# PYRIDAZINE DERIVATIVES FOR MODULATING NUCLEIC ACID SPLICING

## CLAIM OF PRIORITY

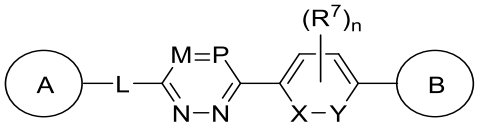
This application claims priority to U.S. Application No. 62/983,537, filed February 28, 2020; U.S. Application No. 63/007,134, filed April 8, 2020; U.S. Application No. 63/040,474, filed June 17, 2020; U.S. Application No. 63/072,781, filed August 31, 2020; and U.S. Application No. 63/126,491, filed 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 another aspect, there is provided a compound of Formula (I-b):




(I-b), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

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

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

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

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

each $R^1$ is independently hydrogen, $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, heterocyclyl, aryl, $C_1$-$C_6$ alkylene-aryl, $C_1$-$C_6$ alkenylene-aryl, $C_1$-$C_6$ alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^8$; or

two $R^1$ groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^8$;

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

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

each $R^4$ is $C_1$-$C_6$-alkyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

each of $R^{5a}$ and $R^{5b}$ is hydrogen, $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

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

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

each $R^7$ is independently $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more $R^9$;

$R^8$ and $R^9$ are each independently $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^{11}$;

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

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

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

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

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

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

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

x is 0, 1, or 2.

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

In another aspect, there is provided 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) as defined above, comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I).

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

In another aspect, there is provided the use of a compound of Formula (I as defined above or the pharmaceutical composition as defined above in the manufacture of a medicament for the treatment of a disease of disorder in a subject.

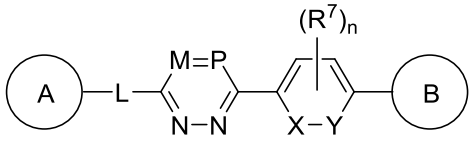
In another aspect, there is provided a compound of Formula (I) as defined above or the pharmaceutical composition as defined above for use in therapy.

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 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), (I-g), or (I-h)) and pharmaceutically acceptable salts, solvates, hydrates, tautomers, or stereoisomers thereof. The present disclosure additionally provides methods of using the compounds of the 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 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), (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 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 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 one example, the present disclosure provides compounds of Formula (I):




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

$C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^{11}$; each $R^A$ is independently hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$ haloalkyl, aryl, heteroaryl, $C_1$-$C_6$ alkylene-aryl, $C_1$-$C_6$ alkylene-heteroaryl, $–C(O)R^D$, or $–S(O)_xR^D$; each of $R^B$ and $R^C$ is independently hydrogen, $C_1$-$C_6$ alkyl, $C_1$-$C_6$-heteroalkyl, cycloalkyl, heterocyclyl, $–OR^A$; or $R^B$ and $R^C$ together with the atom to which they are attached form a 3-7-membered heterocyclyl ring optionally substituted with one or more $R^{10}$; each $R^D$ and $R^E$ is independently hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_1$-$C_6$ heteroalkyl, $C_1$-$C_6$ haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $C_1$-$C_6$ alkylene-aryl, or $C_1$-$C_6$ alkylene-heteroaryl; $R^F$ is hydrogen, $C_1$-$C_6$ alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; $R^{10}$ is $C_1$-$C_6$-alkyl or halo; each $R^{11}$ is independently $C_1$-$C_6$-alkyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, or $–OR^A$; n is 0, 1, 2, 3, or 4; and x is 0, 1, or 2.

