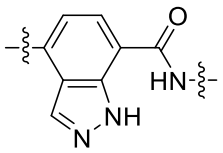
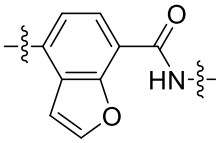
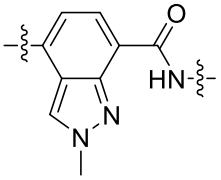
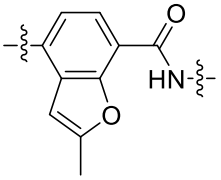
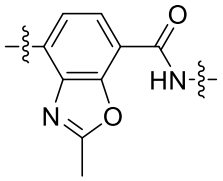
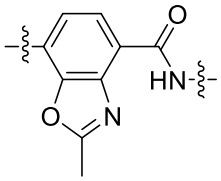
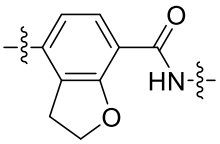
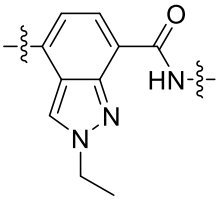
13. The compound of any one of the preceding claims, wherein one of X, Y, and Z is C(R^{3a}) ~~(e.g., CH)~~, and the others of X, Y, and Z are each independently O, N or N(R^{3c}).

14. The compound of any one of the preceding claims, wherein at least one of X, Y, and Z is O.

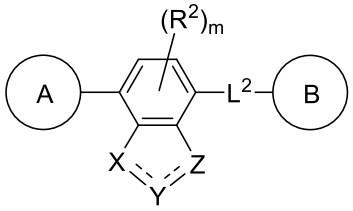
15. The compound of any one of the preceding claims, wherein Z and Y are each independently N or N(R^{3c}), and X is C(R^{3a}) ~~(e.g., CH)~~.

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

17. The compound of any one of the preceding claims, wherein X is C(R^{3a}), Y is C(R^{3a}), and Z is O.

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

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



(I-b)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

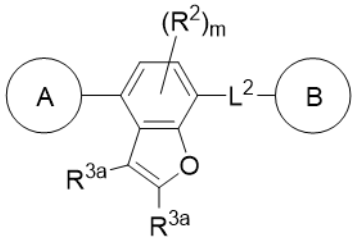
each R^D and R^E is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, C_1-C_6 alkylene-aryl, or C_1-C_6 alkylene-heteroaryl;

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

m is 0, 1, or 2; and

x is 0, 1, or 2.

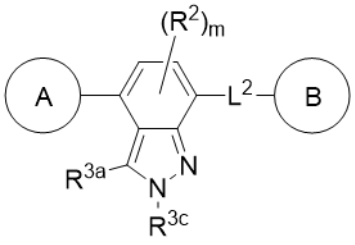
20. The compound of any one of the preceding claims, wherein the compound of Formula (I-a) is a compound of Formula (I-c):



(I-c)

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

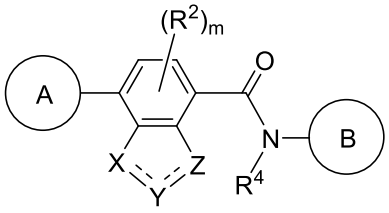
21. The compound of any one of the preceding claims, wherein the compound of Formula (I-a) is a compound of Formula (I-d):



(I-d)

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

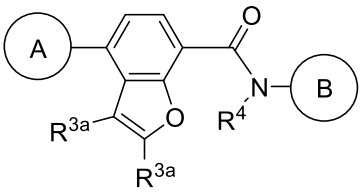
22. The compound of any one of the preceding claims, wherein the compound of Formula (I-a) is a compound of Formula (I-e):



(I-e)

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

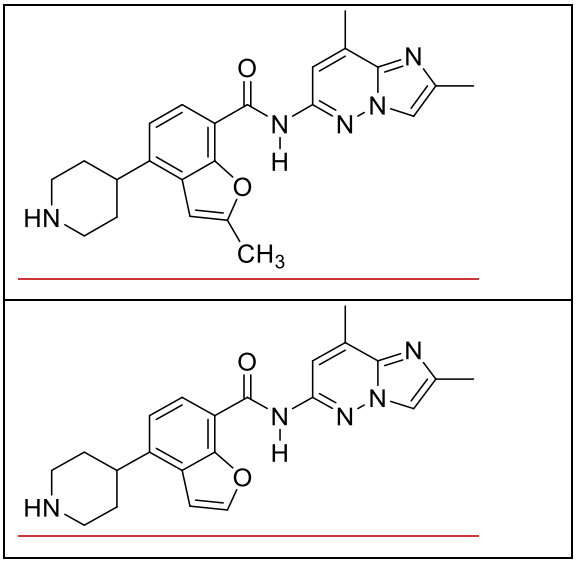
23. The compound of any one of the preceding claims, wherein the compound of Formula (I-a) is a compound of Formula (I-h):

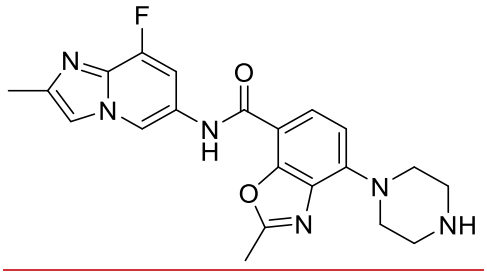


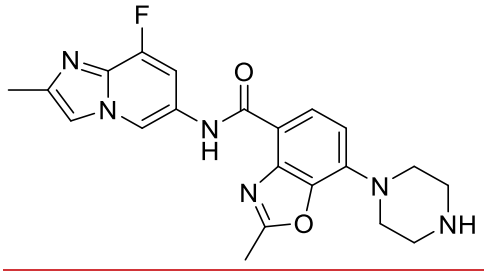
(I-h)

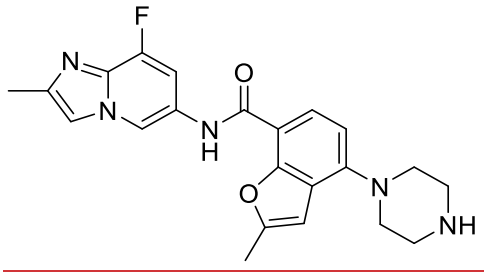
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A, B, L^2, R^{3a}, R^4, m, and subvariables thereof are defined as in claim 1.

