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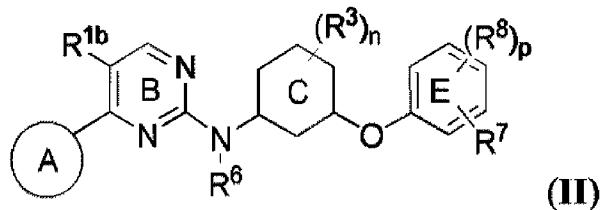
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(54) Titre : DERIVES DE PYRIMIDINE-2-AMINE ET COMPOSITIONS PHARMACEUTIQUES CONNEXES UTILES  
COMME INHIBITEURS DE KINASE 12 DEPENDANTE DES CYCLINES (CDK12)

(54) Title: PYRIMIDIN-2-AMINE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS THEREOF USEFUL AS  
INHIBITORS OF CYCLIN-DEPENDENT KINASE 12 (CDK12)



(57) Abrégé/Abstract:

The present invention provides novel compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. Also provided are methods and kits involving the inventive compounds or compositions for treating and/or preventing proliferative diseases (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, ovarian cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject. Treatment of a subject with a proliferative disease using a compound or composition of the invention may inhibit the aberrant activity of a kinase, such as a cyclin-dependent kinase (CDK) (e.g., CDK12), and therefore, induce cellular apoptosis and/or inhibit transcription in the subject.

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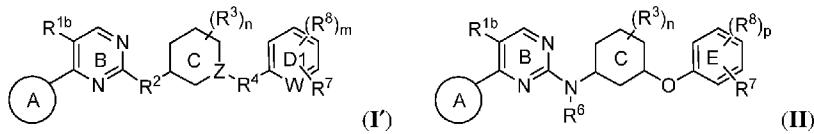
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## (54) Title: INHIBITORS OF CYCLIN-DEPENDENT KINASE 12 (CDK12) AND USES THEREOF



(57) **Abstract:** The present invention provides novel compounds of Formulae (I) and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. Also provided are methods and kits involving the inventive compounds or compositions for treating and/or preventing proliferative diseases (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, ovarian cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject. Treatment of a subject with a proliferative disease using a compound or composition of the invention may inhibit the aberrant activity of a kinase, such as a cyclin-dependent kinase (CDK) (e.g., CDK12), and therefore, induce cellular apoptosis and/or inhibit transcription in the subject.

**PYRIMIDIN-2-AMINE DERIVATIVES AND PHARMACEUTICAL  
COMPOSITIONS THEREOF USEFUL AS INHIBITORS OF CYCLIN-  
DEPENDENT KINASE 12 (CDK12)**

**[0001]**

**BACKGROUND OF THE INVENTION**

**[0002]** The members of the cyclin-dependent kinase (CDK) family play critical regulatory roles in proliferation. There are currently 20 known mammalian CDKs.

**[0003]** CDK12 and CDK13 were identified in cDNA screens for cell cycle regulators. Because their cyclin partners were not yet known, they were initially named CRKRS and CDC2L5 (Ko *et al.*, *J. Cell Sci.*, 2001, 114, 2591-2603; Marqués *et al.*, *Biochem Biophys Res Commun.*, 2000, 279(3):832-837), respectively. They were found to be 1490- and 1512-amino acid proteins, respectively, with a conserved central CTD kinase domain and degenerate RS domains identified in their N- and C-terminal regions (Even *et al.*, *J Cell Biochem.*, 2006, 99(3), 890-904).

**[0004]** Evidence has shown CDK12 and CDK13 play an important role in cancer development. A comprehensive genomic approach identified CDK12 to be one of the most frequently somatically mutated genes in high-grade serous ovarian cancer, the most fatal form of the disease (Erratum, *Nature*, 2011, 474(7353), 609-615). Several identified point mutations in the kinase domain point to the critical importance of the kinase activity of CDK12 for the development/progression of this disease. CDK12 has also been found to contribute to the development of breast cancer. Notably, CDK12 is located on chromosome 17, within the 17q21 locus that contains several candidate genes for breast cancer susceptibility (Kauraniemi *et al.*, *Cancer Res.*, 2001, 61(22), 8235-8240), and it is co-amplified with the tyrosine kinase receptor ERBB2, a protein amplified and overexpressed in about 20% of breast tumors. Gene fusion between CDK12 and ERBB2 was also detected in gastric cancer (Zang *et al.*, *Cancer Res.*, 2011, 71(1), 29-39). CDK12 is also implicated in the modification of tamoxifen sensitivity in estrogen-positive breast cancer *via* the modulation of the mitogen-activated protein kinase pathway (Iorns *et al.*, *Carcinogenesis*, 2009, 30(10):1696-1701).

[0005] Due to the important regulatory functions of kinases, such as CDK12, in cell cycle control, cell proliferation, differentiation, and apoptosis, it is important to develop modulators of the activities of these kinases, including selective modulators (e.g., selective inhibitors), for use as research tools as well as therapeutic agents in the treatment of diseases.

#### SUMMARY OF THE INVENTION

[0006] Cyclin dependent kinases (CDKs) (e.g., cyclin-dependent kinase 12 (CDK12)) are key regulators of the cell cycle. Their successive activation and inactivation drives the cycle forward. The activity of CDKs is regulated by multiple mechanisms such as positive and negative phosphorylation, binding of regulatory proteins like cyclins, and CDK inhibitors. Most CDKs require the phosphorylation of a threonine residue located in the T-loop to achieve full kinase activity. This threonine residue is conserved in all CDKs that function in cell cycle regulation. CDK12 also plays a role in transcription and possibly in DNA repair. This suggests that the CDK12 enzyme complexes are involved in multiple functions in the cell, e.g., cell cycle control, apoptosis, transcription regulation, and DNA repair.

[0007] Cyclin-dependent kinase 12 (CDK12) is recognized as an elongation regulator of RNA polymerase II-mediated transcription through its kinase function of phosphorylation on CTD domain of RNA Pol II. However, the detailed mechanism is not clear, and the exact site of phosphorylation on CTD by CDK12 is still controversial. A genome-wide screening also identified CDK12/cyclin K playing a critical role in mediating genome stability via regulation of expression of DDR genes. The deletion of CDK12/cyclin K severely impaired the expression of several critical regulators of genome stability, such as BRCA1, ATR, FANCI, and FANCD2 proteins in cells. Furthermore, several mutations of CDK12 were already identified in a variety of tumors including ovary, breast, and prostate, and these alterations on CDK12 sensitized these tumors to DNA damage agents, such as cisplatin and its derivatives, and inhibitors of DNA repair, such as PARP inhibitors. Thus, CDK12 is a potential therapeutic target of drugs for cancers and other diseases. Cysteine 1039 on CDK12 is three residues away from CDK7 cysteine 312. Recently solved CDK12 structures show that cysteine 1039 is also targetable with a similar orientation as cysteine 312 on CDK7. Without wishing to be bound by any particular theory, the inventive compounds' selectivity for CDK12 may be due to the compounds' ability to covalently modify a specific cysteine residue of these kinases (e.g., Cys1039 of CDK12). In contrast to THZ1, these compounds however do not bind to cysteine 312 of CDK7 and also do not reversibly inhibit other CDKs. Without wishing to be bound by any particular theory, the irreversible inhibition of CDK12

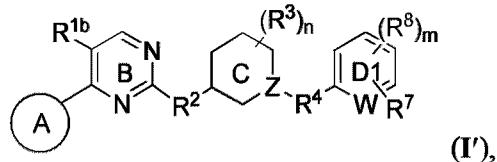
by the inventive compounds results in prolonged disruption of transcription and induction of apoptosis of a diverse subset of cancer cell lines. Genome-wide transcript analysis following inhibitor treatment delineates CDK12-responsive genes important in the maintenance of the cancer cell state. Selective covalent inhibition of CDK12 may be a viable cancer therapeutic strategy.

**[0008]** The present invention provides compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. The compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, may inhibit the activity of a kinase. In certain embodiments, the kinase is a CDK. In certain embodiments, the kinase is CDK12. In certain embodiments, the compounds of Formulae (I') and (II) are selective for CDK12 compared to other kinases. The present invention further provides methods of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, to study the inhibition of a kinase (e.g., CDK12) and as therapeutics for the prevention and/or treatment of diseases associated with the overexpression and/or aberrant (e.g., increased) activity of a kinase (e.g., CDK12). In certain embodiments, the inventive compounds are used for the prevention and/or treatment of proliferative diseases (e.g., cancers (e.g., leukemia, lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, lung cancer), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

**[0009]** The present invention provides compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. The compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, may inhibit the activity of a kinase. The compounds described herein may in certain embodiments selectively inhibit specific CDK subtypes, for example, CDK12. In certain embodiments, the compounds of Formulae (I') and (II) are selective for CDK12 compared to other kinases. The present invention also provides methods

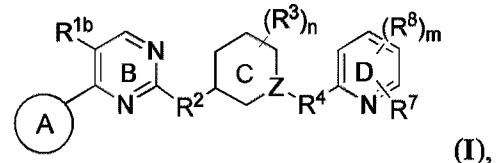
of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, to study the inhibition of a kinase (e.g., CDK12) and as therapeutics for the prevention and/or treatment of diseases associated with the overexpression and/or aberrant activity of a kinase (e.g., CDK12). In certain embodiments, the inventive compounds are used for the prevention and/or treatment of proliferative diseases (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

**[0010]** In one aspect, the present invention provides compounds of Formula (I'):



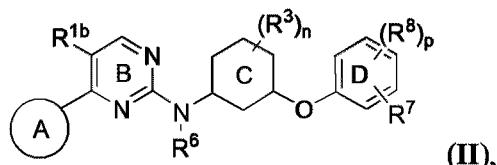
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring A, Z, W, R<sup>1b</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>7</sup>, R<sup>8</sup>, m, and n are as defined herein.

**[0011]** In one aspect, the present invention provides compounds of Formula (I):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring A, Z, R<sup>1b</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>7</sup>, R<sup>8</sup>, m, and n are as defined herein.

**[0012]** In one aspect, the present invention provides compounds of Formula (II):



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring A, R<sup>1b</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, n, and p are as defined herein.

[0013] In another aspect, the present disclosure provides pharmaceutical compositions including a compound described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically or prophylactically effective amount of a compound described herein. The pharmaceutical composition may be useful for treating a proliferative disease in a subject in need thereof, preventing a proliferative disease in a subject in need thereof, inhibiting the activity of a protein kinase in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell. In certain embodiments, the proliferative disease is an inflammatory disease. In certain embodiments, the inflammatory disease is rheumatoid arthritis, Crohn's disease, or fibrosis.

[0014] In another aspect, the present invention provides methods for treating and/or preventing a proliferative disease. Exemplary proliferative diseases which may be treated include diseases associated with overexpression of a cyclin-dependent kinase (CDK), cancer, benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In certain embodiments, the proliferative disease is cancer. In certain embodiments, the cancer is selected from the group consisting of pancreatic cancer, lung cancer (e.g., small cell lung cancer (SCLC), and non-small cell lung cancer), prostate cancer, breast cancer, ovarian cancer, kidney cancer, liver cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, and colorectal cancer. In certain embodiments, the proliferative disease is a benign neoplasm or disease associated with angiogenesis. In certain embodiments, the proliferative disease is an autoinflammatory disease. In certain embodiments, the proliferative disease is an autoimmune disease.

[0015] Another aspect of the invention relates to methods of inhibiting the activity of a kinase (e.g., CDK (e.g., CDK12)) using a compound described herein in a biological sample or subject. In certain embodiments, the method involves the selective inhibition of CDK12.

[0016] Also provided by the present invention are methods of inhibiting the transcription of one or more genes in the cell of a biological sample or subject using a compound described herein. The transcription of genes affected by the activity of CDK12 may be inhibited by a compound of the invention. In certain embodiments, these genes are one or more selected from the group consisting of BRCA1, FANCI, ATR, FANCD2, APEX1, NEK9, CHEK1,

CHEK2, ATM, RAD51C, RAD51D, ORC3L, MDC1, TERF2, ERCC4, FANCF, PARP9, RUNX1, MYB, TAL1, MCL1, MYC, BCL2, ETS1, and EWS-FLI.

[0017] The present invention also provides methods of inhibiting cell growth in a biological sample or subject. In still another aspect, the present invention provides methods of inducing apoptosis of a cell in a biological sample or subject.

[0018] The present invention provides methods for administering to a subject in need thereof an effective amount of a compound, or pharmaceutical composition thereof, as described herein. Also described are methods for contacting a cell with an effective amount of a compound, or pharmaceutical composition thereof, as described herein. In certain embodiments, a method described herein further includes administering to the subject an additional pharmaceutical agent. In certain embodiments, a method described herein further includes contacting the cell with an additional pharmaceutical agent. The methods described herein may further include performing radiotherapy, immunotherapy, and/or transplantation on the subject.

[0019] In yet another aspect, the present invention provides compounds of Formulae (I') and (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, for use in the treatment of a disease (e.g., a proliferative disease such as cancer) in a subject.

[0020] Another aspect of the present disclosure relates to kits comprising a container with a compound, or pharmaceutical composition thereof, as described herein. The kits described herein may include a single dose or multiple doses of the compound or pharmaceutical composition. The kits may be useful in a method of the disclosure. In certain embodiments, the kit further includes instructions for using the compound or pharmaceutical composition. A kit described herein may also include information (e.g. prescribing information) as required by a regulatory agency, such as the U.S. Food and Drug Administration (FDA).

[0021] The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, Examples, Figures, and Claims.

## DEFINITIONS

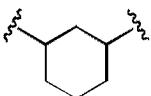
[0022] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75<sup>th</sup> Ed., inside cover, and

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*, 5<sup>th</sup> 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*, 3<sup>rd</sup> Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents described herein.

[0023] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0024] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C<sub>1-6</sub>” is intended to encompass, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>1-6</sub>, C<sub>1-5</sub>, C<sub>1-4</sub>, C<sub>1-3</sub>, C<sub>1-2</sub>, C<sub>2-6</sub>, C<sub>2-5</sub>, C<sub>2-4</sub>, C<sub>2-3</sub>, C<sub>3-6</sub>, C<sub>3-5</sub>, C<sub>3-4</sub>, C<sub>4-6</sub>, C<sub>4-5</sub>, and C<sub>5-6</sub>.

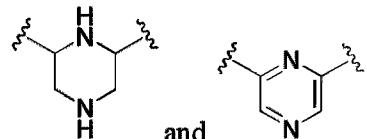
[0025] “Hydrocarbon chain” refers to a substituted or unsubstituted divalent alkyl, alkenyl, or alkynyl group. A hydrocarbon chain includes at least one chain, each node (“carbon unit”) of which including at least one carbon atom, between the two radicals of the hydrocarbon chain. For example, hydrocarbon chain –C<sup>A</sup>H(C<sup>B</sup>H<sub>2</sub>C<sup>C</sup>H<sub>3</sub>)– includes only one carbon unit C<sup>A</sup>. The term “C<sub>x</sub> hydrocarbon chain,” wherein x is a positive integer, refers to a hydrocarbon chain that includes x number of carbon unit(s) between the two radicals of the hydrocarbon chain. If there is more than one possible value of x, the smallest possible value of x is used for the definition of the hydrocarbon chain. For example, –CH(C<sub>2</sub>H<sub>5</sub>)– is a C<sub>1</sub> hydrocarbon chain,



and is a C<sub>3</sub> hydrocarbon chain. When a range of values is used, e.g., a C<sub>1-6</sub> hydrocarbon chain, the meaning of the range is as described herein. A hydrocarbon chain may be saturated (e.g., -(CH<sub>2</sub>)<sub>4</sub>-). A hydrocarbon chain may also be unsaturated and include one or more C=C and/or C≡C bonds anywhere in the hydrocarbon chain. For instance, -CH=CH-(CH<sub>2</sub>)<sub>2</sub>-, -CH<sub>2</sub>-C≡C-CH<sub>2</sub>-, and -C≡C-CH=CH- are all examples of an unsubstituted and unsaturated hydrocarbon chain. In certain embodiments, the hydrocarbon chain is unsubstituted (e.g., -(CH<sub>2</sub>)<sub>4</sub>-). In certain embodiments, the hydrocarbon chain is substituted (e.g., -CH(C<sub>2</sub>H<sub>5</sub>)- and -CF<sub>2</sub>-). Any two substituents on the hydrocarbon chain may be joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring. For

instance, , , , , and , and

are all examples of a hydrocarbon chain. In contrast, in certain embodiments



and are not within the scope of the hydrocarbon chains described herein.

**[0026]** “Alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C<sub>1-20</sub> alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“C<sub>1-10</sub> alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“C<sub>1-9</sub> alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“C<sub>1-8</sub> alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“C<sub>1-7</sub> alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C<sub>1-6</sub> alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C<sub>1-5</sub> alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C<sub>1-4</sub> alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C<sub>1-3</sub> alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C<sub>1-2</sub> alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C<sub>1</sub> alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkyl”).

Examples of C<sub>1-6</sub> alkyl groups include methyl (C<sub>1</sub>), ethyl (C<sub>2</sub>), *n*-propyl (C<sub>3</sub>), isopropyl (C<sub>3</sub>),

*n*-butyl (C<sub>4</sub>), *tert*-butyl (C<sub>4</sub>), *sec*-butyl (C<sub>4</sub>), *iso*-butyl (C<sub>4</sub>), *n*-pentyl (C<sub>5</sub>), 3-pentanyl (C<sub>5</sub>), amyl (C<sub>5</sub>), neopentyl (C<sub>5</sub>), 3-methyl-2-butanyl (C<sub>5</sub>), tertiary amyl (C<sub>5</sub>), and *n*-hexyl (C<sub>6</sub>). Additional examples of alkyl groups include *n*-heptyl (C<sub>7</sub>), *n*-octyl (C<sub>8</sub>) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C<sub>1-10</sub> alkyl (*e.g.*, –CH<sub>3</sub>). In certain embodiments, the alkyl group is substituted C<sub>1-10</sub> alkyl.

[0027] “Alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds, and no triple bonds (“C<sub>2-20</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C<sub>2-10</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C<sub>2-9</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C<sub>2-8</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C<sub>2-7</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C<sub>2-5</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C<sub>2-4</sub> alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C<sub>2-3</sub> alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C<sub>2</sub> alkenyl”). The one or more carbon–carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C<sub>2-4</sub> alkenyl groups include ethenyl (C<sub>2</sub>), 1-propenyl (C<sub>3</sub>), 2-propenyl (C<sub>3</sub>), 1-butenyl (C<sub>4</sub>), 2-butenyl (C<sub>4</sub>), butadienyl (C<sub>4</sub>), and the like. Examples of C<sub>2-6</sub> alkenyl groups include the aforementioned C<sub>2-4</sub> alkenyl groups as well as pentenyl (C<sub>5</sub>), pentadienyl (C<sub>5</sub>), hexenyl (C<sub>6</sub>), and the like. Additional examples of alkenyl include heptenyl (C<sub>7</sub>), octenyl (C<sub>8</sub>), octatrienyl (C<sub>8</sub>), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents. In certain embodiments, the alkenyl group is unsubstituted C<sub>2-10</sub> alkenyl. In certain embodiments, the alkenyl group is substituted C<sub>2-10</sub> alkenyl.

[0028] “Alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds, and optionally one or more double bonds (“C<sub>2-20</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C<sub>2-10</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C<sub>2-9</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C<sub>2-8</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C<sub>2-7</sub>

alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C<sub>2-6</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C<sub>2-5</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C<sub>2-4</sub> alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C<sub>2-3</sub> alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C<sub>2</sub> alkynyl”). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C<sub>2-4</sub> alkynyl groups include, without limitation, ethynyl (C<sub>2</sub>), 1–propynyl (C<sub>3</sub>), 2–propynyl (C<sub>3</sub>), 1–butynyl (C<sub>4</sub>), 2–butynyl (C<sub>4</sub>), and the like. Examples of C<sub>2-6</sub> alkenyl groups include the aforementioned C<sub>2-4</sub> alkynyl groups as well as pentynyl (C<sub>5</sub>), hexynyl (C<sub>6</sub>), and the like. Additional examples of alkynyl include heptynyl (C<sub>7</sub>), octynyl (C<sub>8</sub>), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C<sub>2-10</sub> alkynyl. In certain embodiments, the alkynyl group is substituted C<sub>2-10</sub> alkynyl.