In another example, the present 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), or (I-h)), 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 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 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 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 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 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 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 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 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 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 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 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 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 example of 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 Formula (I) 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 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 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 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 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 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 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 examples, 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 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 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 aspects of 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, and WO 2019/199972. 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, and WO 2019/199972, 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 Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

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

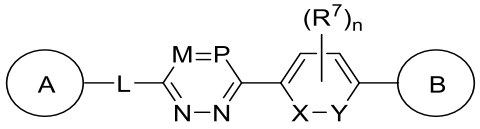
When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "$C_1$-$C_6$ alkyl" is intended to encompass, $C_1$, $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_1$-$C_6$, $C_1$-$C_5$, $C_1$-$C_4$, $C_1$-$C_3$, $C_1$-$C_2$, $C_2$-$C_6$, $C_2$-$C_5$, $C_2$-$C_4$,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

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

As used herein, "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 24 carbon atoms ("$C_1$-$C_{24}$ alkyl"). In some embodiments, an alkyl group has 1 to 12 carbon atoms ("$C_1$-$C_{12}$ alkyl"). In some embodiments, an alkyl group

## CLAIMS

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




(I-b), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

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

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

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

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

each $R^1$ is independently hydrogen, $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, heterocyclyl, aryl, $C_1$-$C_6$ alkylene-aryl, $C_1$-$C_6$ alkenylene-aryl, $C_1$-$C_6$ alkylene-heteroaryl, heteroaryl, halo, cyano, oxo, –$OR^A$, –$NR^BR^C$, –$NR^BC(O)R^D$, –$NO_2$, –$C(O)NR^BR^C$, –$C(O)R^D$, –$C(O)OR^D$, –$SR^E$, or –$S(O)_xR^D$, wherein each alkyl, alkylene, alkenyl, alkenylene, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^8$; or

two $R^1$ groups, together with the atoms to which they are attached, form a 3-7-membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein each cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^8$;

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

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

each $R^4$ is $C_1$-$C_6$-alkyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, halo, cyano, oxo, –$OR^A$, –$NR^BR^C$, –$C(O)R^D$, or –$C(O)OR^D$;

each of $R^{5a}$ and $R^{5b}$ is hydrogen, $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–C(O)R^D$, or $–C(O)OR^D$;

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

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

each $R^7$ is independently $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, halo, oxo, cyano, $NR^BC(O)R^D$, $–C(O)NR^BR^C$, $–C(O)R^D$, or $–SR^E$, wherein alkyl, alkenyl, alkynyl, heteroalkyl, and haloalkyl are optionally substituted with one or more $R^9$;

$R^8$ and $R^9$ are each independently $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, halo, cyano, oxo, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $–NO_2$, $–C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, $–SR^E$, or $–S(O)_xR^D$, wherein each of alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl is optionally substituted with one or more $R^{11}$;

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

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

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

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

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

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

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

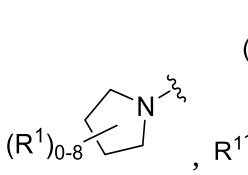
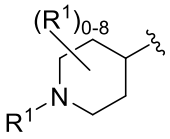
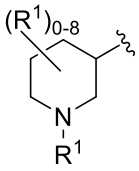
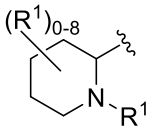
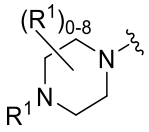
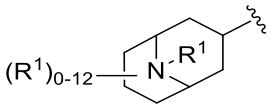
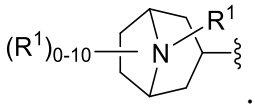
x is 0, 1, or 2.