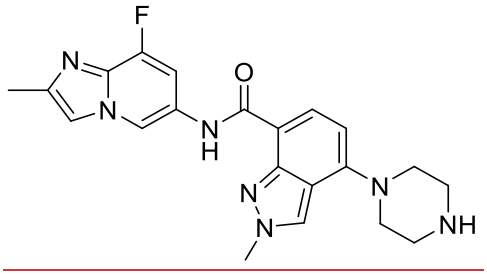
24. The compound of any one of the preceding claims, wherein the compound is selected from ~~a compound listed in Table 1,~~:

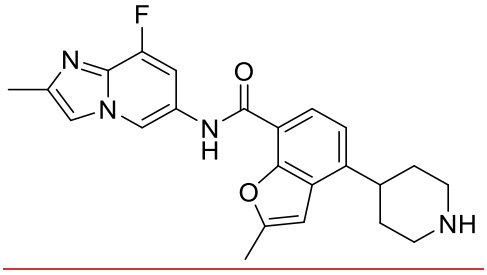


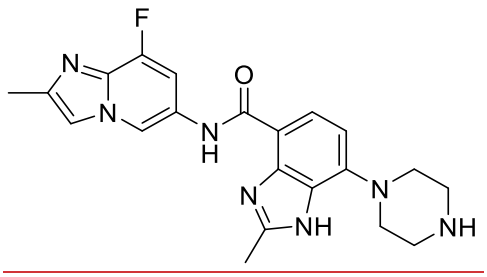


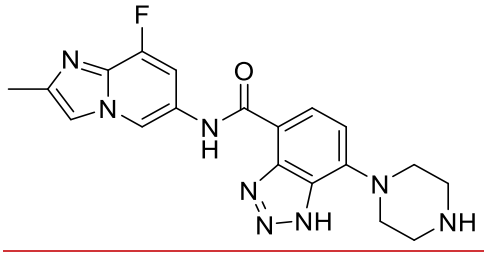


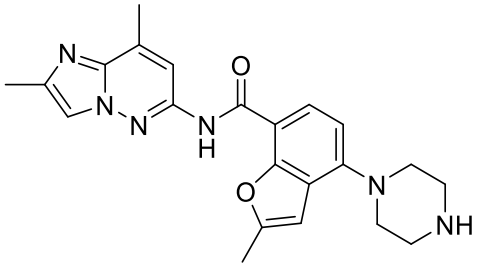


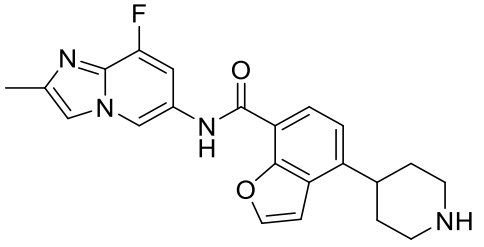


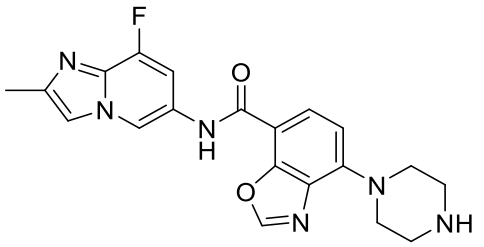


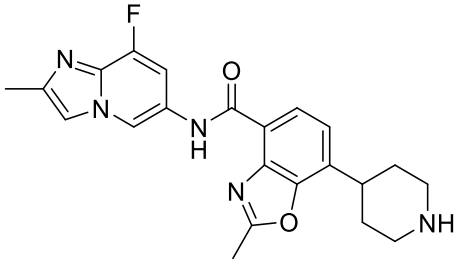


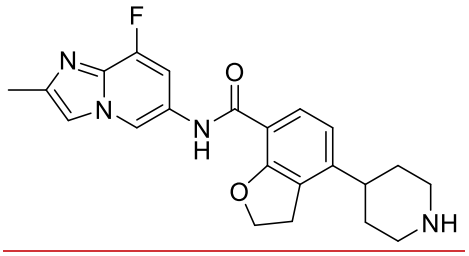


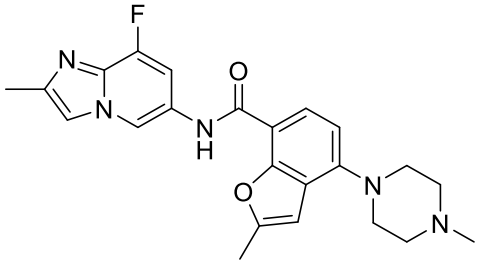


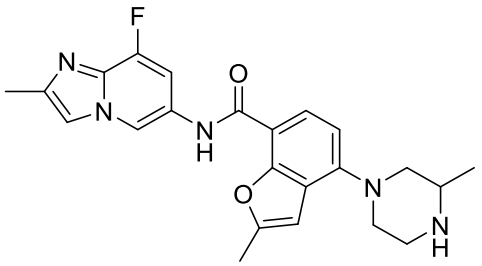