[0029] “Carbocyclyl” or “carbocyclic” refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C<sub>3-10</sub> carbocyclyl”) and ~~www~~ero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C<sub>3-8</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C<sub>3-6</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C<sub>3-6</sub> carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C<sub>5-10</sub> carbocyclyl”). Exemplary C<sub>3-6</sub> carbocyclyl groups include, without limitation, cyclopropyl (C<sub>3</sub>), cyclopropenyl (C<sub>3</sub>), cyclobutyl (C<sub>4</sub>), cyclobutenyl (C<sub>4</sub>), cyclopentyl (C<sub>5</sub>), cyclopentenyl (C<sub>5</sub>), cyclohexyl (C<sub>6</sub>), cyclohexenyl (C<sub>6</sub>), cyclohexadienyl (C<sub>6</sub>), and the like. Exemplary C<sub>3-8</sub> carbocyclyl groups include, without limitation, the aforementioned C<sub>3-6</sub> carbocyclyl groups as well as cycloheptyl (C<sub>7</sub>), cycloheptenyl (C<sub>7</sub>), cycloheptadienyl (C<sub>7</sub>), cycloheptatrienyl (C<sub>7</sub>), cyclooctyl (C<sub>8</sub>), cyclooctenyl (C<sub>8</sub>), bicyclo[2.2.1]heptanyl (C<sub>7</sub>), bicyclo[2.2.2]octanyl (C<sub>8</sub>), and the like. Exemplary C<sub>3-10</sub> carbocyclyl groups include, without limitation, the aforementioned C<sub>3-8</sub> carbocyclyl groups as well as cyclononyl (C<sub>9</sub>), cyclononenyl (C<sub>9</sub>), cyclodecyl (C<sub>10</sub>), cyclodecenyl (C<sub>10</sub>), octahydro-1*H*–indenyl (C<sub>9</sub>), decahydronaphthalenyl (C<sub>10</sub>), spiro[4.5]decanyl (C<sub>10</sub>), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be

partially unsaturated. “Carbocyclyl” also includes ring systems wherein the carbocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclic ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C<sub>3-10</sub> carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C<sub>3-10</sub> carbocyclyl.

[0030] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C<sub>3-10</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C<sub>3-8</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C<sub>3-6</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C<sub>5-6</sub> cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C<sub>5-10</sub> cycloalkyl”). Examples of C<sub>5-6</sub> cycloalkyl groups include cyclopentyl (C<sub>5</sub>) and cyclohexyl (C<sub>6</sub>). Examples of C<sub>3-6</sub> cycloalkyl groups include the aforementioned C<sub>5-6</sub> cycloalkyl groups as well as cyclopropyl (C<sub>3</sub>) and cyclobutyl (C<sub>4</sub>). Examples of C<sub>3-8</sub> cycloalkyl groups include the aforementioned C<sub>3-6</sub> cycloalkyl groups as well as cycloheptyl (C<sub>7</sub>) and cyclooctyl (C<sub>8</sub>). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C<sub>3-10</sub> cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C<sub>3-10</sub> cycloalkyl.

[0031] “Heterocyclyl” or “heterocyclic” refers to a radical of a 3- to 10-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclic ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclic ring, or ring systems

wherein the heterocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclic ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclic ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0032] In some embodiments, a heterocyclyl group is a 5–10 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“5–10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–8 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–6 membered non-aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heterocyclyl”). In some embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0033] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–

membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxeocanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C<sub>6</sub> aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0034] “Aryl” refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 pi electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C<sub>6–14</sub> aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C<sub>6</sub> aryl”; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C<sub>10</sub> aryl”; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C<sub>14</sub> aryl”; e.g., anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C<sub>6–14</sub> aryl. In certain embodiments, the aryl group is substituted C<sub>6–14</sub> aryl.

[0035] “Aralkyl” is a subset of alkyl and aryl and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group. In certain embodiments, the aralkyl is optionally substituted benzyl. In certain embodiments, the aralkyl is benzyl. In certain embodiments, the aralkyl is optionally substituted phenethyl. In certain embodiments, the aralkyl is phenethyl.

[0036] “Heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system (e.g., having 6 or 10 p electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of

attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (e.g., indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (e.g., 2-indolyl) or the ring that does not contain a heteroatom (e.g., 5-indolyl).

[0037] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[0038] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl

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

[0039] “Heteroaralkyl” is a subset of alkyl and heteroaryl and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

[0040] “Partially unsaturated” refers to a group that includes at least one double or triple bond. A “partially unsaturated” ring system is further intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (e.g., aryl or heteroaryl groups) as herein defined. Likewise, “saturated” refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[0041] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, which are divalent bridging groups are further referred to using the suffix *-ene*, *e.g.*, alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene.

[0042] The term “optionally substituted” refers to substituted or unsubstituted.

[0043] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are optionally substituted (*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible

substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0044] Exemplary carbon atom substituents include, but are not limited to, halogen,  $-CN$ ,  $-NO_2$ ,  $-N_3$ ,  $-SO_2H$ ,  $-SO_3H$ ,  $-OH$ ,  $-OR^{aa}$ ,  $-ON(R^{bb})_2$ ,  $-N(R^{bb})_2$ ,  $-N(R^{bb})_3^+X^-$ ,  $-N(OR^{cc})R^{bb}$ ,  $-SH$ ,  $-SR^{aa}$ ,  $-SSR^{cc}$ ,  $-C(=O)R^{aa}$ ,  $-CO_2H$ ,  $-CHO$ ,  $-C(OR^{cc})_2$ ,  $-CO_2R^{aa}$ ,  $-OC(=O)R^{aa}$ ,  $-OCO_2R^{aa}$ ,  $-C(=O)N(R^{bb})_2$ ,  $-OC(=O)N(R^{bb})_2$ ,  $-NR^{bb}C(=O)R^{aa}$ ,  $-NR^{bb}CO_2R^{aa}$ ,  $-NR^{bb}C(=O)N(R^{bb})_2$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{bb})OR^{aa}$ ,  $-OC(=NR^{bb})R^{aa}$ ,  $-OC(=NR^{bb})OR^{aa}$ ,  $-C(=NR^{bb})N(R^{bb})_2$ ,  $-OC(=NR^{bb})N(R^{bb})_2$ ,  $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$ ,  $-C(=O)NR^{bb}SO_2R^{aa}$ ,  $-NR^{bb}SO_2R^{aa}$ ,  $-SO_2N(R^{bb})_2$ ,  $-SO_2R^{aa}$ ,  $-SO_2OR^{aa}$ ,  $-OSO_2R^{aa}$ ,  $-S(=O)R^{aa}$ ,  $-OS(=O)R^{aa}$ ,  $-Si(R^{aa})_3$ ,  $-OSi(R^{aa})_3$ ,  $-C(=S)N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ ,  $-C(=S)SR^{aa}$ ,  $-SC(=S)SR^{aa}$ ,  $-SC(=O)SR^{aa}$ ,  $-OC(=O)SR^{aa}$ ,  $-SC(=O)OR^{aa}$ ,  $-SC(=O)R^{aa}$ ,  $-P(=O)(R^{aa})_2$ ,  $-P(=O)(OR^{cc})_2$ ,  $-OP(=O)(R^{aa})_2$ ,  $-OP(=O)(OR^{cc})_2$ ,  $-P(=O)(N(R^{bb})_2)_2$ ,  $-OP(=O)(N(R^{bb})_2)_2$ ,  $-NR^{bb}P(=O)(R^{aa})_2$ ,  $-NR^{bb}P(=O)(OR^{cc})_2$ ,  $-NR^{bb}P(=O)(N(R^{bb})_2)_2$ ,  $-P(R^{cc})_2$ ,  $-P(OR^{cc})_2$ ,  $-P(R^{cc})_3^+X^-$ ,  $-P(OR^{cc})_3^+X^-$ ,  $-P(R^{cc})_4$ ,  $-P(OR^{cc})_4$ ,  $-OP(R^{cc})_2$ ,  $-OP(R^{cc})_3^+X^-$ ,  $-OP(OR^{cc})_2$ ,  $-OP(OR^{cc})_3^+X^-$ ,  $-OP(R^{cc})_4$ ,  $-OP(OR^{cc})_4$ ,  $-B(R^{aa})_2$ ,  $-B(OR^{cc})_2$ ,  $-BR^{aa}(OR^{cc})$ ,  $C_{1-10}$  alkyl,  $C_{1-10}$  perhaloalkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl, hetero $C_{1-10}$  alkyl, hetero $C_{2-10}$  alkenyl, hetero $C_{2-10}$  alkynyl,  $C_{3-10}$  carbocyclyl, 3-14 membered heterocyclyl,  $C_{6-14}$  aryl, and 5-14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5  $R^{dd}$  groups; wherein  $X^-$  is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group  $=O$ ,  $=S$ ,  $=NN(R^{bb})_2$ ,  $=NNR^{bb}C(=O)R^{aa}$ ,  $=NNR^{bb}C(=O)OR^{aa}$ ,  $=NNR^{bb}S(=O)_2R^{aa}$ ,  $=NR^{bb}$ , or  $=NOR^{cc}$ , each instance of  $R^{aa}$  is, independently, selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  perhaloalkyl,  $C_{2-10}$  alkenyl,  $C_{2-10}$  alkynyl, hetero $C_{1-10}$  alkyl, hetero $C_{2-10}$  alkenyl, hetero $C_{2-10}$  alkynyl,  $C_{3-10}$

carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>aa</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups;

each instance of R<sup>bb</sup> is, independently, selected from hydrogen, -OH, -OR<sup>aa</sup>, -N(R<sup>cc</sup>)<sub>2</sub>, -CN, -C(=O)R<sup>aa</sup>, -C(=O)N(R<sup>cc</sup>)<sub>2</sub>, -CO<sub>2</sub>R<sup>aa</sup>, -SO<sub>2</sub>R<sup>aa</sup>, -C(=NR<sup>cc</sup>)OR<sup>aa</sup>, -C(=NR<sup>cc</sup>)N(R<sup>cc</sup>)<sub>2</sub>, -SO<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, -SO<sub>2</sub>R<sup>cc</sup>, -SO<sub>2</sub>OR<sup>cc</sup>, -SOR<sup>aa</sup>, -C(=S)N(R<sup>cc</sup>)<sub>2</sub>, -C(=O)SR<sup>cc</sup>, -C(=S)SR<sup>cc</sup>, -P(=O)(R<sup>aa</sup>)<sub>2</sub>, -P(=O)(OR<sup>cc</sup>)<sub>2</sub>, -P(=O)(N(R<sup>cc</sup>)<sub>2</sub>)<sub>2</sub>, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> perhaloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, heteroC<sub>1-10</sub>alkyl, heteroC<sub>2-10</sub>alkenyl, heteroC<sub>2-10</sub>alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>bb</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups; wherein X<sup>-</sup> is a counterion;

each instance of R<sup>cc</sup> is, independently, selected from hydrogen, C<sub>1-10</sub> alkyl, C<sub>1-10</sub> perhaloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, heteroC<sub>1-10</sub> alkyl, heteroC<sub>2-10</sub> alkenyl, heteroC<sub>2-10</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>cc</sup> groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups;

each instance of R<sup>dd</sup> is, independently, selected from halogen, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, -SO<sub>2</sub>H, -SO<sub>3</sub>H, -OH, -OR<sup>ee</sup>, -ON(R<sup>ff</sup>)<sub>2</sub>, -N(R<sup>ff</sup>)<sub>2</sub>, -N(R<sup>ff</sup>)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -N(OR<sup>ee</sup>)R<sup>ff</sup>, -SH, -SR<sup>ee</sup>, -SSR<sup>ee</sup>, -C(=O)R<sup>ee</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>R<sup>ee</sup>, -OC(=O)R<sup>ee</sup>, -OCO<sub>2</sub>R<sup>ee</sup>, -C(=O)N(R<sup>ff</sup>)<sub>2</sub>, -OC(=O)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>C(=O)R<sup>ee</sup>, -NR<sup>ff</sup>CO<sub>2</sub>R<sup>ee</sup>, -NR<sup>ff</sup>C(=O)N(R<sup>ff</sup>)<sub>2</sub>, -C(=NR<sup>ff</sup>)OR<sup>ee</sup>, -OC(=NR<sup>ff</sup>)R<sup>ee</sup>, -OC(=NR<sup>ff</sup>)OR<sup>ee</sup>, -C(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -OC(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>C(=NR<sup>ff</sup>)N(R<sup>ff</sup>)<sub>2</sub>, -NR<sup>ff</sup>SO<sub>2</sub>R<sup>ee</sup>, -SO<sub>2</sub>N(R<sup>ff</sup>)<sub>2</sub>, -SO<sub>2</sub>R<sup>ee</sup>, -SO<sub>2</sub>OR<sup>ee</sup>, -OSO<sub>2</sub>R<sup>ee</sup>, -S(=O)R<sup>ee</sup>, -Si(R<sup>ee</sup>)<sub>3</sub>, -OSi(R<sup>ee</sup>)<sub>3</sub>, -C(=S)N(R<sup>ff</sup>)<sub>2</sub>, -C(=O)SR<sup>ee</sup>, -C(=S)SR<sup>ee</sup>, -SC(=S)SR<sup>ee</sup>, -P(=O)(OR<sup>ee</sup>)<sub>2</sub>, -P(=O)(R<sup>ee</sup>)<sub>2</sub>, -OP(=O)(R<sup>ee</sup>)<sub>2</sub>, -OP(=O)(OR<sup>ee</sup>)<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perhaloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, heteroC<sub>1-6</sub>alkyl, heteroC<sub>2-6</sub>alkenyl, heteroC<sub>2-6</sub>alkynyl, C<sub>3-10</sub> carbocyclyl, 3-10 membered heterocyclyl, C<sub>6-10</sub> aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>ee</sup>

groups, or two geminal R<sup>dd</sup> substituents can be joined to form =O or =S; wherein X<sup>-</sup> is a counterion;

each instance of R<sup>ee</sup> is, independently, selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perhaloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, heteroC<sub>1-6</sub> alkyl, heteroC<sub>2-6</sub> alkenyl, heteroC<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, C<sub>6-10</sub> aryl, 3-10 membered heterocyclyl, and 3-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>gg</sup> groups;

each instance of R<sup>ff</sup> is, independently, selected from hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perhaloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, heteroC<sub>1-6</sub> alkyl, heteroC<sub>2-6</sub> alkenyl, heteroC<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-10 membered heterocyclyl, C<sub>6-10</sub> aryl and 5-10 membered heteroaryl, or two R<sup>ff</sup> groups are joined to form a 3-10 membered heterocyclyl or 5-10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>gg</sup> groups; and

each instance of R<sup>gg</sup> is, independently, halogen, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, -SO<sub>2</sub>H, -SO<sub>3</sub>H, -OH, -OC<sub>1-6</sub> alkyl, -ON(C<sub>1-6</sub> alkyl)<sub>2</sub>, -N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -N(C<sub>1-6</sub> alkyl)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -NH(C<sub>1-6</sub> alkyl)<sub>2</sub><sup>+</sup>X<sup>-</sup>, -NH<sub>2</sub>(C<sub>1-6</sub> alkyl)<sup>+</sup>X<sup>-</sup>, -NH<sub>3</sub><sup>+</sup>X<sup>-</sup>, -N(OC<sub>1-6</sub> alkyl)(C<sub>1-6</sub> alkyl), -N(OH)(C<sub>1-6</sub> alkyl), -NH(OH), -SH, -SC<sub>1-6</sub> alkyl, -SS(C<sub>1-6</sub> alkyl), -C(=O)(C<sub>1-6</sub> alkyl), -CO<sub>2</sub>H, -CO<sub>2</sub>(C<sub>1-6</sub> alkyl), -OC(=O)(C<sub>1-6</sub> alkyl), -OCO<sub>2</sub>(C<sub>1-6</sub> alkyl), -C(=O)NH<sub>2</sub>, -C(=O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OC(=O)NH(C<sub>1-6</sub> alkyl), -NHC(=O)(C<sub>1-6</sub> alkyl), -N(C<sub>1-6</sub> alkyl)C(=O)(C<sub>1-6</sub> alkyl), -NHCO<sub>2</sub>(C<sub>1-6</sub> alkyl), -NHC(=O)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -NHC(=O)NH(C<sub>1-6</sub> alkyl), -NHC(=O)NH<sub>2</sub>, -C(=NH)O(C<sub>1-6</sub> alkyl), -OC(=NH)(C<sub>1-6</sub> alkyl), -OC(=NH)OC<sub>1-6</sub> alkyl, -C(=NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -C(=NH)NH(C<sub>1-6</sub> alkyl), -C(=NH)NH<sub>2</sub>, -OC(=NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OC(NH)NH(C<sub>1-6</sub> alkyl), -OC(NH)NH<sub>2</sub>, -NHC(NH)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -NHC(=NH)NH<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1-6</sub> alkyl), -SO<sub>2</sub>N(C<sub>1-6</sub> alkyl)<sub>2</sub>, -SO<sub>2</sub>NH(C<sub>1-6</sub> alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -SO<sub>2</sub>C<sub>1-6</sub> alkyl, -SO<sub>2</sub>OC<sub>1-6</sub> alkyl, -OSO<sub>2</sub>C<sub>1-6</sub> alkyl, -SOC<sub>1-6</sub> alkyl, -Si(C<sub>1-6</sub> alkyl)<sub>3</sub>, -OSi(C<sub>1-6</sub> alkyl)<sub>3</sub>, -C(=S)N(C<sub>1-6</sub> alkyl)<sub>2</sub>, C(=S)NH(C<sub>1-6</sub> alkyl), C(=S)NH<sub>2</sub>, -C(=O)S(C<sub>1-6</sub> alkyl), -C(=S)SC<sub>1-6</sub> alkyl, -SC(=S)SC<sub>1-6</sub> alkyl, -P(=O)(OC<sub>1-6</sub> alkyl)<sub>2</sub>, -P(=O)(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OP(=O)(C<sub>1-6</sub> alkyl)<sub>2</sub>, -OP(=O)(OC<sub>1-6</sub> alkyl)<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> perhaloalkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, heteroC<sub>1-6</sub> alkyl, heteroC<sub>2-6</sub> alkenyl, heteroC<sub>2-6</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, C<sub>6-10</sub> aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R<sup>gg</sup> substituents can be joined to form =O or =S; wherein X<sup>-</sup> is a counterion.

**[0045]** A “counterion” or “anionic counterion” is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (e.g.,  $\text{F}^-$ ,  $\text{Cl}^-$ ,  $\text{Br}^-$ ,  $\text{I}^-$ ),  $\text{NO}_3^-$ ,  $\text{ClO}_4^-$ ,  $\text{OH}^-$ ,  $\text{H}_2\text{PO}_4^-$ ,  $\text{HCO}_3^-$ ,  $\text{HSO}_4^-$ , sulfonate ions (e.g., methansulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (e.g., acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like),  $\text{BF}_4^-$ ,  $\text{PF}_4^-$ ,  $\text{PF}_6^-$ ,  $\text{AsF}_6^-$ ,  $\text{SbF}_6^-$ ,  $\text{B}[3,5-(\text{CF}_3)_2\text{C}_6\text{H}_3]_4^-$ ,  $\text{B}(\text{C}_6\text{F}_5)_4^-$ ,  $\text{BPh}_4^-$ ,  $\text{Al}(\text{OC}(\text{CF}_3)_3)_4^-$ , and carborane anions (e.g.,  $\text{CB}_{11}\text{H}_{12}^-$  or  $(\text{HCB}_{11}\text{Me}_5\text{Br}_6)^-$ ). Exemplary counterions which may be multivalent include  $\text{CO}_3^{2-}$ ,  $\text{HPO}_4^{2-}$ ,  $\text{PO}_4^{3-}$ ,  $\text{B}_4\text{O}_7^{2-}$ ,  $\text{SO}_4^{2-}$ ,  $\text{S}_2\text{O}_3^{2-}$ , carboxylate anions (e.g., tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

**[0046]** “Halo” or “halogen” refers to fluorine (fluoro,  $-\text{F}$ ), chlorine (chloro,  $-\text{Cl}$ ), bromine (bromo,  $-\text{Br}$ ), or iodine (iodo,  $-\text{I}$ ).