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

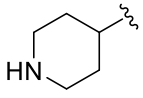
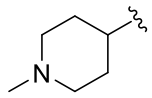
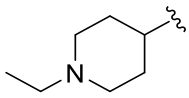
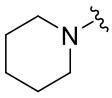
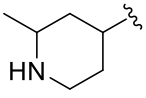
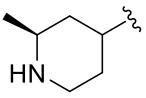
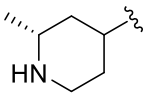
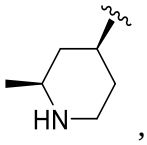
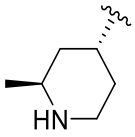
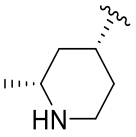
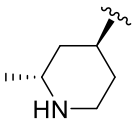
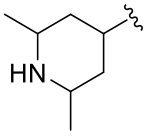
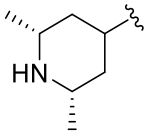
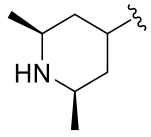
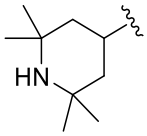
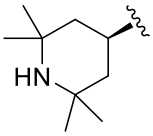
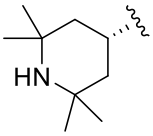
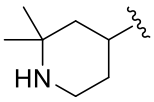
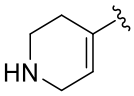
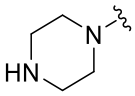
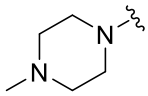
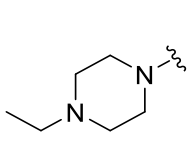
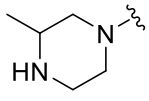
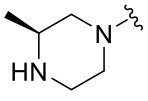
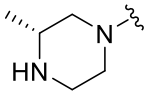
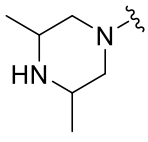
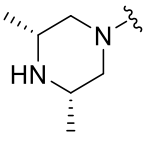
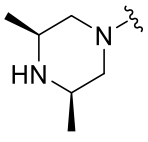
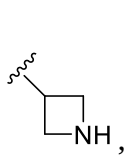
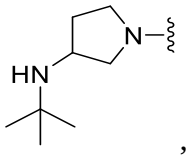
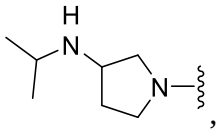
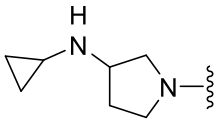
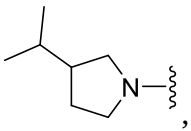
3. The compound of any one of the preceding claims, wherein A is monocyclic heterocyclyl.

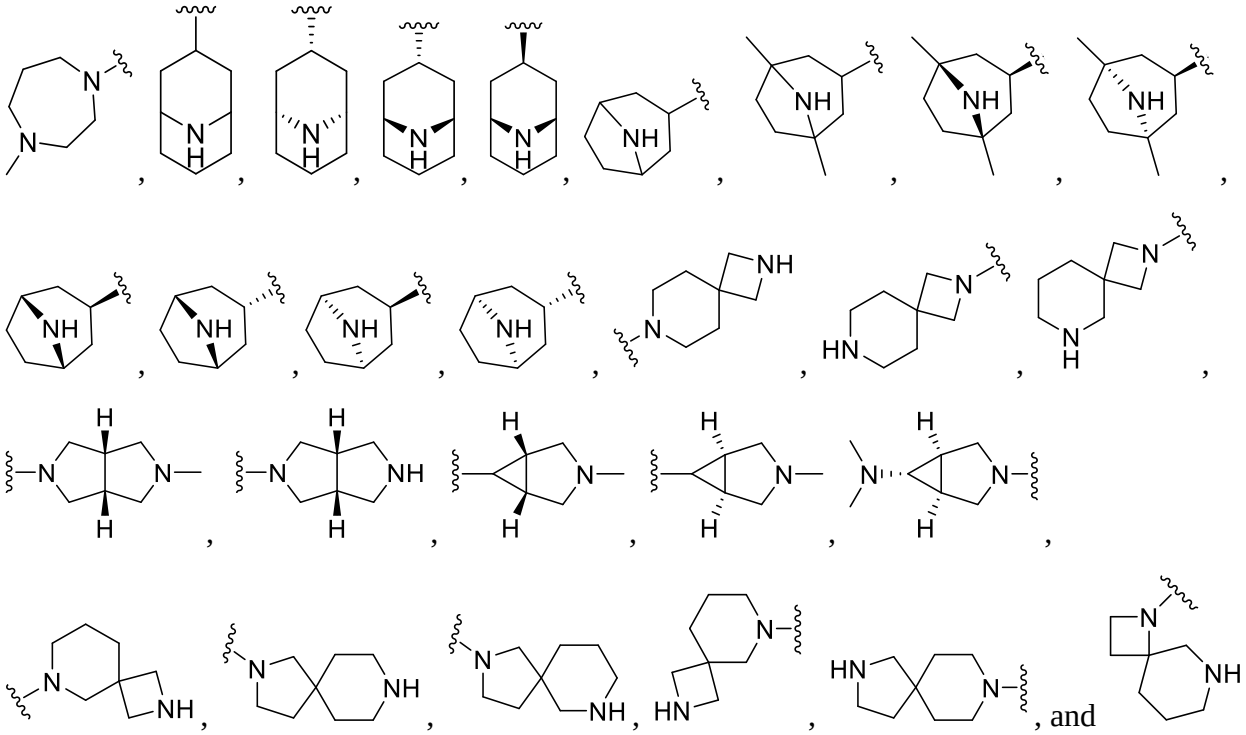
4. The compound of any one of the preceding claims, wherein A is a nitrogen-containing heterocyclyl.