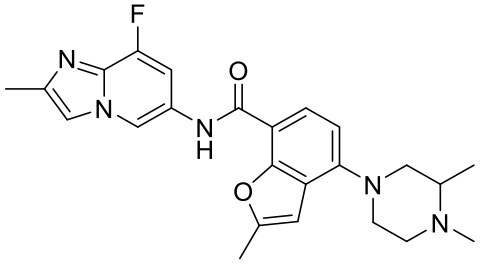


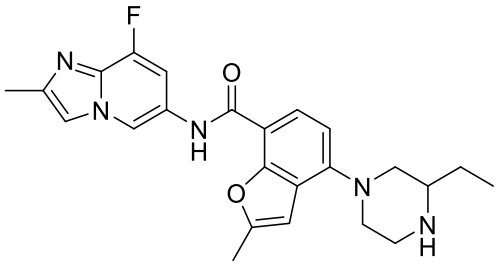


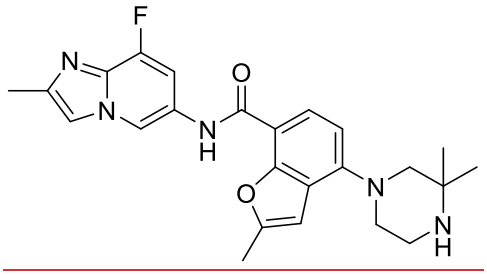


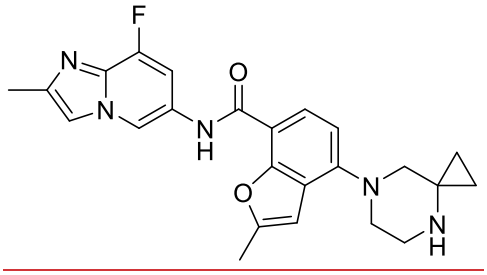


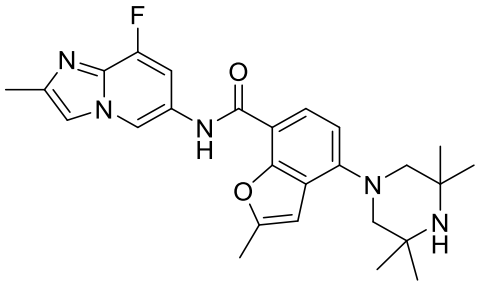


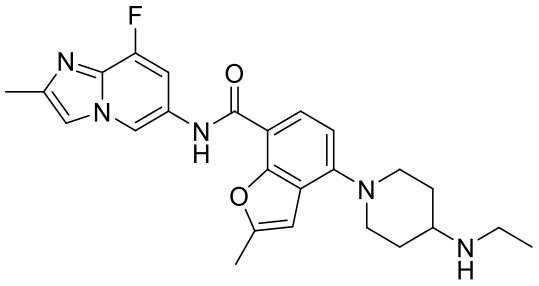


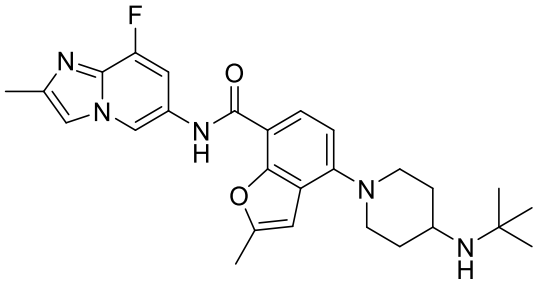


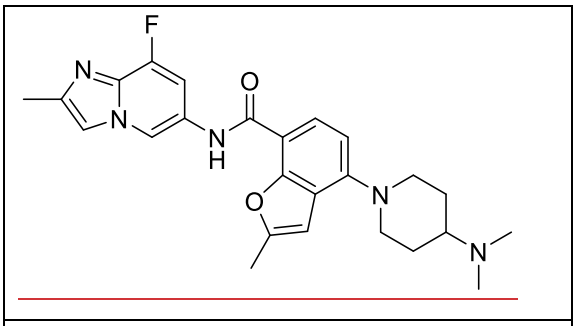


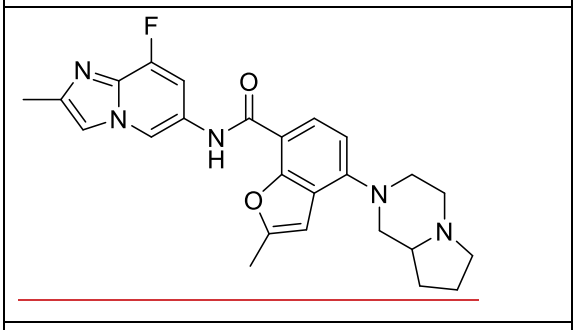


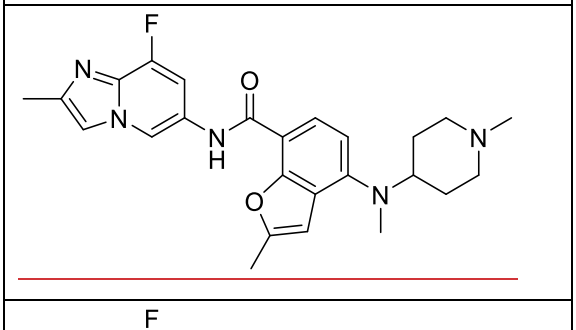


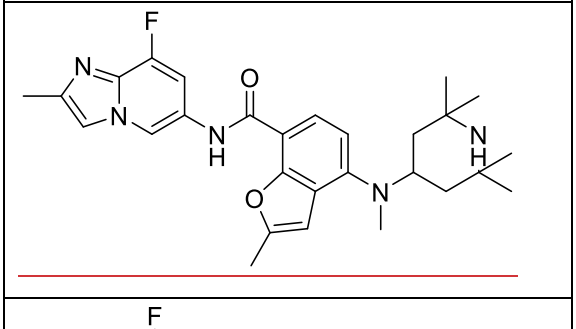


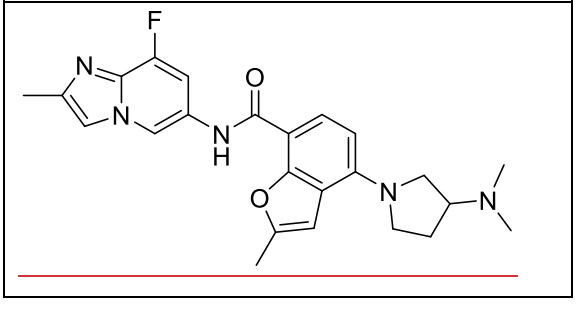


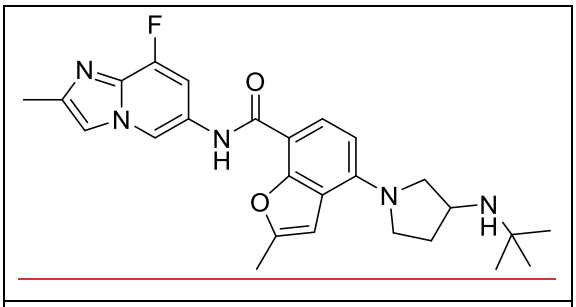


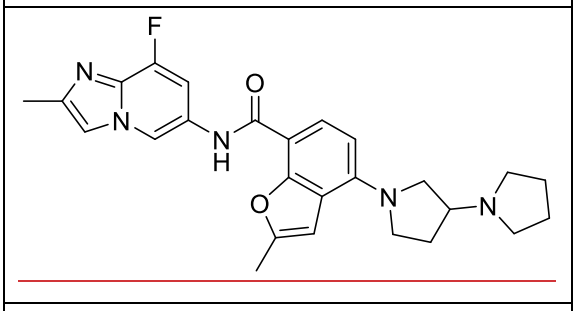