**[0047]** The term “acyl” refers to a group having the general formula  $-\text{C}(=\text{O})\text{R}^{X1}$ ,  $-\text{C}(=\text{O})\text{OR}^{X1}$ ,  $-\text{C}(=\text{O})-\text{O}-\text{C}(=\text{O})\text{R}^{X1}$ ,  $-\text{C}(=\text{O})\text{SR}^{X1}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{X1})_2$ ,  $-\text{C}(=\text{S})\text{R}^{X1}$ ,  $-\text{C}(=\text{S})\text{N}(\text{R}^{X1})_2$ , and  $-\text{C}(=\text{S})\text{S}(\text{R}^{X1})$ ,  $-\text{C}(=\text{NR}^{X1})\text{R}^{X1}$ ,  $-\text{C}(=\text{NR}^{X1})\text{OR}^{X1}$ ,  $-\text{C}(=\text{NR}^{X1})\text{SR}^{X1}$ , and  $-\text{C}(=\text{NR}^{X1})\text{N}(\text{R}^{X1})_2$ , wherein  $\text{R}^{X1}$  is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di- arylamino, or mono- or di- heteroaryl amino; or two  $\text{R}^{X1}$  groups taken together form a 5- to 6-membered heterocyclic ring. Exemplary acyl groups include aldehydes ( $-\text{CHO}$ ), carboxylic acids ( $-\text{CO}_2\text{H}$ ), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents

include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (e.g., aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylarnino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[0048] “Alkoxy” or “alkoxyl” refers to a radical of the formula: —O—alkyl.

[0049] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, —OH, —OR<sup>aa</sup>, —N(R<sup>cc</sup>)<sub>2</sub>, —CN, —C(=O)R<sup>aa</sup>, —C(=O)N(R<sup>cc</sup>)<sub>2</sub>, —CO<sub>2</sub>R<sup>aa</sup>, —SO<sub>2</sub>R<sup>aa</sup>, —C(=NR<sup>bb</sup>)R<sup>aa</sup>, —C(=NR<sup>cc</sup>)OR<sup>aa</sup>, —C(=NR<sup>cc</sup>)N(R<sup>cc</sup>)<sub>2</sub>, —SO<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, —SO<sub>2</sub>R<sup>cc</sup>, —SO<sub>2</sub>OR<sup>cc</sup>, —SOR<sup>aa</sup>, —C(=S)N(R<sup>cc</sup>)<sub>2</sub>, —C(=O)SR<sup>cc</sup>, —C(=S)SR<sup>cc</sup>, —P(=O)(OR<sup>cc</sup>)<sub>2</sub>, —P(=O)(R<sup>aa</sup>)<sub>2</sub>, —P(=O)(N(R<sup>cc</sup>)<sub>2</sub>), C<sub>1-10</sub> alkyl, C<sub>1-10</sub> perhaloalkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, heteroC<sub>1-10</sub>alkyl, heteroC<sub>2-10</sub>alkenyl, heteroC<sub>2-10</sub>alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl, or two R<sup>cc</sup> groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups, and wherein R<sup>aa</sup>, R<sup>bb</sup>, R<sup>cc</sup> and R<sup>dd</sup> are as defined above.

[0050] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, —OH, —OR<sup>aa</sup>, —N(R<sup>cc</sup>)<sub>2</sub>, —C(=O)R<sup>aa</sup>, —C(=O)N(R<sup>cc</sup>)<sub>2</sub>, —CO<sub>2</sub>R<sup>aa</sup>, —SO<sub>2</sub>R<sup>aa</sup>, —C(=NR<sup>cc</sup>)R<sup>aa</sup>, —C(=NR<sup>cc</sup>)OR<sup>aa</sup>, —C(=NR<sup>cc</sup>)N(R<sup>cc</sup>)<sub>2</sub>, —SO<sub>2</sub>N(R<sup>cc</sup>)<sub>2</sub>, —SO<sub>2</sub>R<sup>cc</sup>, —SO<sub>2</sub>OR<sup>cc</sup>, —SOR<sup>aa</sup>, —C(=S)N(R<sup>cc</sup>)<sub>2</sub>, —C(=O)SR<sup>cc</sup>, —C(=S)SR<sup>cc</sup>, C<sub>1-10</sub> alkyl (e.g., aralkyl, heteroaralkyl), C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>3-10</sub> carbocyclyl, 3-14 membered heterocyclyl, C<sub>6-14</sub> aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R<sup>dd</sup> groups, and wherein R<sup>aa</sup>, R<sup>bb</sup>, R<sup>cc</sup> and R<sup>dd</sup> are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3<sup>rd</sup> edition, John Wiley & Sons, 1999.

[0051] For example, nitrogen protecting groups such as amide groups (e.g.,  $-\text{C}(=\text{O})\text{R}^{\text{aa}}$ ) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-dithiobenzoyloxyacetyl)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0052] Nitrogen protecting groups, such as carbamate groups (e.g.,  $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$ ), include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluoroenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (Msz), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-

6-chromonylmethyl carbamate (Troc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0053] Nitrogen protecting groups, such as sulfonamide groups (e.g.,  $-S(=O)_2R^{22}$ ), include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6,-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms),  $\beta$ -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0054] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethylsilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypropylamine, *N*-

(1-isopropyl-4-nitro-2-oxo-3-pyroolin-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N*',*N*'-dimethylaminomethylene)amine, *N*,*N*'-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramides, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

**[0055]** In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an “hydroxyl protecting group”). Oxygen protecting groups include, but are not limited to,  $-R^{aa}$ ,  $-N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ ,  $-C(=O)R^{aa}$ ,  $-CO_2R^{aa}$ ,  $-C(=O)N(R^{bb})_2$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{bb})OR^{aa}$ ,  $-C(=NR^{bb})N(R^{bb})_2$ ,  $-S(=O)R^{aa}$ ,  $-SO_2R^{aa}$ ,  $-Si(R^{aa})_3$ ,  $-P(R^{cc})_2$ ,  $-P(R^{cc})_3^+X^-$ ,  $-P(OR^{cc})_2$ ,  $-P(OR^{cc})_3^+X^-$ ,  $-P(=O)(R^{aa})_2$ ,  $-P(=O)(OR^{cc})_2$ , and  $-P(=O)(N(R^{bb})_2)_2$ , wherein  $X^-$ ,  $R^{aa}$ ,  $R^{bb}$ , and  $R^{cc}$  are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in Protecting Groups in Organic Synthesis, T. W. Greene and P. G. M. Wuts, 3<sup>rd</sup> edition, John Wiley & Sons, 1999.

**[0056]** Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-

(trimethylsilyl)ethoxymethyl (SEMORE), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, tetrahydrothiopyran, 1–methoxycyclohexyl, 4–methoxytetrahydropyranyl (MTHP), 4–methoxytetrahydrothiopyran, 4–methoxytetrahydrothiopyran S,S–dioxide, 1–[(2–chloro–4–methyl)phenyl]–4–methoxypiperidin–4–yl (CTMP), 1,4–dioxan–2–yl, tetrahydrofuran, tetrahydrothiofuran, 2,3,3a,4,5,6,7,7a–octahydro–7,8,8–trimethyl–4,7–methanobenzofuran–2–yl, 1–ethoxyethyl, 1–(2–chloroethoxy)ethyl, 1–methyl–1–methoxyethyl, 1–methyl–1–benzyloxyethyl, 1–methyl–1–benzyloxy–2–fluoroethyl, 2,2,2–trichloroethyl, 2–trimethylsilylethyl, 2–(phenylselenyl)ethyl, *t*–butyl, allyl, *p*–chlorophenyl, *p*–methoxyphenyl, 2,4–dinitrophenyl, benzyl (Bn), *p*–methoxybenzyl, 3,4–dimethoxybenzyl, *o*–nitrobenzyl, *p*–nitrobenzyl, *p*–halobenzyl, 2,6–dichlorobenzyl, *p*–cyanobenzyl, *p*–phenylbenzyl, 2–picolyl, 4–picolyl, 3–methyl–2–picolyl *N*–oxido, diphenylmethyl, *p,p'*–dinitrobenzhydryl, 5–dibenzosuberyl, triphenylmethyl,  $\alpha$ –naphthyl diphenylmethyl, *p*–methoxyphenyl diphenylmethyl, di(*p*–methoxyphenyl)phenylmethyl, tri(*p*–methoxyphenyl)methyl, 4–(4’–bromophenacyloxyphenyl)diphenylmethyl, 4,4’,4”–tris(4,5–dichlorophthalimidophenyl)methyl, 4,4’,4”–tris(levulinoyloxyphenyl)methyl, 4,4’,4”–tris(benzoxyloxyphenyl)methyl, 3–(imidazol–1–yl)bis(4’,4”–dimethoxyphenyl)methyl, 1,1–bis(4–methoxyphenyl)–1’–pyrenylmethyl, 9–anthryl, 9–(9–phenyl)xanthenyl, 9–(9–phenyl–10–oxo)anthryl, 1,3–benzodisulfuran–2–yl, benzisothiazolyl S,S–dioxide, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*–butyldimethylsilyl (TBDMS), *t*–butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri–*p*–xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*–butylmethoxyphenylsilyl (TBMPs), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*–chlorophenoxyacetate, 3–phenylpropionate, 4–oxopentanoate (levulinate), 4,4–(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4–methoxycrotonate, benzoate, *p*–phenylbenzoate, 2,4,6–trimethylbenzoate (mesitoate), alkyl methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate alkyl allyl carbonate, alkyl *p*–nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*–methoxybenzyl carbonate, alkyl 3,4–dimethoxybenzyl carbonate, alkyl *o*–nitrobenzyl

carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinate, (*E*)-2-methyl-2-butenoate, *o*-(methoxyacetyl)benzoate,  $\alpha$ -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamide, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

**[0057]** In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a “thiol protecting group”). Sulfur protecting groups include, but are not limited to,  $-R^{aa}$ ,  $-N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ ,  $-C(=O)R^{aa}$ ,  $-CO_2R^{aa}$ ,  $-C(=O)N(R^{bb})_2$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{bb})OR^{aa}$ ,  $-C(=NR^{bb})N(R^{bb})_2$ ,  $-S(=O)R^{aa}$ ,  $-SO_2R^{aa}$ ,  $-Si(R^{aa})_3$ ,  $-P(R^{cc})_2$ ,  $-P(R^{cc})_3^+X^-$ ,  $-P(OR^{cc})_2$ ,  $-P(OR^{cc})_3^+X^-$ ,  $-P(=O)(R^{aa})_2$ ,  $-P(=O)(OR^{cc})_2$ , and  $-P(=O)(N(R^{bb})_2)_2$ , wherein  $R^{aa}$ ,  $R^{bb}$ , and  $R^{cc}$  are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3<sup>rd</sup> edition, John Wiley & Sons, 1999.

**[0058]** As used herein, a “leaving group” (LG) is an art-understood term referring to a molecular fragment that departs with a pair of electrons in heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. As used herein, a leaving group can be an atom or a group capable of being displaced by a nucleophile. See, for example, Smith, *March’s Advanced Organic Chemistry* 6th ed. (501-502). Exemplary leaving groups include, but are not limited to, halo (e.g., chloro, bromo, iodo) and activated substituted hydroxyl groups (e.g.,  $-OC(=O)SR^{aa}$ ,  $-OC(=O)R^{aa}$ ,  $-OCO_2R^{aa}$ ,  $-OC(=O)N(R^{bb})_2$ ,  $-OC(=NR^{bb})R^{aa}$ ,  $-OC(=NR^{bb})OR^{aa}$ ,  $-OC(=NR^{bb})N(R^{bb})_2$ ,  $-OS(=O)R^{aa}$ ,  $-OSO_2R^{aa}$ ,  $-OP(R^{cc})_2$ ,  $-OP(R^{cc})_3$ ,  $-OP(=O)_2R^{aa}$ ,  $-OP(=O)(R^{aa})_2$ ,  $-OP(=O)(OR^{cc})_2$ ,  $-OP(=O)_2N(R^{bb})_2$ , and  $-OP(=O)(NR^{bb})_2$ , wherein  $R^{aa}$ ,  $R^{bb}$ , and  $R^{cc}$  are as defined herein). Examples of suitable leaving groups include, but are not limited to, halogen (such as F, Cl, Br, or I (iodine)), alkoxy carbonyloxy, aryloxy carbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (e.g., acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N,O*-dimethylhydroxylamino, pixyl, and haloformates. In some cases, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, –

OTs), methanesulfonate (mesylate, -OMs), *p*-bromobenzenesulfonyloxy (brosylate, -OBs), or trifluoromethanesulfonate (triflate, -OTf). In some cases, the leaving group is a brosylate, such as *p*-bromobenzenesulfonyloxy. In some cases, the leaving group is a nosylate, such as 2-nitrobenzenesulfonyloxy. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide (e.g., formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

[0059] These and other exemplary substituents are described in more detail in the Detailed Description, Figures, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

#### *Other definitions*

[0060] The following definitions are more general terms used throughout the present application:

[0061] The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate,

persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and  $N^+(C_{1-4} \text{ alkyl})_4^-$  salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate, and aryl sulfonate.

[0062] The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds of Formulae (I') and (II) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0063] The term “hydrate” refers to a compound that is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula  $R \cdot x \text{ H}_2\text{O}$ , wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ( $R \cdot 0.5 \text{ H}_2\text{O}$ )), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ( $R \cdot 2 \text{ H}_2\text{O}$ ) and hexahydrates ( $R \cdot 6 \text{ H}_2\text{O}$ )).

[0064] The term “tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of  $\pi$  electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[0065] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0066] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[0067] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[0068] The term “polymorphs” refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0069] The term “prodrugs” refer to compounds, including derivatives of the compounds of Formulae (I') and (II), which have cleavable groups and become by solvolysis or under physiological conditions the compounds of Formulae (I') and (II) which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, ester derivatives and the like. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed

anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C<sub>1</sub> to C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl, aryl, C<sub>7</sub>-C<sub>12</sub> substituted aryl, and C<sub>7</sub>-C<sub>12</sub> arylalkyl esters of the compounds of Formulae (I') and (II) may be preferred.

[0070] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non-human animal may be a transgenic animal.

[0071] The terms “administer,” “administering,” or “administration,” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof.

[0072] The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a “pathological condition” (*e.g.*, a disease, disorder, or condition, or one or more signs or symptoms thereof) described herein. In some embodiments, treatment may be administered after one or more signs or symptoms have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0073] The terms “condition,” “disease,” and “disorder” are used interchangeably.

[0074] An “effective amount” of a compound of Formula (I') or (II) refers to an amount sufficient to elicit the desired biological response, *i.e.*, treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound of Formula (I') or (II) may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses

therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of an inventive compound may reduce the tumor burden or stop the growth or spread of a tumor.

[0075] A “therapeutically effective amount” of a compound of Formula (I') or (II) is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0076] A “prophylactically effective amount” of a compound of Formula (I') or (II) is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0077] A “proliferative disease” refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (e.g., metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (e.g., collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, “malignant neoplasms”), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases.

[0078] The terms “neoplasm” and “tumor” are used interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be “benign” or “malignant,” depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A “benign neoplasm” is

generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain “benign” tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor’s neoplastic cells, and these tumors are referred to as “pre-malignant neoplasms.” An exemplary pre-malignant neoplasm is a teratoma. In contrast, a “malignant neoplasm” is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites.

[0079] The term “metastasis,” “metastatic,” or “metastasize” refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a “secondary tumor” or “secondary cell mass” of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[0080] The term “cancer” refers to a malignant neoplasm (*Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (e.g., lymphangiosarcoma, lymphangioendothelioma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (e.g., cholangiocarcinoma); bladder cancer; breast cancer (e.g., adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (e.g., meningioma, glioblastoma, glioma (e.g., astrocytoma, oligodendrogloma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (e.g., cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (e.g., colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endothelioma (e.g., Kaposi’s sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (e.g., uterine cancer, uterine sarcoma); esophageal cancer (e.g., adenocarcinoma of the esophagus, Barrett’s adenocarcinoma); Ewing’s sarcoma; eye cancer (e.g., intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer;

gastric cancer (e.g., stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (e.g., head and neck squamous cell carcinoma, oral cancer (e.g., oral squamous cell carcinoma), throat cancer (e.g., laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (e.g., leukemia such as acute lymphocytic leukemia (ALL) (e.g., B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (e.g., B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (e.g., B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (e.g., B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (e.g., B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (e.g., B-cell NHL such as diffuse large cell lymphoma (DLCL) (e.g., diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (e.g., mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (e.g., cutaneous T-cell lymphoma (CTCL) (e.g., mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (e.g., alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (e.g., nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma); liver cancer (e.g., hepatocellular cancer (HCC), malignant hepatoma); lung cancer (e.g., bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (e.g., systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (e.g., polycythemia vera (PV), essential thrombocythosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (e.g., neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (e.g., gastroenteropancreatic

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

**[0081]** The term “angiogenesis” refers to the formation and the growth of new blood vessels. Normal angiogenesis occurs in the healthy body of a subject for healing wounds and for restoring blood flow to tissues after injury. The healthy body controls angiogenesis through a number of means, *e.g.*, angiogenesis-stimulating growth factors and angiogenesis inhibitors. Many disease states, such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, and psoriasis, are characterized by abnormal (*i.e.*, increased or excessive) angiogenesis. Abnormal or pathological angiogenesis refers to angiogenesis greater than that in a normal body, especially angiogenesis in an adult not related to normal angiogenesis (*e.g.*, menstruation or wound healing). Abnormal angiogenesis can provide new blood vessels that feed diseased tissues and/or destroy normal tissues, and in the case of cancer, the new vessels can allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases). In certain embodiments, the angiogenesis is pathological angiogenesis.

**[0082]** An “inflammatory disease” refers to a disease caused by, resulting from, or resulting in inflammation. The term “inflammatory disease” may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from

infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthroseitis, rheumatoid arthritis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (e.g., Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (e.g., poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis.

[0083] An "autoimmune disease" refers to a disease arising from an inappropriate immune response of the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (e.g., in autoimmune thyroiditis) or involve a particular tissue in different places (e.g., Goodpasture's disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases

is typically with immunosuppression, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodpasture's syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosus, rheumatoid, arthritis, psoriatic arthritis, systemic lupus erythematosus, psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener's granulomatosis, microscopic polyangiitis), uveitis, Sjogren's syndrome, Crohn's disease, Reiter's syndrome, ankylosing spondylitis, Lyme arthritis, Guillain-Barré syndrome, Hashimoto's thyroiditis, and cardiomyopathy.

**[0084]** The term "autoinflammatory disease" refers to a category of diseases that are similar but different from autoimmune diseases. Autoinflammatory and autoimmune diseases share common characteristics in that both groups of disorders result from the immune system attacking a subject's own tissues and result in increased inflammation. In autoinflammatory diseases, a subject's innate immune system causes inflammation for unknown reasons. The innate immune system reacts even though it has never encountered autoantibodies or antigens in the subject. Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs. Autoinflammatory diseases include, but are not limited to, familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS), deficiency of the interleukin-1 receptor antagonist (DIRA), and Behcet's disease.

**[0085]** The term "biological sample" refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucus, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample. Biological samples also include those biological samples that are transgenic, such as transgenic oocyte, sperm cell, blastocyst, embryo, fetus, donor cell, or cell nucleus.