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


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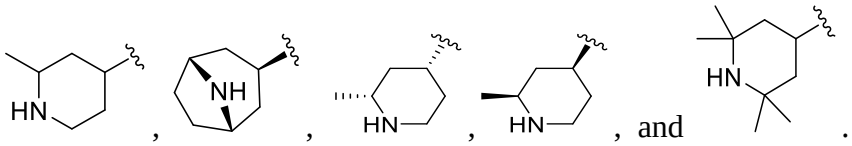
6. The compound of any one of the preceding claims, wherein A is selected from


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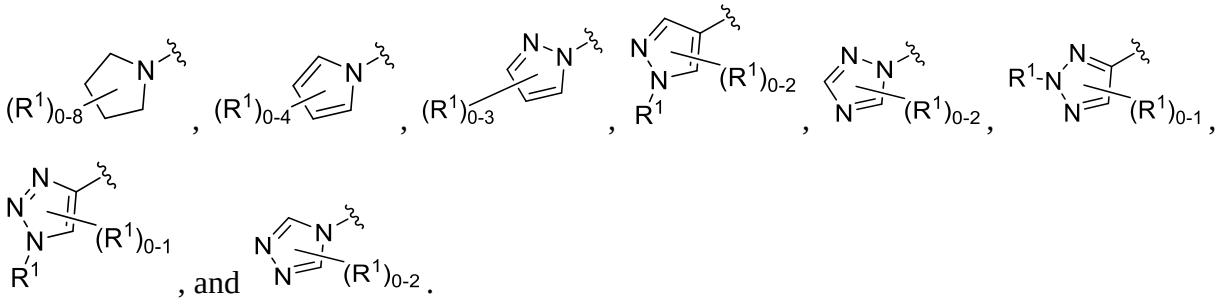
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7. The compound of any one of the preceding claims, wherein A is selected from

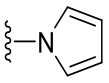
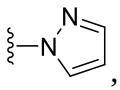
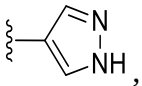
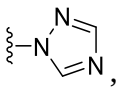
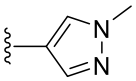
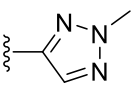
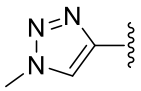
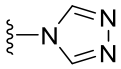
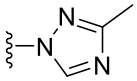
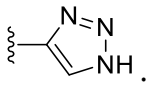


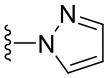
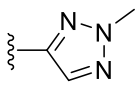
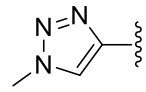
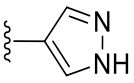
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8. The compound of any one of the preceding claims, wherein B is selected from



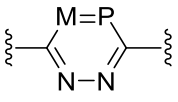
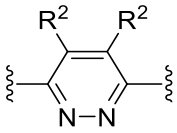
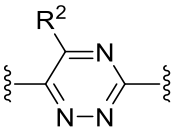
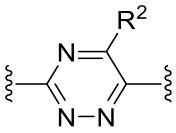
.

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

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

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

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

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

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

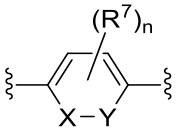
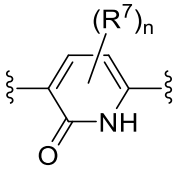
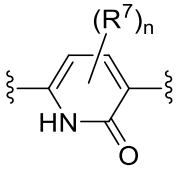
15. The compound of any one of the preceding claims, wherein one of X and Y is C($R^{5a}$)($R^{5b}$) and the other of X and Y is N($R^{5c}$).