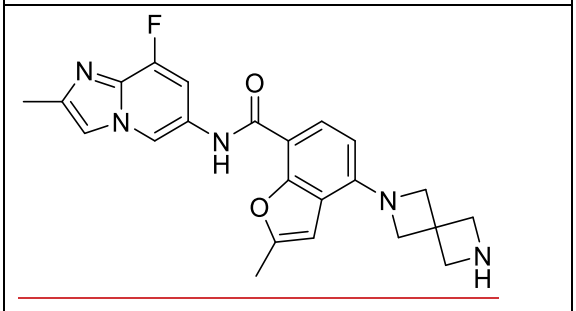


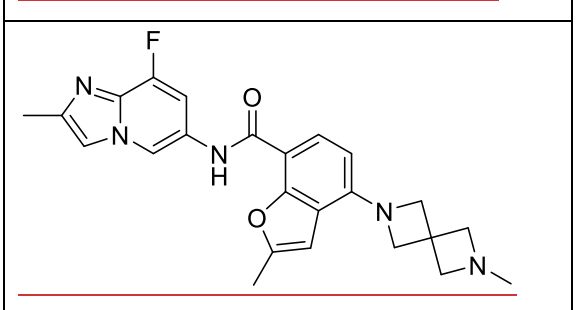


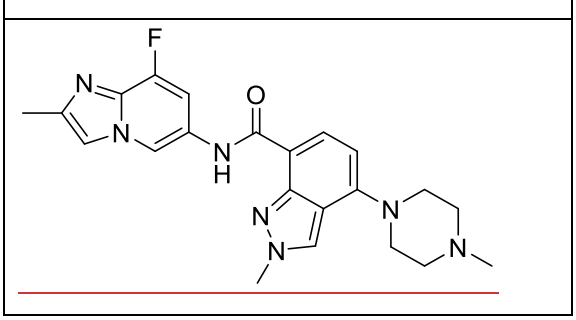


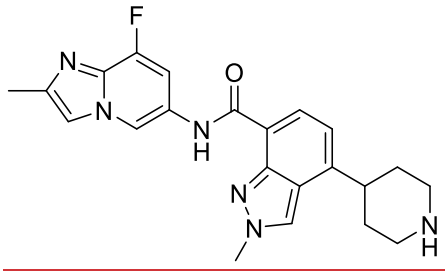


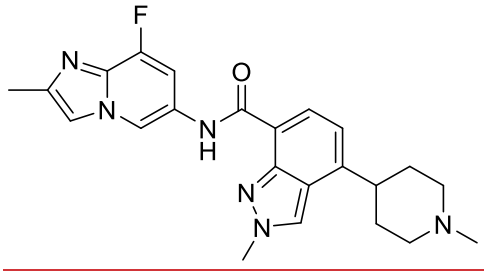


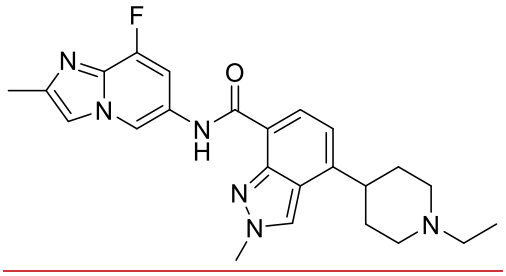


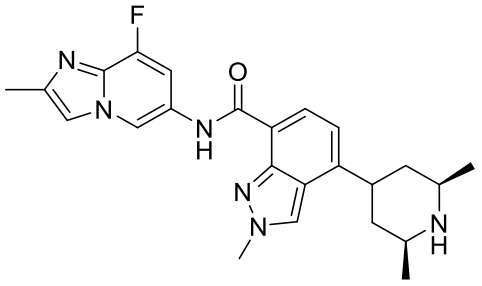


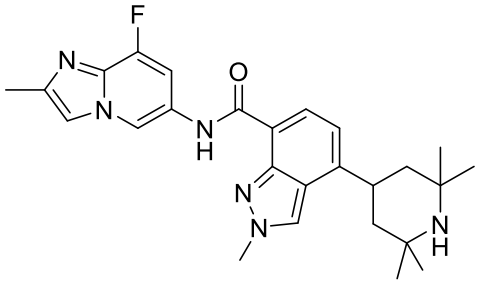


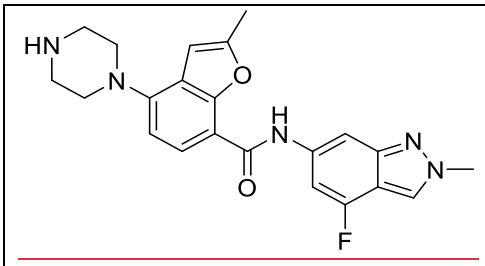
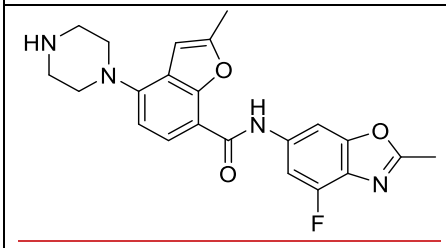
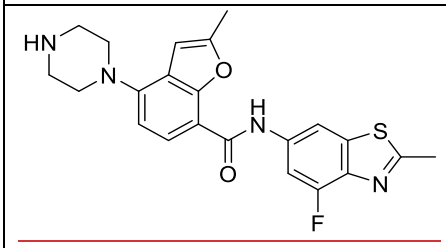
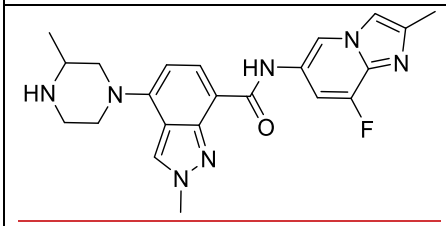
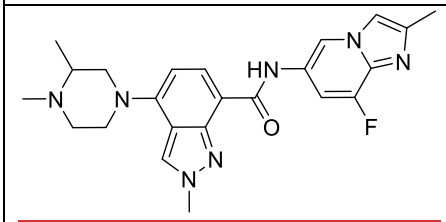
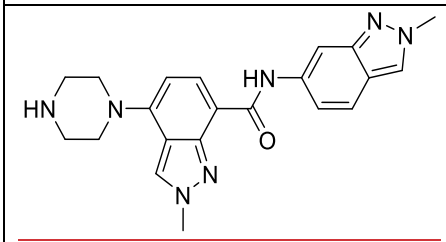