[0086] A “protein” or “peptide” comprises a polymer of amino acid residues linked together by peptide bonds. The term refers to proteins, polypeptides, and peptides of any size, structure, or function. Typically, a protein will be at least three amino acids long. A protein may refer to an individual protein or a collection of proteins. Inventive proteins preferably contain only natural amino acids, although non-natural amino acids (*i.e.*, compounds that do not occur in nature but that can be incorporated into a polypeptide chain) and/or amino acid analogs as are known in the art may alternatively be employed. Also, one or more of the amino acids in an inventive protein may be modified, for example, by the addition of a chemical entity such as a carbohydrate group, a hydroxyl group, a phosphate group, a farnesyl group, an isofarnesyl group, a fatty acid group, a linker for conjugation or functionalization, or other modification. A protein may also be a single molecule or may be a multi-molecular complex. A protein may be a fragment of a naturally occurring protein or peptide. A protein may be naturally occurring, recombinant, or synthetic, or any combination of these.

[0087] The term “kinase” refers to any enzyme that catalyzes the addition of phosphate groups to an amino acid residue of a substrate (*e.g.*, a protein or nucleoside). For example, a serine kinase catalyzes the addition of a phosphate group to serine residue in a protein. In certain embodiments, the kinase is a protein kinase. Examples of kinases include, but are not limited to, a CMGC kinase (*e.g.*, a cyclin-dependent kinase (CDK, *e.g.*, CDK1, CDK2, CDK2, CDK4, CDK5, CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK13, CDK14, CDK16, CDK20), a mitogen-activated protein kinase (MAPK, *e.g.*, MAPK1, MAPK3, MAPK4, MAPK6, MAPK7, MAPK8, MAPK9, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK15), a glycogen synthase kinase 3 (GSK3, *e.g.*, GSK3 $\alpha$ , GSK3 $\beta$ ), or a CDC-like kinase (CLK, *e.g.*, CLK1, CLK2, CLK3, CLK4)), an AGC kinase (*e.g.*, protein kinase A (PKA), protein kinase C (PKC), protein kinase G (PKG)), a Ca<sup>2+</sup>/calmodulin-dependent protein kinase (CaM kinase, *e.g.*, a specialized CaM kinase, a multifunctional CaM kinase), a casein kinase 1 (CK1, *e.g.*, CK1alpha, CK1beta 1, CK1gamma 1, CK1gamma 2, CK1gamma 3, CK1delta, CK1epsilon), a STE kinase (*e.g.*, a homolog of yeast Sterile 7, Sterile 11, or Sterile 20 kinase), a tyrosine kinase (TK, *e.g.*, a receptor tyrosine kinase (RTK), a non-receptor tyrosine kinase (nRTK)), and a tyrosine-kinase-like kinase (TKL, *e.g.*, a mixed lineage kinase (MLK), RAF, a serine threonine kinase receptor (STKR), a leucine rich repeat kinase (LRRK), a LIM domain kinase (LIMK), a testis

expressed serine kinase (TESK), an IL1 receptor associated kinase (IRAK), a receptor interacting protein kinase (RIPK)).

**[0088]** The term “CDK” refers to a cyclin-dependent kinase. A CDK binds a cyclin (e.g., Cyclin H), which is a regulatory protein. CDKs phosphorylate their substrates at serines and threonines. The consensus sequence for the phosphorylation site in the amino acid sequence of a CDK substrate is [S/T\*]PX[K/R], where S/T\* is the phosphorylated serine or threonine, P is proline, X is any amino acid, K is lysine, and R is arginine. CDKs include CDK1, CDK2, CDK2, CDK4, CDK5, CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK14, CDK16, and CDK20.

**[0089]** CDK7, cyclin-dependent kinase 7, is a CDK, wherein the substrate is Cyclin H, MAT1 (e.g., MNAT1), or Cyclin H and MAT1. CDK7 is alternatively referred to as CAK1, HCAK, MO15, STK1, CDKN7, and p39MO15. Non-limiting examples of the nucleotide and protein sequences for human CDK7 are described in GenBank Accession Number:

NP\_001790. The amino acid sequence of this CDK7 is as follows:

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MA LDVKSRAKRYEKLDFLGE GQFATVYKARDKNTNQIVAIKKIKLGH RSEAKDGINR  
TALREIKL I QELSHPNI I GLLDAFGHKSNISLVFDFMETDLEVIKDN SLV LTPSHI  
KAYMLMTLQGLEYLHQHWILH RDLKPNNLLDENGVLKLADFGLA KSFGSPN RAYTH  
QVVTRWYRAPELLFGARMYGVGVDMWAVGCILAELL RVPFLPGDSDL DQLTRIFET  
LGTPTEEQWPDMCSLPDYVTFKSFPG I PLHHI FSAAGDDLLDLI QGLFLFNP CARIT  
ATQALKMKYFSNRPGPTPGCQLPRPNCPVETLKEQSNPALAIKRKRTEALEQGLPK  
KLIF (SEQ ID NO:1)
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**[0090]** CDK12, cyclin-dependent kinase 12, is a CDK, wherein the substrate is Cyclin K or flavopiridol. CDK12 is alternatively referred to as Cdc2-related kinase, CDC2-related protein kinase 7, Cell division cycle 2-related protein kinase 7, Cell division protein kinase 12, CRK7, CRKR, CRKRS, cyclin-dependent kinase 12, or KIAA0904. Non-limiting examples of the nucleotide and protein sequences for human CDK12 are described in Uniprot Number: Q9NYV4. The amino acid sequence of this CDK12 is as follows:

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MPNSERHGGKKDGSGGASGTLQPSGGSSNSRERHRLVSKHKRHKSKHSKDMGLVTPEA  
ASLGTVIKPLVEYDDIISSDTFSDDMAFKLDRRENDERRGSDRS DR LHKHRHHQHRRSR  
DLLKAKQTEKEKSQEVS SKSGSMKDRISGSSKRSNEETDDYGKAQVAKSSKESRSSKLH  
KEKTRKERELKSGHKDRSKSHRKRET PKSYKTVDSPKRRSRSPHRK WSDSSKQDDSPSGA  
SYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSPPYKEPSAYQSSTRSPSPYSRRQR  
SVSPYSRRRSSSYERSGSYSGRSPSPYGR RRS SPSFLSKRSLSRSPSRKSMKSRSRSP  
AYSRHSSSHSKKKRSSSRHSSISP VRLPLNSSLGAELS RKK KERA AAAA AKMDGKES  
KGSPVFLPRKENSSVEAKD S GLESKKLPRSVKLEKSAPDTEL VNVTHLNTEVKNSSDTGK  
VKLDENSEKHLVKDLKAQGTRDSKPIALKEEIVTPKETETSEKTPPLPTIASPPPPLP  
TTT P P QTPPLPPLPPIPALPQOPPLPPSQPAFSQV PASSTSTLPPSTHSKTS A VSSQAN
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SQPPVQSVKTQSVTAAIPHLKTSTLPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQ  
 RTRHLLTDLPLPPELPGGDLSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWG  
 KRCVDKFDIIGIIGEGTYGQVYAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQ  
 LIHRSVVMKIEVTDKQDALDFKKDKGAFYLVFYEYMDHDLMLLESGLVHFSEDHIKSF  
 KQLMEGLEYCHKKNFLHRDIKCSNILLNNSGQIKLADFGILARLYNSEEESRPYTNKVITLW  
 YRPPELLGEERYTPAIDVWSCGICLGEELFTKKPQIFQANLELAQLELISRLCGSPCPAVW  
 PDVIKLPYFNTMVKPKQYRRRLREEFSFIPSAALDLLDHMLTLDP SKRCTAEQTLQSDFL  
 KDVELSKMAPPDLPHWQDCHELWSKKRRQRQSGVVVEPPPSKTSRKETTSGTSTEPVK  
 NSSPAPPQAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQTDLSPQMAQLNI  
 HSNPEMQQQLEALNQSI SALTEATSQQQDSETMAPEESLKEAPSAPVILPSAEQTTLEAS  
 STPADMQNIALAVLLSQLMKTQE PAGSLEENNSDKNSGPQGPRRTPTMPQEEAACPPHIL  
 PPEKRPPEPPGPPPPPPPLVEGDLSSAPQELNPAVTAALLQLLSQPEAEPPGHLPEH  
 QALRPMEYSTRPRPNRTYGNTDGPETGFSAIIDERNSGPALTESLVQTLVKNRTFSGSL  
 SHLGESSSYQGTGSVQFPGDQDLRFARVPLALHPVVGQFLKAEGSSNSVVHAETKLQNY  
 GELPGTTGASSSGAGLHWGGPTQSSAYGKLYRGPTRVPPRGGRGRGVPY (SEQ ID NO:2)

**[0091]** CDK13, cyclin-dependent kinase 13, is a CDK, wherein the relevant cyclin is cyclin K and a reference inhibitor is the pan-CDK inhibitor flavopiridol and the c-terminal domain (CTD) of RNA-polymerase II is a physiological substrate. CDK13 is alternatively referred to as CHED; CDC2L; CDC2L5; or hCDK13. Non-limiting examples of the nucleotide and protein sequences for human CDK12 are described in GenBank Accession Number M80629. The amino acid sequence of this CDK13 is as follows:

MPSSSDTALGGGGGLSWAEKKLEERRKRRRFLSPQQPPLLLPQQLQPPPPPPPLF  
 LAAPGTAAAAAAAAASSSCFSPGPPLLEVKR LARGKRRAGGRQKRRRGPRAGQEAEKRRV  
 FSLPQPQDGGGGASSGGVTPLVEYEDVSSQSEQQLLLGASAATAATAAGGTGGSGGS  
 PASSSGTQRRGEGSERRPRRDRRSSGRSKERHREHRRDQORGSEASKSRSRHSHSGE  
 ERAEVAKSGSSSSGRRKSASATSSSSRKDRDSKAHSRTKSSKEPPSAYKEPPKAY  
 REDKTEPKAYRRRSLSPLGGRDDSPVSHRASQSLRSRKSPSPAGGGSPYSRRLPRSPS  
 PYSPYRSPSYRHSSYERGGDVSPSPYSSSWRRSRSPYSPVLRSGKRSRSPYSSRHS  
 RSRSRHRLSRSRSRHSSISPSTLT KSSLAAEILKNKKARAEEAARAAEAKAAEATKAA  
 EAAAKAAKASNTSTPTKGNTETSASASQTNHVVKVKKIKIEHAPS PSSGGTLKNDKAKTK  
 PPLQVTKVENNLIVDKATKKAVIVGKESKSAATKEESVSLKEKTPLTPSIGAKEKEQHV  
 ALVTSTLPLPLPMLPEDKEADSLRGNI SVKAVKKEVEKKLRCLLADLPLPPELPGGDD  
 LSKSPEEKKTATQLHSKRRPKICGPRYGETKEKDI DWGKRCVDKFDIIGIIGEGTYGQVY  
 KARDKDTGEMVALKKVRLDNEKEGFPITAIREIKILRQLTHQSIINMKEIVTDKE DALDF  
 KKDKGAFYLVFYEYMDHDLMLLESGLVHFENH IKSFM RQQLMEGLDYCHKKNFLHRDIK  
 SNILLNNRGQIKLADFGILARLYSSEEESRPYTNKVITLWYRPELLGEERYTPAIDVWSC  
 GCILGEELFTKKPQIFQANQELAOLELISRICGSPCPAVWPDV KLPYFNTMVKPKQYRRKL  
 REEFVFIPAAALDLFDYMLALDPSKRC TAEQALQCEFLRDVEPSKMP PDLPLWQDCHEL  
 WSKKRRRQKQMGMTDDVSTIKAPRKDLSLGLDDSRNTPQGVLPSSQLKSQGSSNVAPVK

TGPGQHLNHSELAILLNLQSKTSVNMAFDVQVLNIKVNSETOQQQLNキンLPAGILATGE  
KQTDPSKQQESSKPLGGIQPKVETDAAQAAVQSAFVLLTQLIKAQQSKQKD  
VLEERENGSGHEASLQLRPPPEPSTPVSGQDDLIQHQDMRILELTPEDRPRILPPDQR  
PPEPPEPPPVTEEDLDYRTENQHVPTTSSSLTDPHAGVKAALLQLLAQHQPQDDPKREGG  
IDYQAGDTYVSTSDYKDNFGSSSFSSAPYVSNDLGSSSAPPLERRSFIGNSDIQSLDNY  
STASSHSGGPPQPSAFSEFPSSVAGYDIYLNAQGMLFSGDKDHRFEYSHGPIAVLANS  
SDPSTGPESTHPLPAKMHNYYGGNLQENPSGPSLMHGQTWTSPAQGPYSGYRGHIST  
STGRGRGRGLPY (SEQ ID NO:3)

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0092] The accompanying drawings illustrate several embodiments of the invention and together with the description, serve to explain the principles of the invention.

[0093] *Figure 1.* Cyclin K pull down with THZ1-biotin probe. Exemplary compound BSJ-01-175-1 selectively binds intracellular CDK12/13-cyclin K complexes, and not CDK7-cyclin H complexes.

[0094] Jurkat cells were treated with THZ1 (1  $\mu$ M), compound BSJ-01-175-1 (1  $\mu$ M), or DMSO vehicle control for 6 hrs. Clarified cellular lysates from each treatment condition were then incubated with either 1  $\mu$ M THZ1-biotin, a concentration that binds CDK7-cyclin H, CDK12-cyclin K, and CDK13-cyclin K complexes. Lysates were incubated with THZ1-biotin overnight at 4 degrees Celsius. Subsequent addition of streptavidin -coated beads permits the immunoprecipitation of the indicated protein complexes. Following washing of beads with lysis buffer, the immunoprecipitated proteins were eluted from the beads by boiling in SDS buffer. Western blotting for cyclin K was used to identify precipitated CDK12-cyclin K or CDK13-cyclin K complexes. Western blotting for cyclin H was used to identify precipitated CDK7-cyclin H complexes. As THZ1 and compound BSJ-01-175-1 bind to their intended targets covalently, pretreatment of cells with these compounds would be expected to block subsequent capture and immunoprecipitation of these protein complexes with THZ1-biotin. The western blot data indicates that THZ1 binds intracellular CDK12-cyclin K, CDK13-cyclin K and CDK7-cyclin H complexes, while compound BSJ-01-175-1 binds intracellular CDK12-cyclin K and CDK13-cyclin K complexes selectively (and not CDK7-cyclin H).

[0095] *Figure 2* shows inhibition of Jurkat cell viability by exemplified compounds at a concentration of 1.0  $\mu$ M for 6 hours, followed by lysing and pulldown with Biotin-THZ1, and subsequent blot for cyclin K (Cyc K) and cyclin H (Cyc H). Compounds BSJ-01-033, BSJ-01-175, BSJ-01-202, BSJ-02-139, BSJ-02-109 and BSJ-02-108 show a loss in cyclin K

pulldown, indicating loss of CDK12 binding and BSJ-02-139 and BSJ-02-108 also show a loss in cyclin H pulldown, indicating loss of CDK7 binding.

[0096] *Figure 3.* shows exemplary mass spectrum labeling of CDK12 with compound BSJ-01-175. Compound BSJ-01-175 is able to label CDK12 once treated with a 5-fold excess of compound BSJ-01-175 for 1 hour at room temperature.

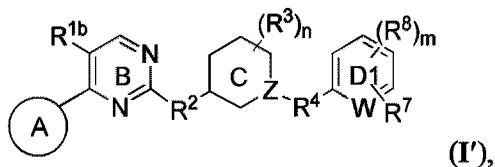
## **DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION**

[0097] The present invention provides compounds, which inhibit the activity of a kinase, for the prevention and/or treatment of a proliferative disease of a subject. In certain embodiments, the inventive compounds inhibit the activity of cyclin-dependent kinase (CDK). In certain embodiments, the inventive compounds inhibit the activity of cyclin-dependent kinase 12 (CDK12). The present invention further provides methods of using the compounds described herein, *e.g.*, as biological probes to study the inhibition of the activity of a kinase (*e.g.*, CDK (*e.g.*, CDK12)), and as therapeutics, *e.g.*, in the prevention and/or treatment of diseases associated with the overexpression and/or aberrant activity of the kinase (*e.g.*, CDK (*e.g.*, CDK12)). In certain embodiments, the diseases are proliferative diseases. The proliferative diseases include, but are not limited to, cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In certain embodiments, the cancer is associated with the overexpression and/or aberrant activity of a kinase (*e.g.*, CDK (*e.g.*, CDK12)). Also provided by the present disclosure are pharmaceutical compositions, kits, methods, and uses of a compound of Formulae (I') or (II) as described herein.

## *Compounds*

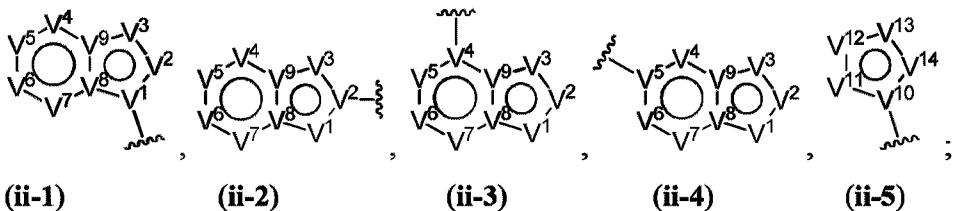
**[0098]** In certain embodiments, a compound described herein is a compound of any one of Formulae (I') and (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[0099] In one aspect of the present invention, provided are compounds of Formula (I'):



and pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomers thereof, wherein:

Ring A is an optionally substituted heteroaryl ring of any one of the Formulae (ii-1)-(ii-5):



or an optionally substituted 6-membered aryl or heteroaryl ring;  
 each instance of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ ,  $V^9$ ,  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  is independently O, S, N,  $N(R^{A1})$ , C, or  $C(R^{A2})$ ;

Z is  $-\text{CH}-$  or  $-\text{N}-$ ;

each instance of  $R^{A1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each instance of  $R^{A2}$  is independently selected from hydrogen, halogen, -CN, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{A2a}$ ,  $-N(R^{A2b})_2$ , and  $-SR^{A2a}$ , wherein  $R^{A2a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of  $R^{A2b}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or optionally two instances of  $R^{A2b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

any two  $R^{A1}$ , any two  $R^{A2}$ , or one  $R^{A1}$  and one  $R^{A2}$  are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

each of R<sup>1b</sup> is independently selected from hydrogen, halogen, optionally substituted

acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -OR<sup>B1a</sup>, -N(R<sup>B1b</sup>)<sub>2</sub>, and -SR<sup>B1a</sup>, wherein each occurrence of R<sup>B1a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom,

wherein each occurrence of R<sup>B1b</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or optionally two instances of R<sup>B1b</sup> are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

R<sup>2</sup> is -O-, -S-, -N(R<sup>6</sup>)-, or an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkylene, wherein one or more methylene units of the alkylene are optionally and independently replaced with -O-, -S-, or -N(R<sup>6</sup>)-;

each instance of R<sup>3</sup>, if present, is independently selected from halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -OR<sup>C1</sup>, -N(R<sup>C1a</sup>)<sub>2</sub>, and -SR<sup>C1</sup>, wherein each occurrence of R<sup>C1</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of R<sup>C1a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or optionally two instances of R<sup>C1a</sup> are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two R<sup>3</sup> groups bound to the same ring carbon atom are taken together to form =O, or  
 two R<sup>3</sup> groups bound to the same or different ring carbon atoms are joined to form an  
 optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted  
 aryl, or optionally substituted heteroaryl ring;

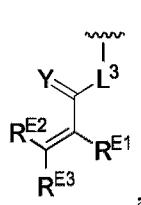
R<sup>4</sup> is selected from a bond, -C(=O)-, -O-, -S-, -N(R<sup>6</sup>)-, -S(=O)<sub>2</sub>-, and optionally  
 substituted C<sub>1</sub>-C<sub>4</sub> alkylene, wherein:

one or more methylene units of the alkylene other than a methylene unit bound to a  
 nitrogen atom is optionally and independently replaced with

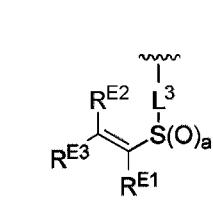
-C(=O), -O-, -S-, -N(R<sup>6</sup>)-, or -S(=O)<sub>2</sub>-;

each R<sup>6</sup> is independently selected from hydrogen and -C<sub>1</sub>-C<sub>6</sub> alkyl;