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

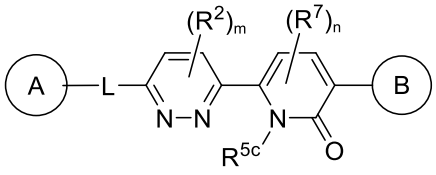
17. The compound of any one of the preceding claims, wherein X is $N(R^{5c})$ (e.g., NH) and Y is $C(R^{5a})(R^{5b})$ (e.g., C(O)).

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

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

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

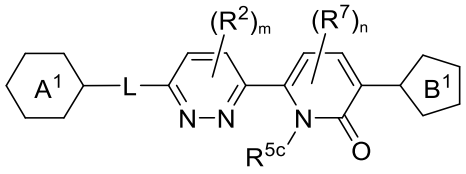
21. The compound of any one of claims 1-19, wherein the compound is a compound of Formula (I-c):



(I-c),

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

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



(I-d),

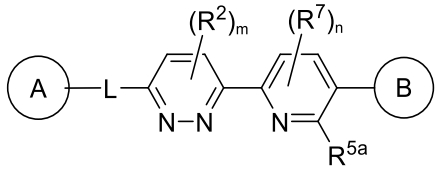
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

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

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

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

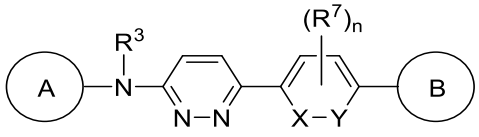
23. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-e):



(I-e),

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

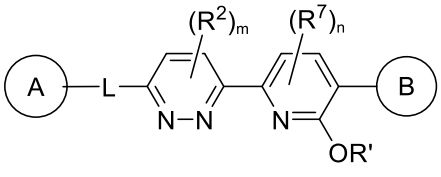
24. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-f):



(I-f),

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

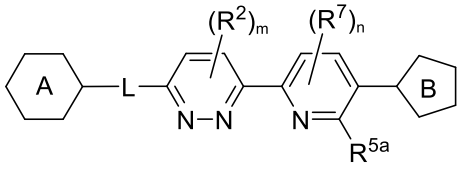
25. The compound of any one of claims 1-20, wherein the compound is a compound of Formula (I-g):



(I-g),

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein A, B, L, R', $R^2$, $R^7$, m, n, and subvariables thereof are as described in claim 1, R' is hydrogen, $C_1$-$C_6$-alkyl, $C_2$-$C_6$-alkenyl, $C_2$-$C_6$-alkynyl, $C_1$-$C_6$-heteroalkyl, $C_1$-$C_6$-haloalkyl, cycloalkyl, $–C(O)R^D$, or $–C(O)OR^D$..

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




(I-h),

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

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

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

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

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

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

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

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

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

32. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, wherein the compound increases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by qPCR.

33. The compound of any one of claims 1-27, or the pharmaceutical composition of claim 28, wherein the compound decreases splicing at splice site on a target nucleic acid (e.g., an RNA, e.g., a pre-mRNA), by about 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or more, e.g., as determined by qPCR %.

34. A method of forming a complex comprising a component of a spliceosome (e.g., a major spliceosome component or a minor spliceosome component), a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA), and a compound of Formula (I) according to any one of claims 1-27, comprising contacting the nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) with a compound of Formula (I).

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

36. A method of altering the conformation of a nucleic acid (e.g., a DNA, RNA, e.g., a pre-mRNA) comprising contacting the nucleic acid with a compound of Formula (I) according to any one of claims 1-27 or the pharmaceutical composition of claim 28.

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

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

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

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

41. Use of a compound of Formula (I) according to any one of claims 1-27 or the pharmaceutical composition of claim 28 in the manufacture of a medicament for the treatment of a disease of disorder in a subject.

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

43. The use of claim 41, wherein the disease or disorder comprises a neurological disease or disorder, autoimmune disease or disorder, immunodeficiency disease or disorder, lysosomal storage disease or disorder, cardiovascular disease or disorder, metabolic disease or disorder, respiratory disease or disorder, renal disease or disorder, or infectious disease.

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

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

46. A compound of Formula (I) according to any one of claims 1-27 or the pharmaceutical composition of claim 28 for use in therapy.