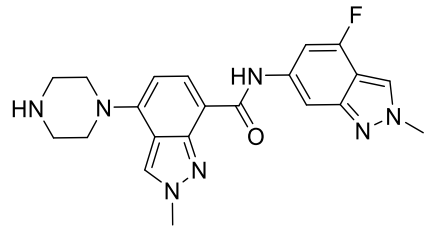


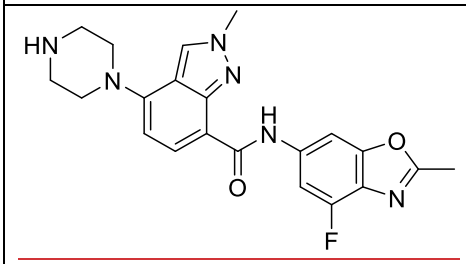


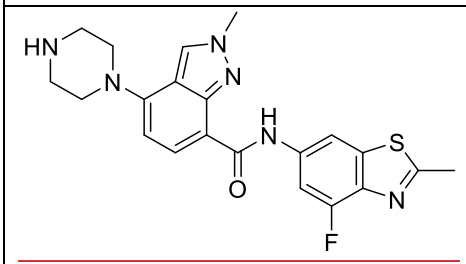


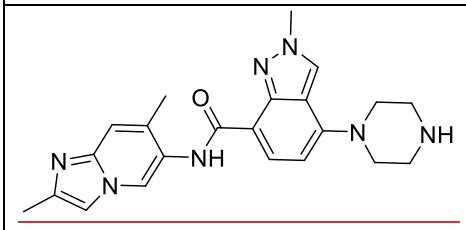


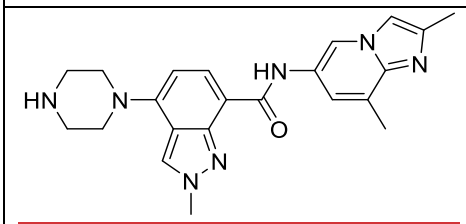







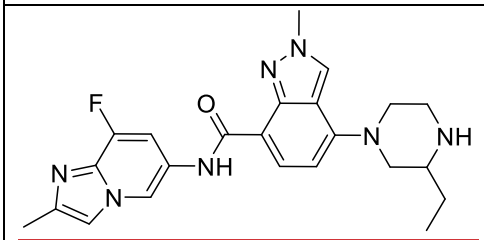


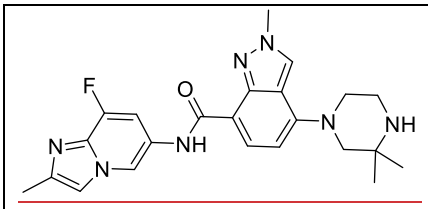
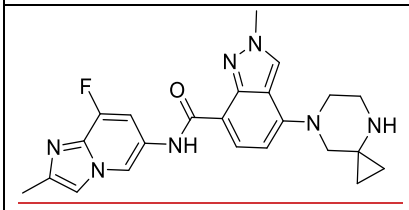
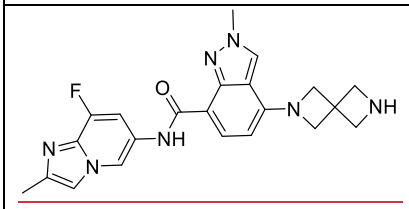
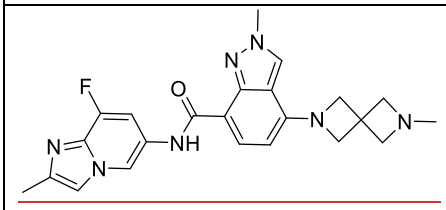
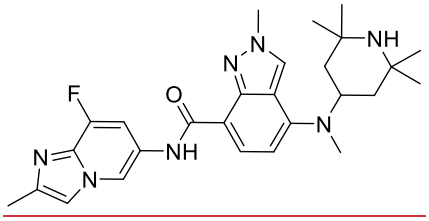
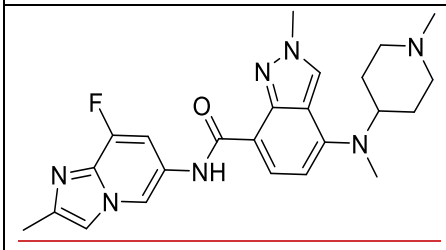
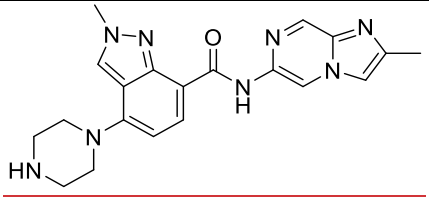


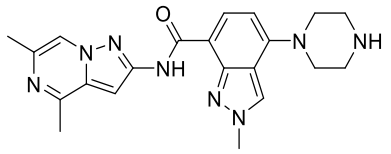