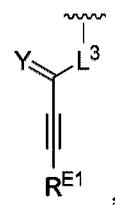
R<sup>7</sup> is a warhead of formula:



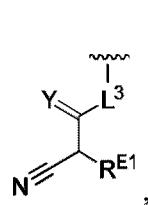
(i-1)



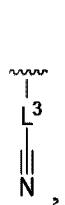
(i-2)



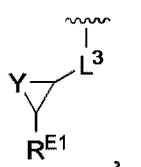
(i-3)



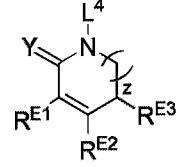
(i-4)



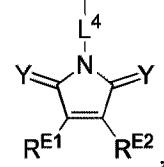
(i-5)



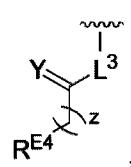
(i-6)



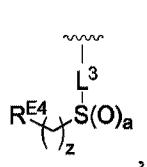
(i-7)



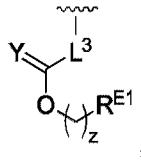
(i-8)



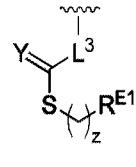
(i-9)



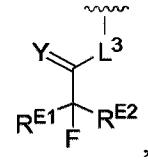
(i-10)



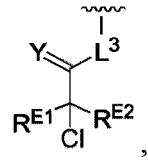
(i-11)



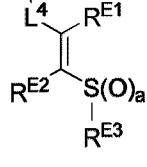
(i-12)



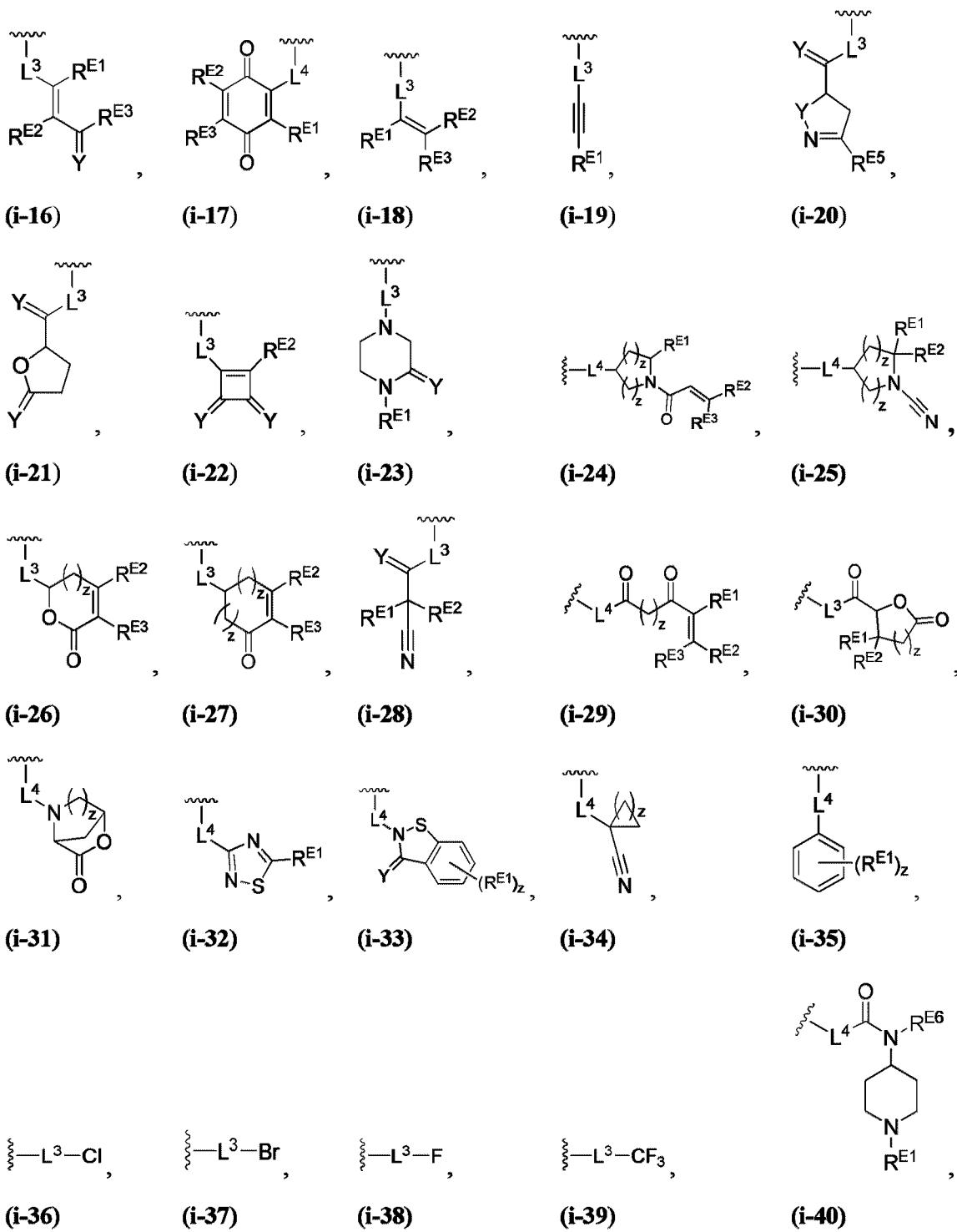
(i-13)

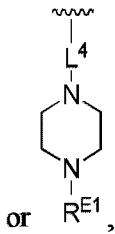


(i-14)



(i-15)





(i-41)

wherein:

$L^3$  is a bond or an optionally substituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C=O-$ ,  $-O-$ ,  $-S-$ ,  $-NR^{L3a}-$ ,  $-NR^{L3a}C(=O)-$ ,  $-C(=O)NR^{L3a}-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-NR^{L3a}C(=S)-$ ,  $-C(=S)NR^{L3a}-$ , *trans*- $CR^{L3b}=CR^{L3b}-$ , *cis*- $CR^{L3b}=CR^{L3b}-$ ,  $-C=C-$ ,  $-S(=O)-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^{L3a}-$ ,  $-NR^{L3a}S(=O)-$ ,  $-S(=O)_2-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^{L3a}-$ , or  $-NR^{L3a}S(=O)_2-$ , wherein  $R^{L3a}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group, and wherein each occurrence of  $R^{L3b}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{L3b}$  groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$L^4$  is a bond or an optionally substituted, branched or unbranched  $C_{1-6}$  hydrocarbon chain;

each of  $R^{E1}$ ,  $R^{E2}$ , and  $R^{E3}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-CN$ ,  $-CH_2OR^{EE}$ ,  $-CH_2N(R^{EE})_2$ ,  $-CH_2SR^{EE}$ ,  $-OR^{EE}$ ,  $-N(R^{EE})_2$ ,  $-Si(R^{EE})_3$ , or  $-SR^{EE}$ , wherein each instance of  $R^{EE}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{EE}$  groups are joined to form an optionally substituted heterocyclic ring; or  $R^{E1}$  and  $R^{E3}$ , or  $R^{E2}$  and  $R^{E3}$ , or  $R^{E1}$  and  $R^{E2}$  are joined

to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$R^{E4}$  is a leaving group;

$R^{E5}$  is halogen;

$R^{E6}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

each instance of  $Y$  is independently  $O$ ,  $S$ , or  $NR^{E7}$ , wherein  $R^{E7}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

$a$  is 1 or 2;

each instance of  $z$  is independently 0, 1, 2, 3, 4, 5, or 6, as valency permits; and

$W$  is  $-CR^{D1}-$  or  $-N=$ ;

each instance of  $R^8$ , if present, is independently selected from hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{D1}$ ,  $-N(R^{D1a})_2$ , and  $-SR^{D1}$ , wherein each occurrence of  $R^{D1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom,

wherein each occurrence of  $R^{D1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and a nitrogen protecting group, or optionally two instances of  $R^{D1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

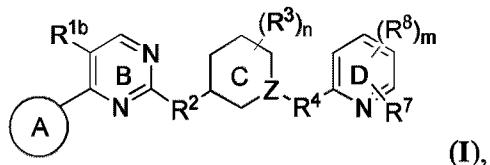
two  $R^8$  groups are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

$m$  is 0, 1, 2, 3 or 4; and

$n$  is 0, 1, 2, 3, 4, 5 or 6.

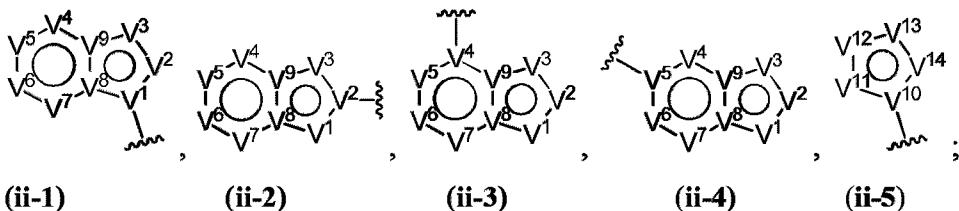
**[00100]** In certain embodiments, a compound of Formula (I') is of of Formula (I).

[00101] In one aspect of the present invention, provided are compounds of Formula (I):



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein:

Ring A is an optionally substituted heteroaryl ring of any one of the Formulae (ii-1)-(ii-5):



or an optionally substituted 6-membered aryl or heteroaryl ring;  
 each instance of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ ,  $V^9$ ,  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  is independently O, S, N,  $N(R^{A1})$ , C, or  $C(R^{A2})$ ;

Z is  $-\text{CH}-$  or  $-\text{N}-$ ;  
each instance of  $\text{R}^{\text{A}1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each instance of  $R^{A2}$  is independently selected from hydrogen, halogen, -CN, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{A2a}$ ,  $-N(R^{A2b})_2$ , and  $-SR^{A2a}$ , wherein  $R^{A2a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of  $R^{A2b}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl,

optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{A2b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

any two  $R^{A1}$ , any two  $R^{A2}$ , or one  $R^{A1}$  and one  $R^{A2}$  are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

each of  $R^{1b}$  is independently selected from hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -CN, -OR<sup>B1a</sup>, -N( $R^{B1b}$ )<sub>2</sub>, and -SR<sup>B1a</sup>, wherein each occurrence of  $R^{B1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of  $R^{B1b}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{B1b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

$R^2$  is -O-, -S-, -N( $R^6$ )-, or an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkylene, wherein one or more methylene units of the alkylene are optionally and independently replaced with -O-, -S-, or -N( $R^6$ )-;

each instance of  $R^3$ , if present, is independently selected from halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -OR<sup>C1</sup>, -N( $R^{C1a}$ )<sub>2</sub>, and -SR<sup>C1</sup>, wherein each occurrence of  $R^{C1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group

when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom:

wherein each occurrence of  $R^{C1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{C1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^3$  groups bound to the same ring carbon atom are taken together to form =O, or  
two  $R^3$  groups bound to the same or different ring carbon atoms are joined to form an  
optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted  
aryl, or optionally substituted heteroaryl ring;

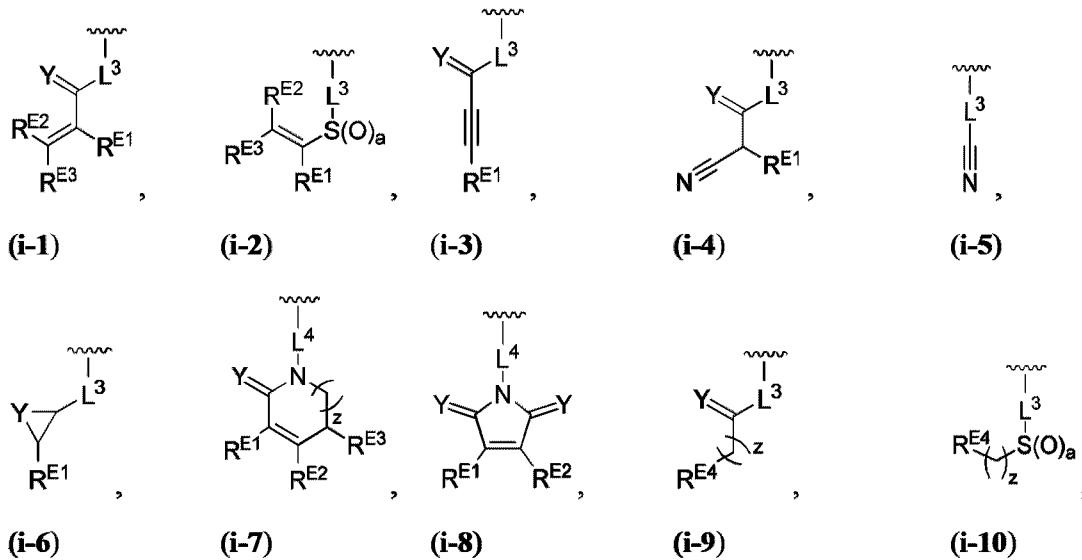
$R^4$  is selected from a bond,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-N(R^6)-$ ,  $-S(=O)_2-$ , or an optionally substituted  $C_1-C_4$  alkylene, wherein:

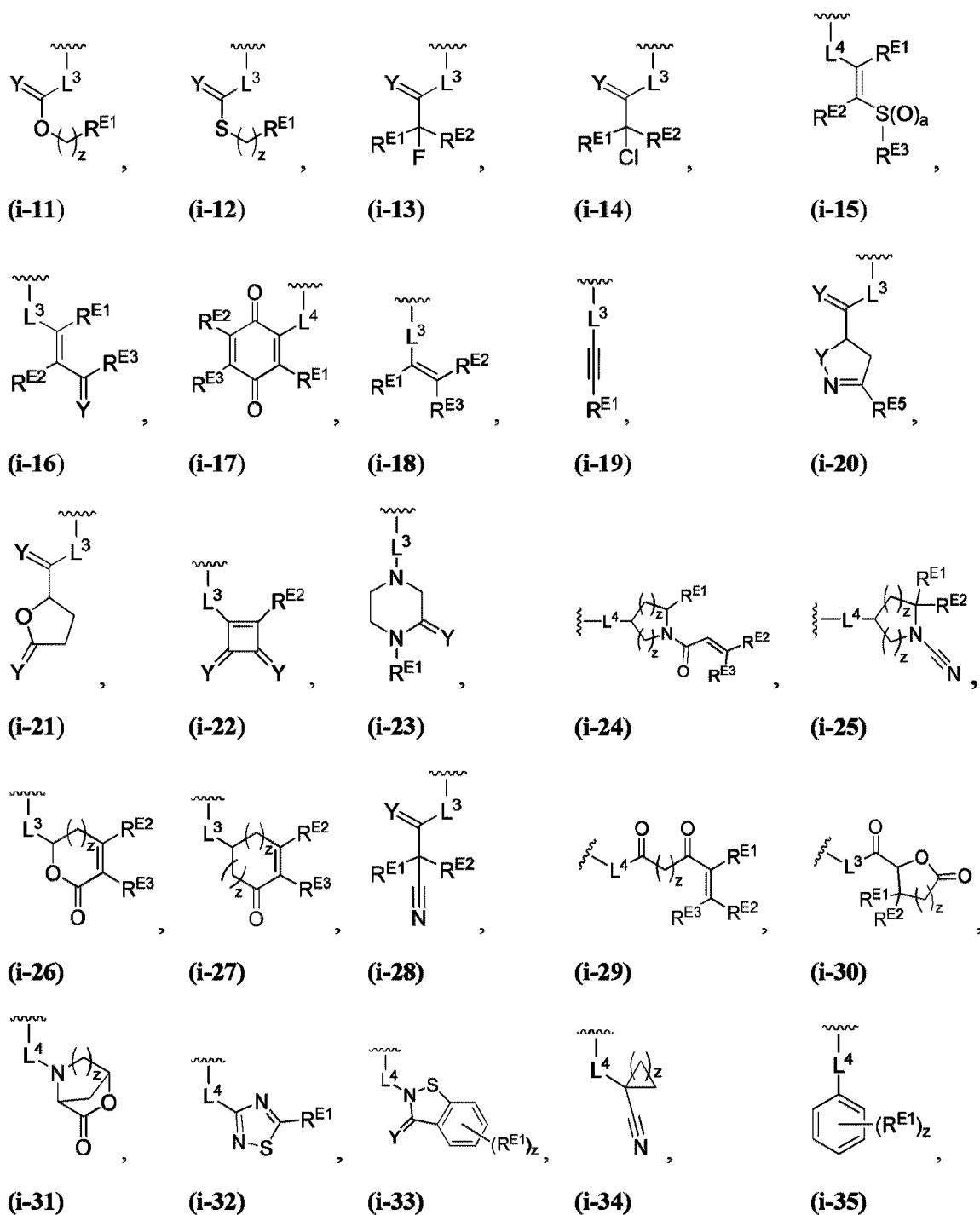
one or more methylene units of the alkylene other than a methylene unit bound to a nitrogen atom is optionally and independently replaced with –

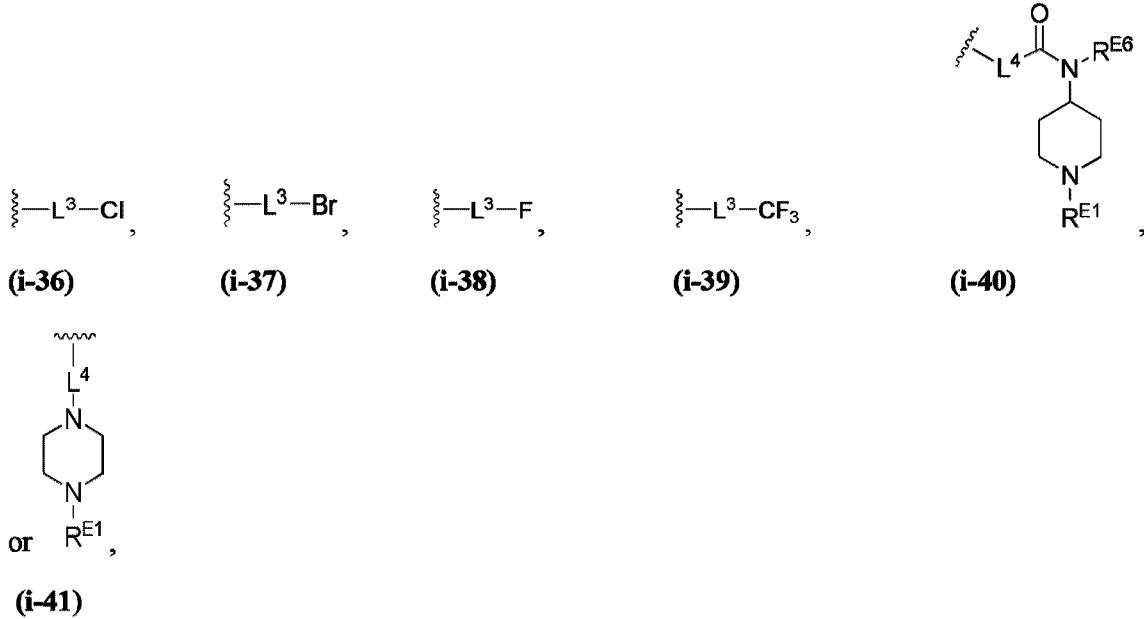
C(=O), -O-, -S-, -N(R<sup>6</sup>)-, or -S(=O)₂-;

each R<sup>6</sup> is independently selected from hydrogen and -C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>7</sup> is a warhead of formula:







wherein:

$L^3$  is a bond or an optionally substituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C=O-$ ,  $-O-$ ,  $-S-$ ,  $-NR^{L3a}-$ ,  $-NR^{L3a}C(=O)-$ ,  $-C(=O)NR^{L3a}-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-NR^{L3a}C(=S)-$ ,  $-C(=S)NR^{L3a}-$ , *trans*- $CR^{L3b}=CR^{L3b}-$ , *cis*- $CR^{L3b}-CR^{L3b}-$ ,  $-C\equiv C-$ ,  $-S(=O)-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^{L3a}-$ ,  $-NR^{L3a}S(=O)-$ ,  $-S(=O)_2-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^{L3a}-$ , or  $-NR^{L3a}S(=O)_2-$ , wherein  $R^{L3a}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group, and wherein each occurrence of  $R^{L3b}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{L3b}$  groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$L^4$  is a bond or an optionally substituted, branched or unbranched  $C_{1-6}$  hydrocarbon chain;

each of  $R^{E1}$ ,  $R^{E2}$ , and  $R^{E3}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-CN$ ,  $-CH_2OR^{EE}$ ,  $-CH_2N(R^{EE})_2$ ,  $-CH_2SR^{EE}$ ,  $-OR^{EE}$ ,  $-N(R^{EE})_2$ ,  $-Si(R^{EE})_3$ , or  $-SR^{EE}$ , wherein each instance of  $R^{EE}$  is

independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{EE}$  groups are joined to form an optionally substituted heterocyclic ring; or  $R^{E1}$  and  $R^{E3}$ , or  $R^{E2}$  and  $R^{E3}$ , or  $R^{E1}$  and  $R^{E2}$  are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$R^{E4}$  is a leaving group;

$R^{E5}$  is halogen;

$R^{E6}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

each instance of  $Y$  is independently O, S, or  $NR^{E7}$ , wherein  $R^{E7}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

$a$  is 1 or 2;

each instance of  $z$  is independently 0, 1, 2, 3, 4, 5, or 6, as valency permits;

and

each instance of  $R^8$ , if present, is independently selected from hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{D1}$ ,  $-N(R^{D1a})_2$ , and  $-SR^{D1}$ , wherein each occurrence of  $R^{D1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom;

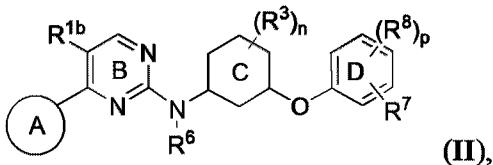
wherein each occurrence of  $R^{D1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{D1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^8$  groups are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

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

n is 0, 1, 2, 3, 4, 5 or 6.