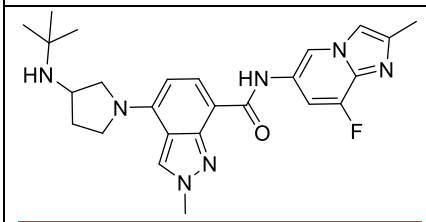


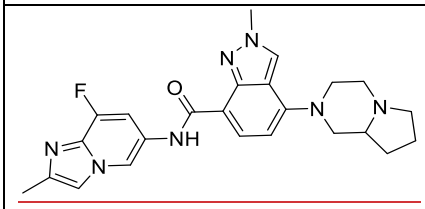


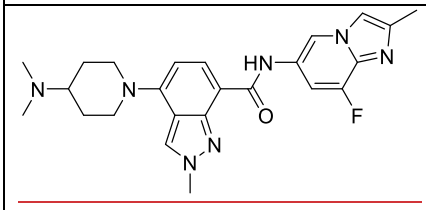


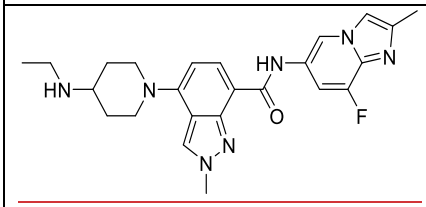








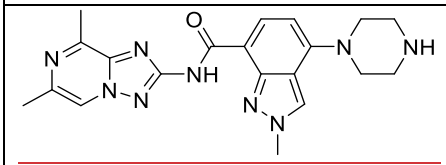


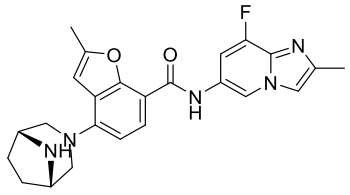


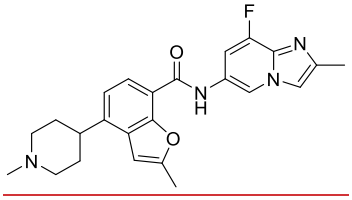


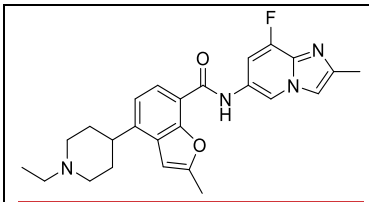
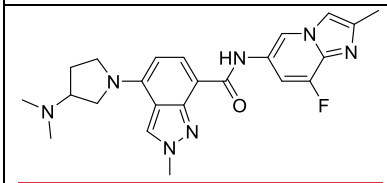
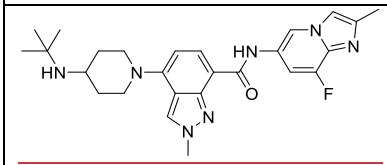
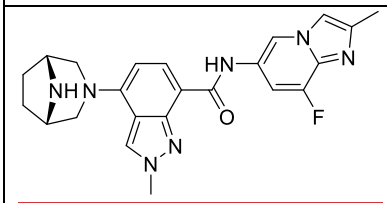
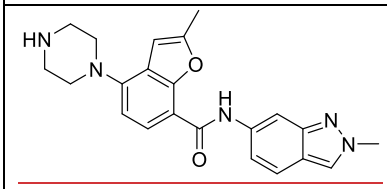
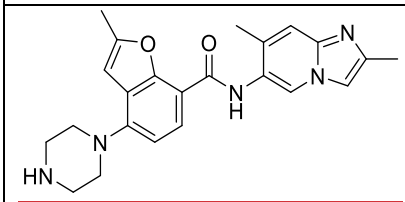
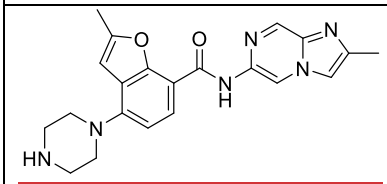
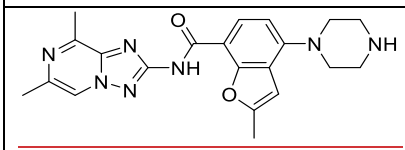


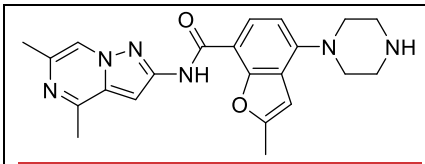
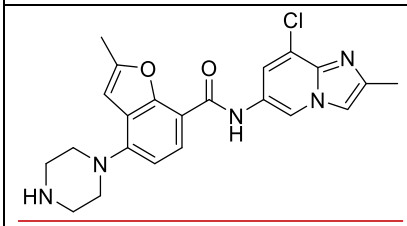
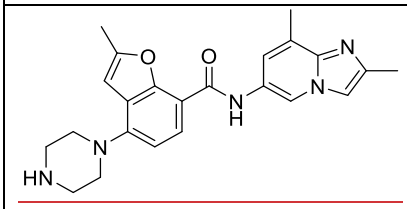
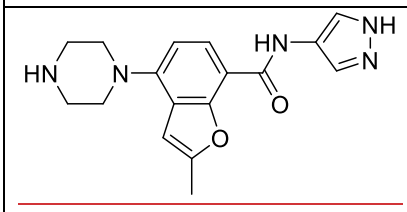
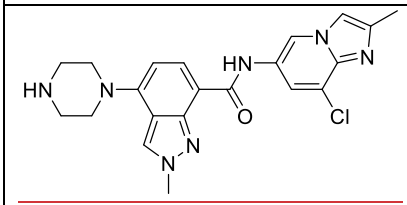
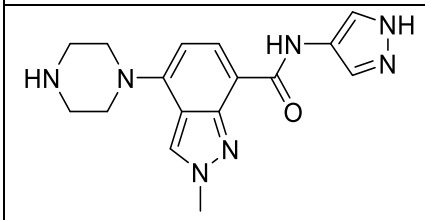
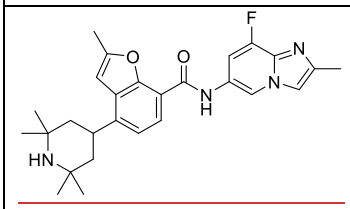
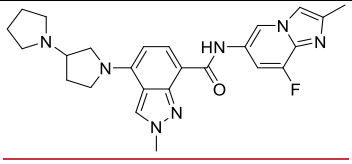


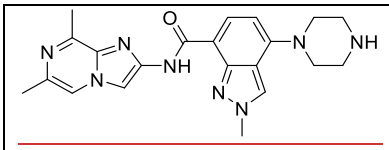
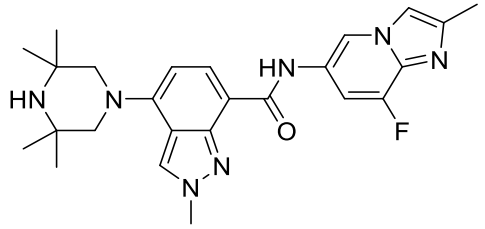
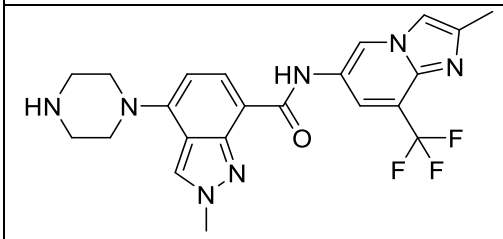
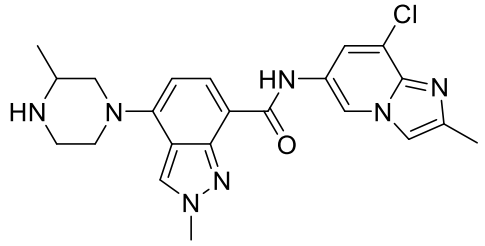
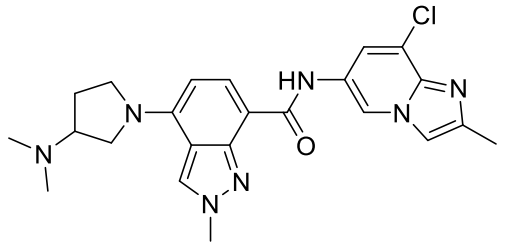
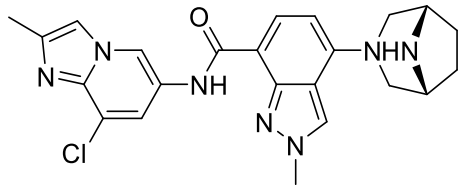
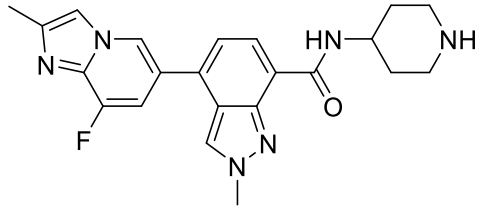