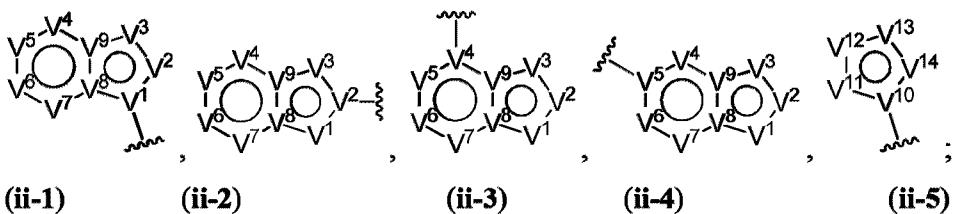
[00102] In certain embodiments, a compound described herein is of Formula (II):



(II),

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein:

Ring A is an optionally substituted heteroaryl ring of any one of the Formulae (ii-1)-(ii-5):



or an optionally substituted 6-membered aryl or heteroaryl ring;

each instance of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, V<sup>9</sup>, V<sup>10</sup>, V<sup>11</sup>, V<sup>12</sup>, V<sup>13</sup>, and V<sup>14</sup> is independently O, S, N(R<sup>A1</sup>), C, or C(R<sup>A2</sup>);

each instance of R<sup>A1</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each instance of R<sup>A2</sup> is independently selected from hydrogen, halogen, -CN, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, -OR<sup>A2a</sup>, -N(R<sup>A2b</sup>)<sub>2</sub>, and -SR<sup>A2a</sup>, wherein R<sup>A2a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of R<sup>A2b</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally

substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{A2b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

any two  $R^{A1}$ , any two  $R^{A2}$ , or one  $R^{A1}$  and one  $R^{A2}$  are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

each of  $R^{1b}$  is independently selected from hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-CN$ ,  $-OR^{B1a}$ ,  $-N(R^{B1b})_2$ , and  $-SR^{B1a}$ , wherein each occurrence of  $R^{B1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of  $R^{B1b}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{B1b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

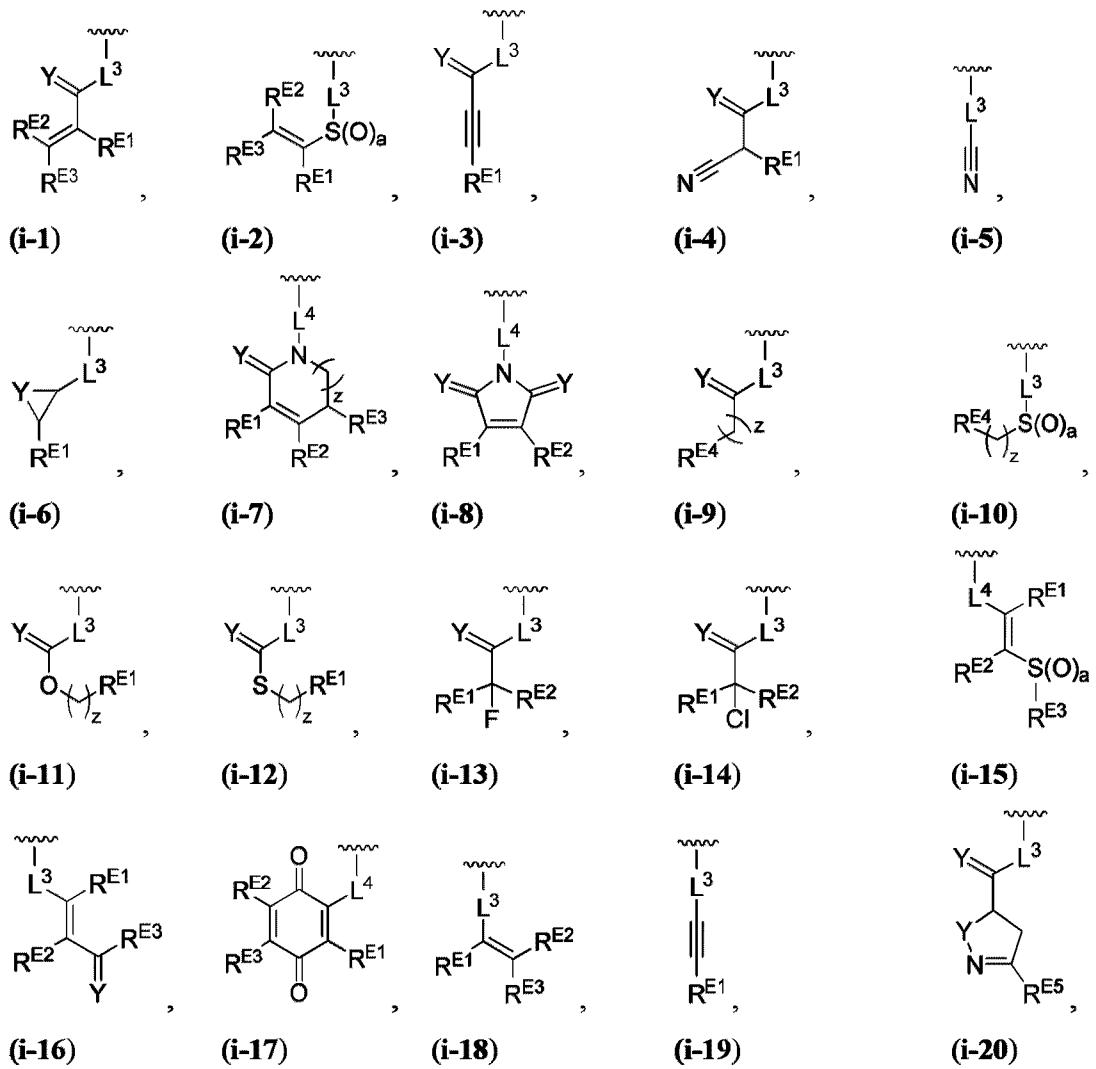
each instance of  $R^3$ , if present, is independently selected from halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{C1}$ ,  $-N(R^{C1a})_2$ , and  $-SR^{C1}$ , wherein each occurrence of  $R^{C1}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

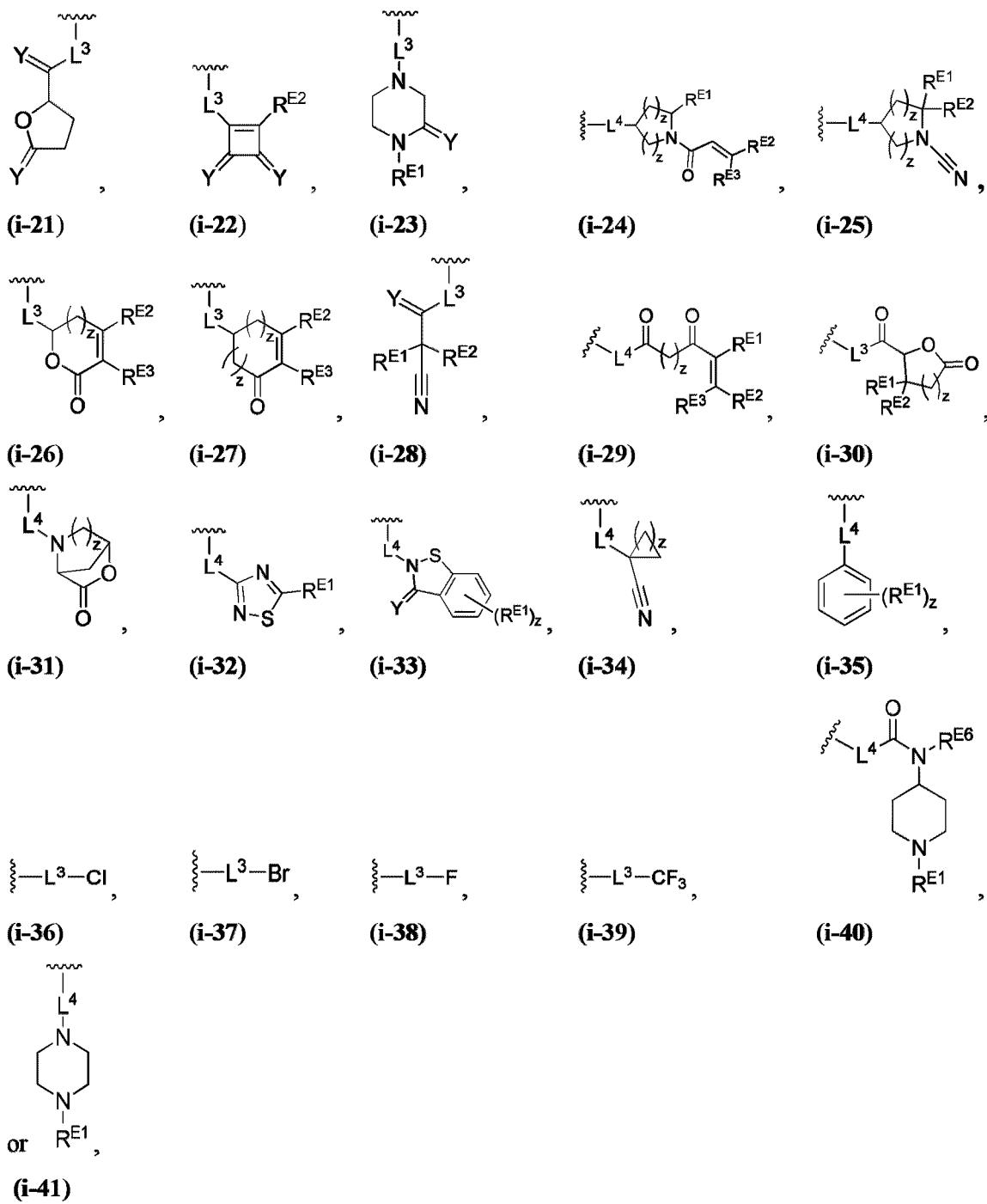
wherein each occurrence of  $R^{C1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{C1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^3$  groups bound to the same ring carbon atom are taken together to form  $=O$ , or  
two  $R^3$  groups bound to the same or different ring carbon atoms are joined to form an  
optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted  
aryl, or optionally substituted heteroaryl ring;

each R<sup>6</sup> is independently selected from hydrogen and -C<sub>1</sub>-C<sub>6</sub> alkyl;

$R^7$  is a warhead of formula:





wherein:

L<sup>3</sup> is a bond or an optionally substituted C<sub>1-4</sub> hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with –C=O–, –O–, –S–, –NR<sup>L3a</sup>–, –NR<sup>L3a</sup>C(=O)–, –C(=O)NR<sup>L3a</sup>–, –SC(=O)–, –C(=O)S–, –OC(=O)–, –C(=O)O–, –NR<sup>L3a</sup>C(=S)–, –C(=S)NR<sup>L3a</sup>–, *trans*–CR<sup>L3b</sup>=CR<sup>L3b</sup>–, *cis*–CR<sup>L3b</sup>=CR<sup>L3b</sup>–, –C≡C–, –S(=O)–, –S(=O)O–, –OS(=O)–, –S(=O)NR<sup>L3a</sup>–, –NR<sup>L3a</sup>S(=O)–, –S(=O)<sub>2</sub>–, –S(=O)<sub>2</sub>O–, –

$\text{OS(=O)}_2-$ ,  $-\text{S(=O)}_2\text{NR}^{\text{L3a}}-$ , or  $-\text{NR}^{\text{L3a}}\text{S(=O)}_2-$ , wherein  $\text{R}^{\text{L3a}}$  is hydrogen, substituted or unsubstituted  $\text{C}_{1-6}$  alkyl, or a nitrogen protecting group, and wherein each occurrence of  $\text{R}^{\text{L3b}}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $\text{R}^{\text{L3b}}$  groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$\text{L}^4$  is a bond or an optionally substituted, branched or unbranched  $\text{C}_{1-6}$  hydrocarbon chain;

each of  $\text{R}^{\text{E1}}$ ,  $\text{R}^{\text{E2}}$ , and  $\text{R}^{\text{E3}}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-\text{CN}$ ,  $-\text{CH}_2\text{OR}^{\text{EE}}$ ,  $-\text{CH}_2\text{N}(\text{R}^{\text{EE}})_2$ ,  $-\text{CH}_2\text{SR}^{\text{EE}}$ ,  $-\text{OR}^{\text{EE}}$ ,  $-\text{N}(\text{R}^{\text{EE}})_2$ ,  $-\text{Si}(\text{R}^{\text{EE}})_3$ , or  $-\text{SR}^{\text{EE}}$ , wherein each instance of  $\text{R}^{\text{EE}}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $\text{R}^{\text{EE}}$  groups are joined to form an optionally substituted heterocyclic ring; or  $\text{R}^{\text{E1}}$  and  $\text{R}^{\text{E3}}$ , or  $\text{R}^{\text{E2}}$  and  $\text{R}^{\text{E3}}$ , or  $\text{R}^{\text{E1}}$  and  $\text{R}^{\text{E2}}$  are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$\text{R}^{\text{E4}}$  is a leaving group;

$\text{R}^{\text{E5}}$  is halogen;

$\text{R}^{\text{E6}}$  is hydrogen, substituted or unsubstituted  $\text{C}_{1-6}$  alkyl, or a nitrogen protecting group;

each instance of  $\text{Y}$  is independently  $\text{O}$ ,  $\text{S}$ , or  $\text{NR}^{\text{E7}}$ , wherein  $\text{R}^{\text{E7}}$  is hydrogen, substituted or unsubstituted  $\text{C}_{1-6}$  alkyl, or a nitrogen protecting group;

$\text{a}$  is 1 or 2;

each instance of  $\text{z}$  is independently 0, 1, 2, 3, 4, 5, or 6, as valency permits; and

each instance of  $\text{R}^8$ , if present, is independently selected from hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-\text{OR}^{\text{D1}}$ ,  $-\text{N}(\text{R}^{\text{D1a}})_2$ , and  $-\text{SR}^{\text{D1}}$ , wherein each occurrence of  $\text{R}^{\text{D1}}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl,

optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

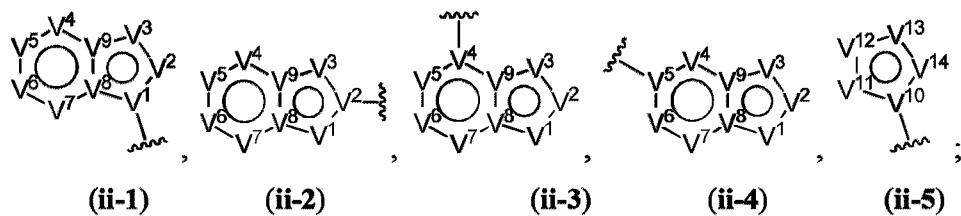
wherein each occurrence of  $R^{D1a}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of  $R^{D1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^8$  groups are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

$n$  is 0, 1, 2, 3, 4, 5 or 6; and

$p$  is 0, 1, 2, 3, 4, or 5.

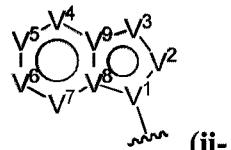
[00103] As generally defined herein in Formulae (I') and (II), Ring A is an optionally substituted heteroaryl ring of any one of the Formulae (ii-1)-(ii-5):



or an optionally substituted 6-membered aryl or heteroaryl ring; wherein each instance of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ ,  $V^9$ ,  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  is independently O, S, N( $R^{A1}$ ), C, or C( $R^{A2}$ ).

[00104] Compounds of Formulae (I') and (II) include Ring A. In certain embodiments, Ring A is an optionally substituted monocyclic heteroaryl ring fused with an optionally substituted monocyclic aryl ring. In certain embodiments, Ring A is an optionally substituted 6-membered aryl ring. In certain embodiments, Ring A is an optionally substituted 6-membered heteroaryl ring. In certain embodiments, Ring A is an optionally substituted bicyclic heteroaryl ring. In certain embodiments, Ring A is an optionally substituted monocyclic heteroaryl ring fused with another optionally substituted monocyclic heteroaryl ring. Ring A may be an optionally substituted 6,5-membered heteroaryl ring or an optionally substituted 5,6-membered heteroaryl ring. In certain embodiments, Ring A is an optionally substituted monocyclic 5-membered heteroaryl ring fused with an optionally substituted monocyclic 6-

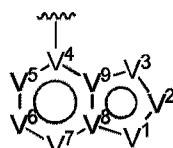
membered aryl ring. In certain embodiments, Ring A is an optionally substituted monocyclic 5-membered heteroaryl ring fused with an optionally substituted monocyclic 6-membered heteroaryl ring. The point of attachment of Ring A to Ring B may be at any atom of Ring A, as valency permits. In certain embodiments, Ring A is of Formula (ii-1):



as valency permits. In certain embodiments, Ring A is of Formula (ii-1): (ii-1)



1). In certain embodiments, Ring A is of Formula (ii-2): (ii-2). In certain

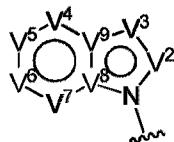


embodiments, Ring A is of Formula (ii-3): (ii-3). In certain embodiments,

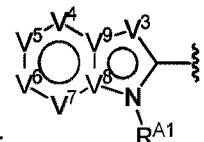


Ring A is of Formula (ii-4): (ii-4). As generally described herein, in

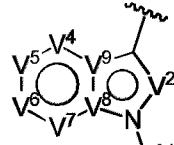
Formulae (I') and (II),  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  of Ring A may each independently be O, S, N,  $NR^{A1}$ , C, or  $CR^{A2}$ , as valency permits. In certain embodiments,  $V^1$  is O, S, N or  $NR^{A1}$ . In certain embodiments,  $V^1$  is N or  $NR^{A1}$ . In certain embodiments, Ring A is of



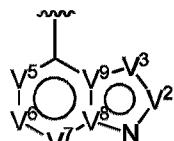
formula: . In certain embodiments, Ring A is of formula: . In



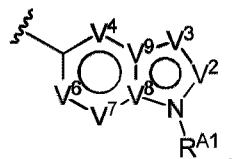
formula: . In certain embodiments, Ring A is of formula: . In



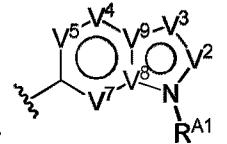
certain embodiments, Ring A is of formula: . In certain embodiments, Ring A



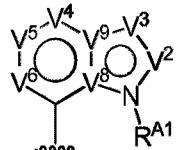
is of formula: . In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula:

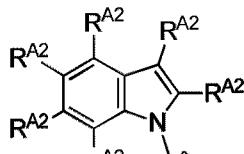


. In



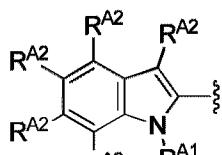
certain embodiments, Ring A is of formula:

**[100105]** In certain embodiments, only one of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> is selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain embodiments, only one of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> is selected from the group consisting of N and NR<sup>A1</sup>. In certain embodiments, V<sup>1</sup> is N or NR<sup>A1</sup>; V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently C or CR<sup>A2</sup>; and therefore, Ring A is an optionally substituted indole ring. In certain



embodiments, Ring A is of Formula (iii-1):

(iii-1). In certain



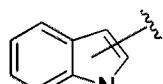
embodiments, Ring A is of Formula (iii-2):

(iii-2). In certain embodiments,

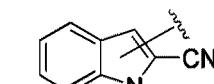


Ring A is of Formula (iii-3):

(iii-3). In certain embodiments, Ring A is



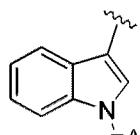
of formula:



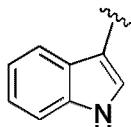
or

.