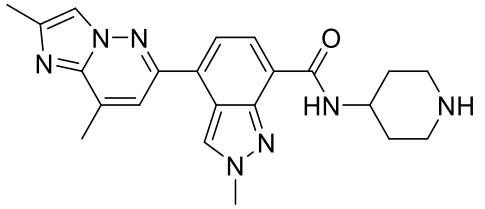
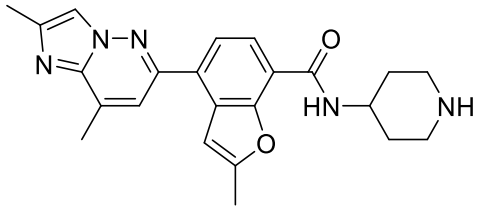
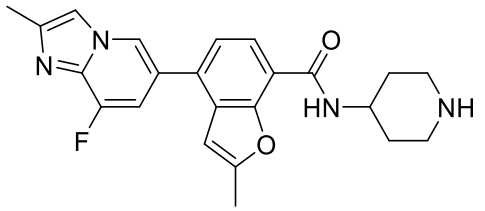
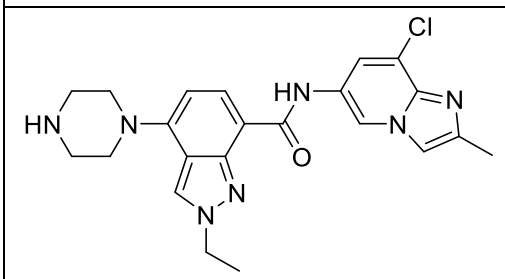
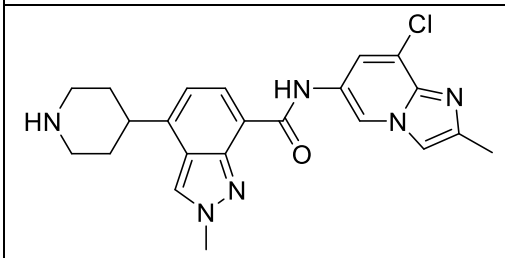
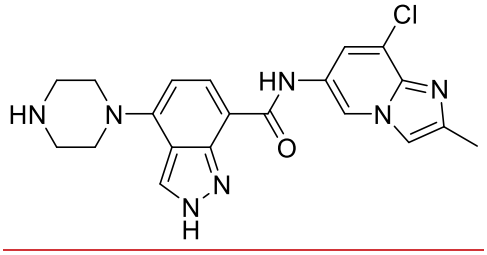


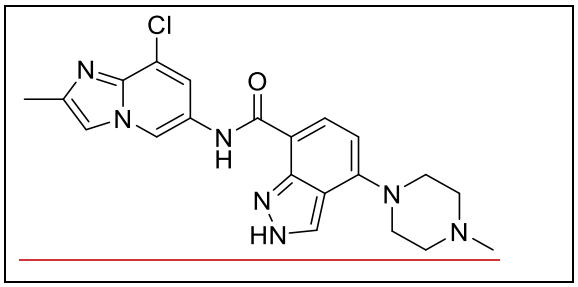




or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

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

26. The compound of any one of claims 1-24, or the pharmaceutical composition of claim 25, wherein the compound alters a target nucleic acid ~~(e.g., an RNA, e.g., a pre-mRNA)~~.

27. The compound of any one of claims 1-24, or the pharmaceutical composition of claim 25, wherein the compound binds to a target nucleic acid ~~(e.g., an RNA, e.g., a pre-mRNA)~~.

28. The compound of any one of claims 1-24, or the pharmaceutical composition of claim 25, wherein the compound stabilizes a target nucleic acid ~~(e.g., an RNA, e.g., a pre-mRNA)~~.

29. The compound of any one of claims 1-24, or the pharmaceutical composition of claim 25, wherein the compound increases splicing at splice site on a target nucleic acid ~~(e.g., an RNA, e.g., a pre-mRNA)~~, by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, ~~e.g.,~~ as determined by qPCR.

30. The compound of any one of claims 1-24, or the pharmaceutical composition of claim 25, wherein the compound decreases splicing at splice site on a target nucleic acid ~~(e.g., an RNA, e.g., a pre-mRNA)~~, by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, ~~e.g.,~~ as determined by qPCR %.

31. 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-a) or a composition thereof according to any one of claims 1-25:

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

32. The method of claim 31, wherein the component of a spliceosome is recruited to the nucleic acid in the presence of the compound of Formula (I-a).

33. 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-a) according to any one of claims 1-24, or the pharmaceutical composition of claim 25.

34. The method of claim 33, wherein the altering comprises forming a bulge in the nucleic acid.

35. The method of claim 33, wherein the altering comprises stabilizing a bulge in the nucleic acid.

36. The method of claim 33, wherein the altering comprises reducing a bulge in the nucleic acid.

37. The method of any one of any one of claims 33-36, wherein the nucleic acid comprises a splice site.

38. ~~A composition for use in treating a disease or disorder in a subject comprising administering to the subject~~ Use of a compound of Formula (I-a) according to any one of claims 1-24 or the pharmaceutical composition of claim 25 in the manufacture of a medicament for the treatment of a disease or disorder selected from: proliferative disease, 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 .

39. The ~~composition for~~ use of claim 38, wherein the disease or disorder comprises a proliferative disease ~~(e.g., cancer, a benign neoplasm, or angiogenesis)~~.

40. The ~~composition for~~ use of claim 38, 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.

41. The ~~composition for~~ use of claim 38, wherein the disease or disorder comprises neurological disease or disorder.

42. The ~~composition for~~ use of claim 38 or claim 41, wherein the disease or disorder comprises Huntington's disease.

43. A compound of Formula (I-a) according to any one of claims 1-24 or the pharmaceutical composition of claim 25 for use in therapy.