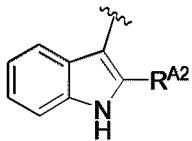
In certain embodiments, Ring A is of formula:



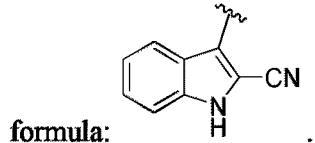
. In certain embodiments, Ring A is of formula:



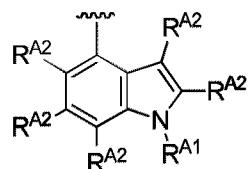
. In certain



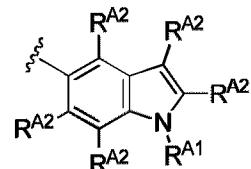
embodiments, Ring A is of formula:



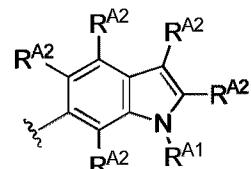
. In certain embodiments, Ring A is of



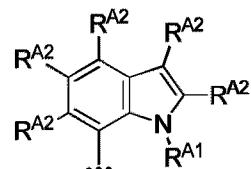
[00106] In certain embodiments, Ring A is of Formula (iii-4): (iii-4). In certain embodiments, Ring A is of Formula (iii-5):



(iii-5). In certain embodiments, Ring A is of Formula (iii-6):

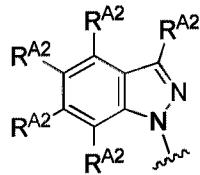


(iii-6). In certain embodiments, Ring A is of Formula (iii-7):



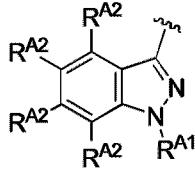
(iii-7).

[00107] In certain embodiments, only two of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain embodiments, only two of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently selected from the group consisting of N and NR<sup>A1</sup>. In certain embodiments, V<sup>1</sup> is N or NR<sup>A1</sup>; and only one of V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> is N or NR<sup>A1</sup>. In certain embodiments, V<sup>1</sup> and V<sup>2</sup> are each independently N or NR<sup>A1</sup>; V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently C or CR<sup>A2</sup>; and therefore, Ring A is an optionally substituted indazole ring. In



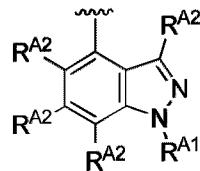
certain embodiments, Ring A is of formula:

. In certain embodiments, Ring

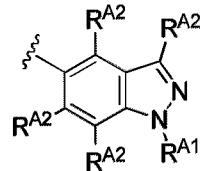


A is of formula:

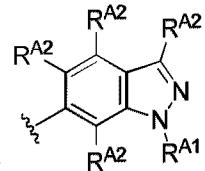
. In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula:

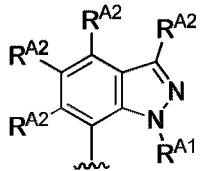


. In certain embodiments, Ring A is of formula:

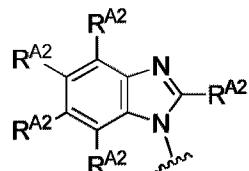


. In certain

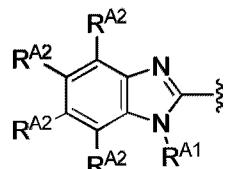
embodiments, Ring A is of formula:



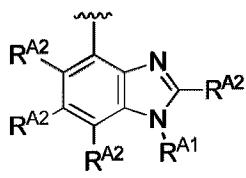
**[00108]** In certain embodiments, V<sup>1</sup> and V<sup>3</sup> are each independently N or NR<sup>A1</sup>; V<sup>2</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently C or CR<sup>A2</sup>, and therefore, Ring A is an optionally substituted benzimidazole ring. In certain embodiments, Ring A is of Formula (iv-1):



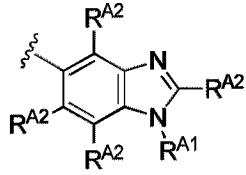
(iv-1). In certain embodiments, Ring A is of Formula (iv-2):



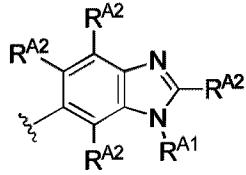
(iv-2). In certain embodiments, Ring A is of Formula (iv-3):



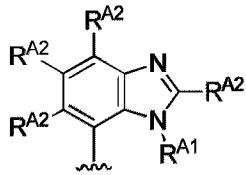
(iv-3). In certain embodiments, Ring A is of Formula (iv-4):



(iv-4). In certain embodiments, Ring A is of Formula (iv-5):

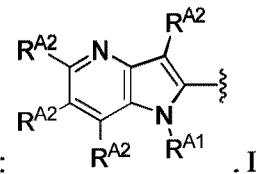
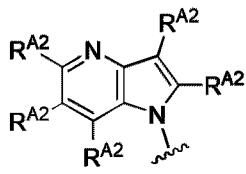


(iv-5). In certain embodiments, Ring A is of Formula (iv-6):

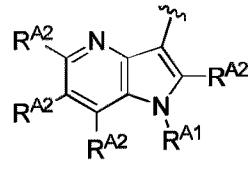


(iv-6).

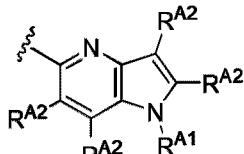
[00109] In certain embodiments, V<sup>1</sup> and V<sup>4</sup> are each independently N or NR<sup>A1</sup>; V<sup>2</sup>, V<sup>3</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently C or CR<sup>A2</sup>; and therefore, Ring A is an optionally substituted 4-azaindazole ring. In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula: . In

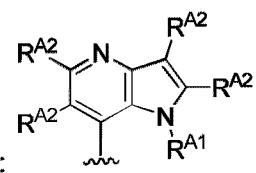
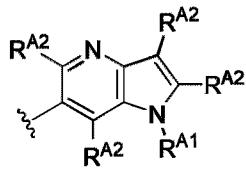


certain embodiments, Ring A is of formula: . In certain embodiments,



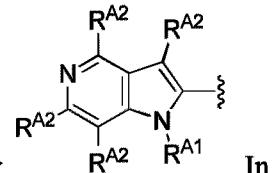
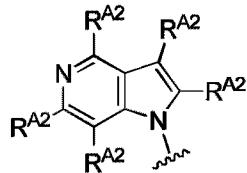
Ring A is of formula:

. In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula: .

**[00110]** In certain embodiments,  $V^1$  and  $V^5$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ , and therefore, Ring A is an optionally substituted 5-azaindazole ring. In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula:

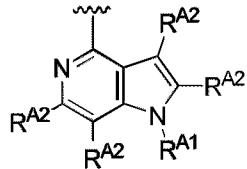


certain embodiments, Ring A is of formula:

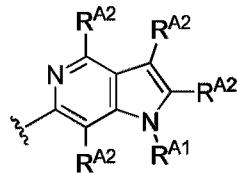


. In certain embodiments,

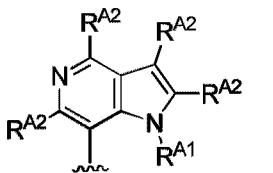
Ring A is of formula:



. In certain embodiments, Ring A is of formula:

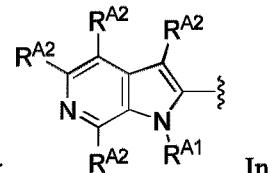
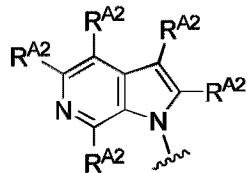


. In certain embodiments, Ring A is of formula:

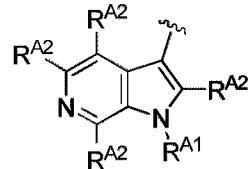


.

**[00111]** In certain embodiments,  $V^1$  and  $V^6$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ , and therefore, Ring A is an optionally substituted 6-azaindole ring. In certain embodiments, Ring A is of formula:

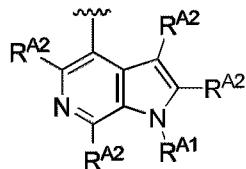


. In certain embodiments, Ring A is of formula:



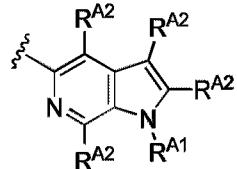
certain embodiments, Ring A is of formula:

. In certain embodiments,

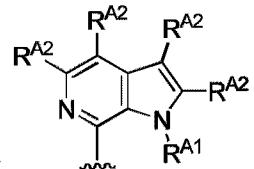


Ring A is of formula:

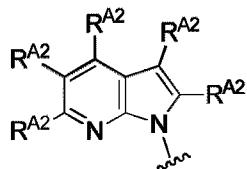
. In certain embodiments, Ring A is of formula:



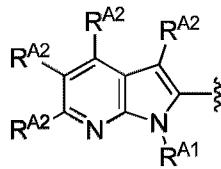
. In certain embodiments, Ring A is of formula:



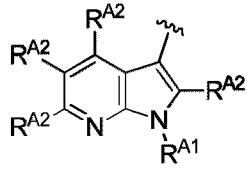
**[00112]** In certain embodiments, V<sup>1</sup> and V<sup>7</sup> are each independently N or NR<sup>A1</sup>; V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently C or CR<sup>A2</sup>; and therefore, Ring A is an optionally substituted 7-azaindole ring. In certain embodiments, Ring A is of Formula (v-1):



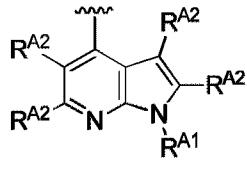
(v-1). In certain embodiments, Ring A is of Formula (v-2):



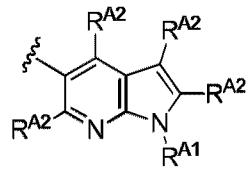
(v-2). In certain embodiments, Ring A is of Formula (v-3):



(v-3). In certain embodiments, Ring A is of Formula (v-4):

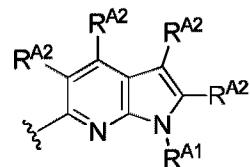


(v-4).



In certain embodiments, Ring A is of Formula (v-5):

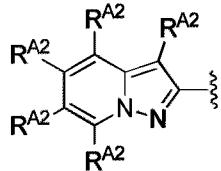
(v-5). In certain



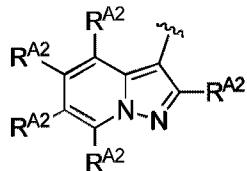
embodiments, Ring A is of Formula (v-6):

(v-6).

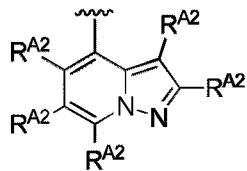
**[00113]** In certain embodiments,  $V^1$  and  $V^8$  are each independently N or  $NR^{A1}$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ , and  $V^9$  are each independently C or  $CR^{A2}$ , and therefore, Ring A is an optionally substituted 8-azaindole ring. In certain embodiments, Ring A is of Formula (vi-1):



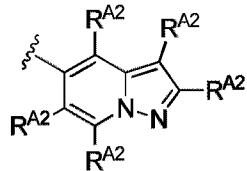
(vi-1). In certain embodiments, Ring A is of Formula (vi-2):



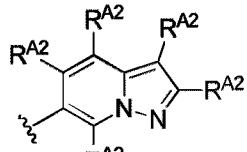
(vi-2). In certain embodiments, Ring A is of Formula (vi-3):



(vi-3). In certain embodiments, Ring A is of Formula (vi-4):

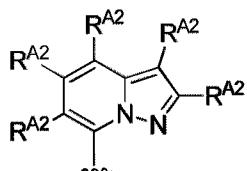


(vi-4).



In certain embodiments, Ring A is of Formula (vi-5):

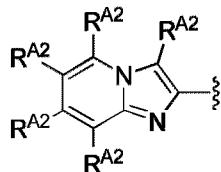
(vi-5). In certain



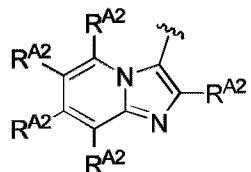
embodiments, Ring A is of Formula (vi-6):

(vi-6).

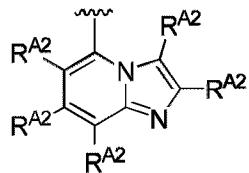
**[00114]** In certain embodiments,  $V^1$  and  $V^9$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ , and  $V^8$  are each independently C or  $CR^{A2}$ , and therefore, Ring A is an optionally substituted 9-azaindole ring. In certain embodiments, Ring A is of formula:



. In certain embodiments, Ring A is of formula:

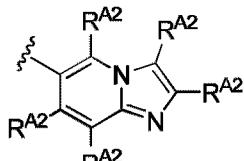


. In



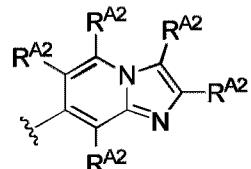
certain embodiments, Ring A is of formula:

. In certain embodiments,

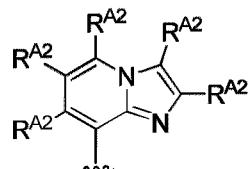


Ring A is of formula:

. In certain embodiments, Ring A is of formula:



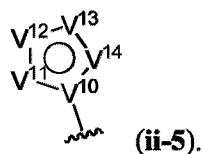
. In certain embodiments, Ring A is of formula:



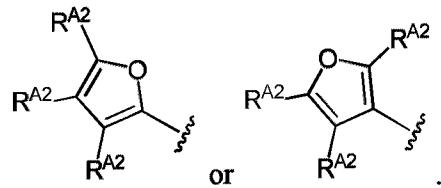
. In certain embodiments, Ring A is of formula:

**[00115]** In certain embodiments, only three of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain embodiments, only three of V<sup>1</sup>, V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently selected from the group consisting of N and NR<sup>A1</sup>. In certain embodiments, V<sup>1</sup> is N or NR<sup>A1</sup>; and only two of V<sup>2</sup>, V<sup>3</sup>, V<sup>4</sup>, V<sup>5</sup>, V<sup>6</sup>, V<sup>7</sup>, V<sup>8</sup>, and V<sup>9</sup> are each independently N or NR<sup>A1</sup>.

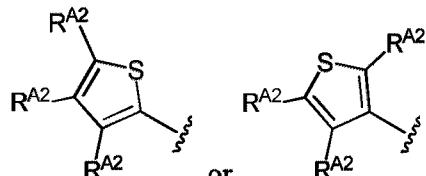
**[00116]** As generally described herein, in Formulae (I') and (II), Ring A may also be an optionally substituted 5-membered heteroaryl ring. In certain embodiments, Ring A is of Formula (ii-5):



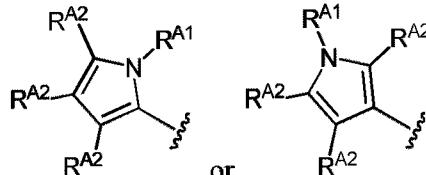
**[00117]** As generally described herein, in Formulae (I') and (II), V<sup>10</sup>, V<sup>11</sup>, V<sup>12</sup>, V<sup>13</sup>, and V<sup>14</sup> of Ring A may each independently be O, S, N, NR<sup>A1</sup>, C, or CR<sup>A2</sup>, as valency permits. In certain embodiments, only one of V<sup>10</sup>, V<sup>11</sup>, V<sup>12</sup>, V<sup>13</sup>, and V<sup>14</sup> is selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain embodiments, Ring A is of formula:



or

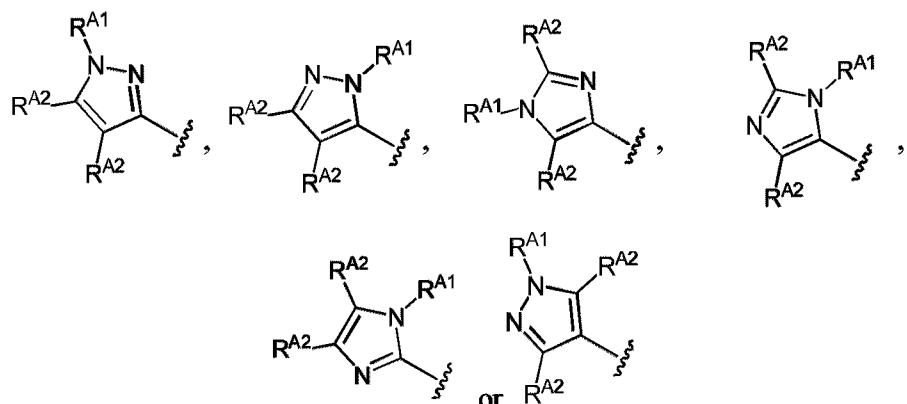


[00118] In certain embodiments, Ring A is of formula:

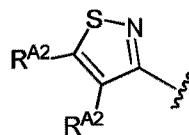
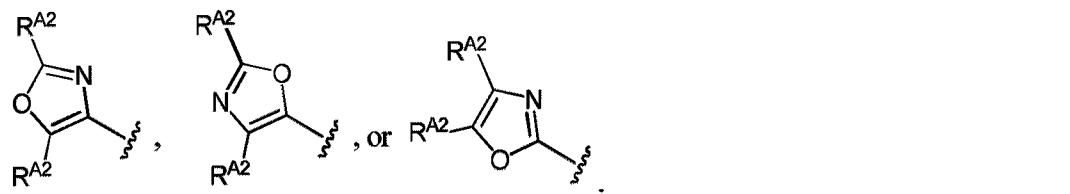


[00119] In certain embodiments, Ring A is of formula:

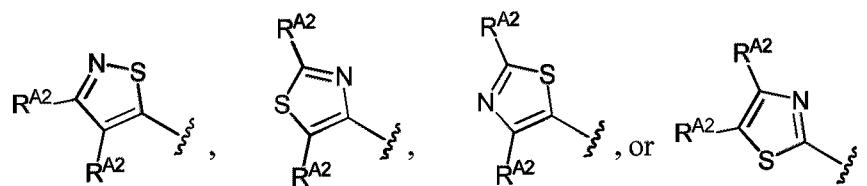
[00120] In certain embodiments, only two of V<sup>10</sup>, V<sup>11</sup>, V<sup>12</sup>, V<sup>13</sup>, and V<sup>14</sup> are independently selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain embodiments, Ring A is of formula:

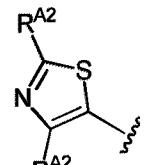


[00121] In certain embodiments, Ring A is of formula:

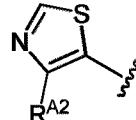


[00122] In certain embodiments, Ring A is of formula:

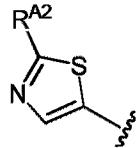




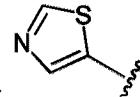
[00123] In certain embodiments, Ring A is of Formula (vii): (vii).



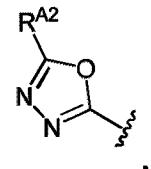
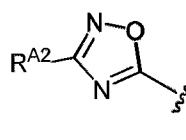
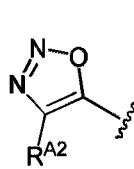
[00124] In certain embodiments, Ring A is of formula: . In certain embodiments,



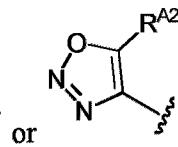
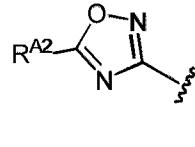
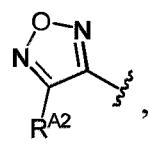
Ring A is of formula: . In certain embodiments, Ring A is of formula:



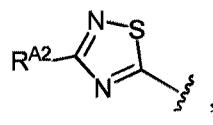
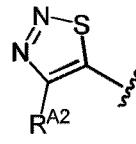
[00125] In certain embodiments, only three of V<sup>10</sup>, V<sup>11</sup>, V<sup>12</sup>, V<sup>13</sup>, and V<sup>14</sup> are each independently selected from the group consisting of O, S, N, and NR<sup>A1</sup>. In certain



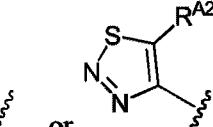
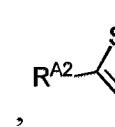
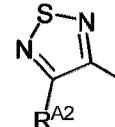
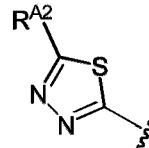
embodiments, Ring A is of formula: ,



, or .

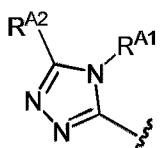
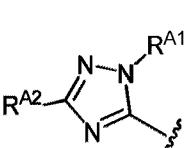
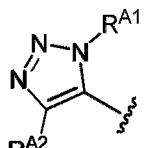
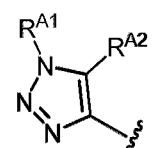
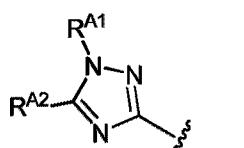


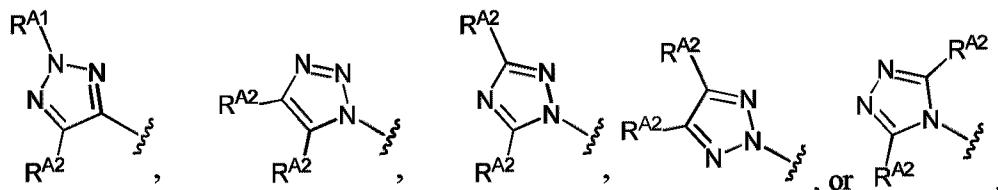
[00126] In certain embodiments, Ring A is of formula: ,



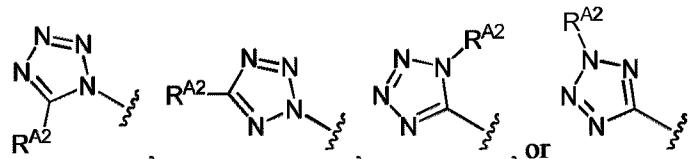
, or .

[00127] In certain embodiments, Ring A is of formula:





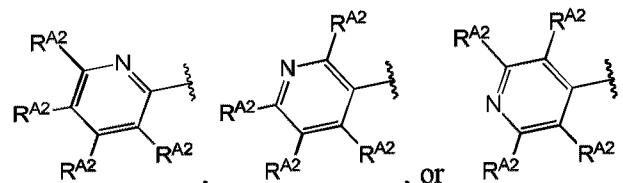
**[00128]** In certain embodiments, only four of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  are each independently selected from the group consisting of N and  $NR^{A1}$ . In certain embodiments, Ring A is of formula:



**[00129]** In certain embodiments, Ring A is an optionally substituted 6-membered aryl ring. In certain embodiments, Ring A is optionally substituted phenyl. In certain embodiments, Ring A is an optionally substituted 6-membered heteroaryl ring. In certain embodiments, Ring A is of Formula (ii-6):

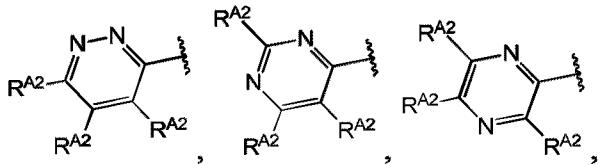


**(ii-6).** In certain embodiments,  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  of Ring A may each independently be N, C, or  $CR^{A2}$ , as valency permits. In certain embodiments, only one of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  is N. In certain embodiments, Ring A is of formula:

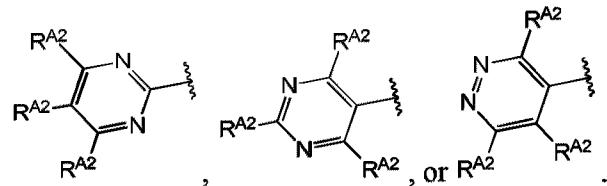


In certain embodiments, only two of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  are N. In certain

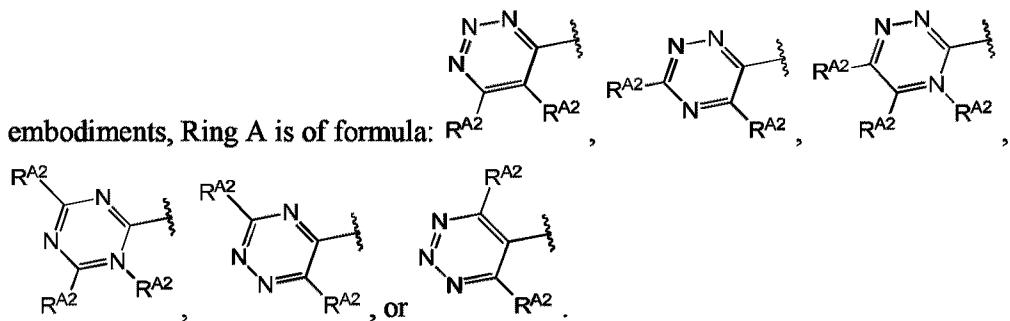
embodiments, Ring A is of formula:



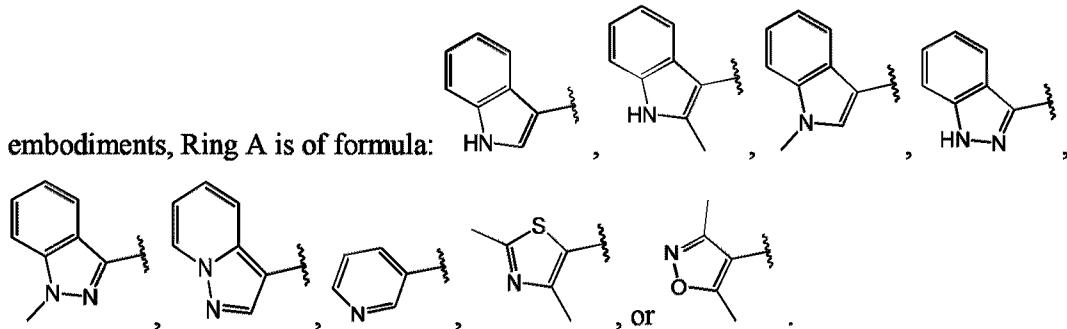
embodiments, Ring A is of formula:



In certain embodiments, only three of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  are N. In certain



[00130] In certain embodiments, Ring A is of Formula (ii-1), (ii-5), or (ii-6). In certain



[00131] As generally described herein, in Formulae (I') and (III), Ring A may be substituted with one or more  $R^{A1}$  groups when the  $R^{A1}$  group is attached to a nitrogen atom. In certain embodiments, at least one instance of  $R^{A1}$  is H (hydrogen). In certain embodiments, at least one instance of  $R^{A1}$  is halogen. In certain embodiments, at least one instance of  $R^{A1}$  is F (fluorine). In certain embodiments, at least one instance of  $R^{A1}$  is Cl (chlorine). In certain embodiments, at least one instance of  $R^{A1}$  is Br (bromine). In certain embodiments, at least one instance of  $R^{A1}$  is I (iodine). In certain embodiments, at least one instance of  $R^{A1}$  is substituted acyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted acyl. In certain embodiments, at least one instance of  $R^{A1}$  is acetyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted acetyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted alkyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted alkyl. In certain embodiments, at least one instance of  $R^{A1}$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one instance of  $R^{A1}$  is methyl. In certain embodiments, at least one instance of  $R^{A1}$  is ethyl. In certain embodiments, at least one instance of  $R^{A1}$  is propyl. In certain embodiments, at least one instance of  $R^{A1}$  is butyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted alkenyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted alkenyl. In certain embodiments, at least one instance of  $R^{A1}$  is vinyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted alkynyl. In certain

embodiments, at least one instance of  $R^{A1}$  is unsubstituted alkynyl. In certain embodiments, at least one instance of  $R^{A1}$  is ethynyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted carbocyclyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted carbocyclyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted heterocyclyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted heterocyclyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted aryl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted aryl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted phenyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted phenyl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted heteroaryl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted heteroaryl. In certain embodiments, at least one instance of  $R^{A1}$  is substituted pyridyl. In certain embodiments, at least one instance of  $R^{A1}$  is unsubstituted pyridyl. In certain embodiments, at least one instance of  $R^{A1}$  is a nitrogen protecting group (e.g., Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00132] In certain embodiments, at least one  $R^{A1}$  is hydrogen, C<sub>1-6</sub> alkyl, or a nitrogen protecting group. In certain embodiments, all instances of  $R^{A1}$  are each independently hydrogen, C<sub>1-6</sub> alkyl, or a nitrogen protecting group. In certain embodiments, all instances of  $R^{A1}$  are hydrogen.

[00133] In Formulae (I') and (II), Ring A may be substituted with one or more  $R^{A2}$  groups when the  $R^{A2}$  group is attached to a carbon atom. In certain embodiments, at least one  $R^{A2}$  is H. In certain embodiments, at least one  $R^{A2}$  is halogen. In certain embodiments, at least one  $R^{A2}$  is F. In certain embodiments, at least one  $R^{A2}$  is Cl. In certain embodiments, at least one  $R^{A2}$  is Br. In certain embodiments, at least one  $R^{A2}$  is I (iodine). In certain embodiments, at least one  $R^{A2}$  is substituted acyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted acyl. In certain embodiments, at least one  $R^{A2}$  is acetyl. In certain embodiments, at least one  $R^{A2}$  is substituted acetyl. In certain embodiments, at least one  $R^{A2}$  is substituted alkyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted alkyl. In certain embodiments, at least one  $R^{A2}$  is C<sub>1-6</sub> alkyl. In certain embodiments, at least one  $R^{A2}$  is methyl. In certain embodiments, at least one  $R^{A2}$  is ethyl. In certain embodiments, at least one  $R^{A2}$  is propyl. In certain embodiments, at least one  $R^{A2}$  is butyl. In certain embodiments, at least one  $R^{A2}$  is substituted alkenyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted alkenyl. In certain embodiments, at least one  $R^{A2}$  is vinyl. In certain embodiments, at least one  $R^{A2}$  is substituted alkynyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted alkynyl. In

certain embodiments, at least one  $R^{A2}$  is ethynyl. In certain embodiments, at least one  $R^{A2}$  is substituted carbocyclyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted carbocyclyl. In certain embodiments, at least one  $R^{A2}$  is substituted heterocyclyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted heterocyclyl. In certain embodiments, at least one  $R^{A2}$  is substituted aryl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted aryl. In certain embodiments, at least one  $R^{A2}$  is substituted phenyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted phenyl. In certain embodiments, at least one  $R^{A2}$  is substituted heteroaryl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted heteroaryl. In certain embodiments, at least one  $R^{A2}$  is substituted pyridyl. In certain embodiments, at least one  $R^{A2}$  is unsubstituted pyridyl. In certain embodiments, at least one  $R^{A2}$  is  $-CN$ . In certain embodiments, at least one  $R^{A2}$  is  $-OR^{A2a}$ . In certain embodiments, at least one  $R^{A2}$  is  $-N(R^{A2b})_2$ . In certain embodiments, at least one  $R^{A2}$  is  $-SR^{A2a}$ .

[00134] In certain embodiments, two  $R^{A2}$  groups are each independently halogen, optionally substituted alkyl, or optionally substituted aryl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are each independently halogen or optionally substituted alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are halogen; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are optionally substituted alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are  $C_{1-6}$  alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are methyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are ethyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are propyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are butyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are optionally substituted aryl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, two  $R^{A2}$  groups are optionally substituted phenyl; and all other instances of  $R^{A2}$  are hydrogen.

[00135] In certain embodiments, one  $R^{A2}$  group is halogen, optionally substituted alkyl, or optionally substituted aryl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is halogen or optionally substituted alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is optionally substituted alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is  $C_{1-6}$  alkyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is methyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is ethyl; and all other

instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is propyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is butyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is optionally substituted aryl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, one  $R^{A2}$  is optionally substituted phenyl; and all other instances of  $R^{A2}$  are hydrogen. In certain embodiments, all instances of  $R^{A2}$  are hydrogen.

[00136] In certain embodiments, when  $R^{A2}$  is  $-OR^{A2a}$  or  $-SR^{A2a}$ ,  $R^{A2a}$  is H. In certain embodiments,  $R^{A2a}$  is halogen. In certain embodiments,  $R^{A2a}$  is F. In certain embodiments,  $R^{A2a}$  is Cl. In certain embodiments,  $R^{A2a}$  is Br. In certain embodiments,  $R^{A2a}$  is I (iodine). In certain embodiments,  $R^{A2a}$  is substituted acyl. In certain embodiments,  $R^{A2a}$  is unsubstituted acyl. In certain embodiments,  $R^{A2a}$  is acetyl. In certain embodiments,  $R^{A2a}$  is substituted acetyl. In certain embodiments,  $R^{A2a}$  is substituted alkyl. In certain embodiments,  $R^{A2a}$  is unsubstituted alkyl. In certain embodiments,  $R^{A2a}$  is C<sub>1-6</sub> alkyl. In certain embodiments,  $R^{A2a}$  is methyl. In certain embodiments,  $R^{A2a}$  is ethyl. In certain embodiments,  $R^{A2a}$  is propyl. In certain embodiments,  $R^{A2a}$  is butyl. In certain embodiments,  $R^{A2a}$  is substituted alkenyl. In certain embodiments,  $R^{A2a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{A2a}$  is vinyl. In certain embodiments,  $R^{A2a}$  is substituted alkynyl. In certain embodiments,  $R^{A2a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{A2a}$  is ethynyl. In certain embodiments,  $R^{A2a}$  is substituted carbocyclyl. In certain embodiments,  $R^{A2a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{A2a}$  is substituted heterocyclyl. In certain embodiments,  $R^{A2a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{A2a}$  is substituted aryl. In certain embodiments,  $R^{A2a}$  is unsubstituted aryl. In certain embodiments,  $R^{A2a}$  is substituted phenyl. In certain embodiments,  $R^{A2a}$  is unsubstituted phenyl. In certain embodiments,  $R^{A2a}$  is substituted heteroaryl. In certain embodiments,  $R^{A2a}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{A2a}$  is substituted pyridyl. In certain embodiments,  $R^{A2a}$  is unsubstituted pyridyl. In certain embodiments,  $R^{A2a}$  is an oxygen protecting group when attached to an oxygen atom (e.g., silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl). In certain embodiments,  $R^{A2a}$  is a sulfur protecting group when attached to a sulfur atom. In certain embodiments,  $R^{A2a}$  is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

[00137] In certain embodiments, when  $R^{A2}$  is  $-N(R^{A2b})_2$ , at least one  $R^{A2b}$  is H. In certain embodiments, at least one  $R^{A2b}$  is halogen. In certain embodiments, at least one  $R^{A2b}$  is F. In certain embodiments, at least one  $R^{A2b}$  is Cl. In certain embodiments, at least one  $R^{A2b}$  is Br. In certain embodiments, at least one  $R^{A2b}$  is I (iodine). In certain embodiments, at least one

$R^{A2b}$  is substituted acyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted acyl. In certain embodiments, at least one  $R^{A2b}$  is acetyl. In certain embodiments, at least one  $R^{A2b}$  is substituted acetyl. In certain embodiments, at least one  $R^{A2b}$  is substituted alkyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted alkyl. In certain embodiments, at least one  $R^{A2b}$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^{A2b}$  is methyl. In certain embodiments, at least one  $R^{A2b}$  is ethyl. In certain embodiments, at least one  $R^{A2b}$  is propyl. In certain embodiments, at least one  $R^{A2b}$  is butyl. In certain embodiments, at least one  $R^{A2b}$  is substituted alkenyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted alkenyl. In certain embodiments, at least one  $R^{A2b}$  is vinyl. In certain embodiments, at least one  $R^{A2b}$  is substituted alkynyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted alkynyl. In certain embodiments, at least one  $R^{A2b}$  is ethynyl. In certain embodiments, at least one  $R^{A2b}$  is substituted carbocyclyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted carbocyclyl. In certain embodiments, at least one  $R^{A2b}$  is substituted heterocyclyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted heterocyclyl. In certain embodiments, at least one  $R^{A2b}$  is substituted aryl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted aryl. In certain embodiments, at least one  $R^{A2b}$  is substituted phenyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted phenyl. In certain embodiments, at least one  $R^{A2b}$  is substituted heteroaryl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted heteroaryl. In certain embodiments, at least one  $R^{A2b}$  is substituted pyridyl. In certain embodiments, at least one  $R^{A2b}$  is unsubstituted pyridyl. In certain embodiments, at least one  $R^{A2b}$  is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one  $R^{A2b}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments, two  $R^{A2b}$  groups are joined to form a substituted heterocyclic ring. In certain embodiments, two  $R^{A2b}$  groups are joined to form an unsubstituted heterocyclic ring.

[00138] In Formulae (I') and (II), any two instances of  $R^{A1}$ , any two instances of  $R^{A2}$ , or one instance of  $R^{A1}$  and one instance of  $R^{A2}$  may be joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring. In certain embodiments, two instances of  $R^{A1}$  are joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments, two instances of  $R^{A1}$  are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of  $R^{A1}$  are joined to form a substituted or unsubstituted aryl ring. In certain embodiments, two instances of  $R^{A1}$  are joined to form a substituted or unsubstituted

heteroaryl ring. In certain embodiments, two instances of  $R^{A2}$  are joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments, two instances of  $R^{A2}$  are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, two instances of  $R^{A2}$  are joined to form a substituted or unsubstituted aryl ring. In certain embodiments, two instances of  $R^{A2}$  are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form a substituted carbocyclic ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form an unsubstituted carbocyclic ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form a substituted heterocyclic ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form an unsubstituted heterocyclic ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form a substituted aryl ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form an unsubstituted aryl ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form a substituted heteroaryl ring. In certain embodiments, one instance of  $R^{A1}$  and one instance of  $R^{A2}$  are joined to form an unsubstituted heteroaryl ring.

**[00139]** As generally defined herein, Formulae (I') and (II) include substituent  $R^{1b}$ . In certain embodiments,  $R^{1b}$  is H. In certain embodiments,  $R^{1b}$  is halogen. In certain embodiments,  $R^{1b}$  is F. In certain embodiments,  $R^{1b}$  is Cl. In certain embodiments,  $R^{1b}$  is Br. In certain embodiments,  $R^{1b}$  is I (iodine). In certain embodiments,  $R^{1b}$  is substituted acyl. In certain embodiments,  $R^{1b}$  is unsubstituted acyl. In certain embodiments,  $R^{1b}$  is acetyl. In certain embodiments,  $R^{1b}$  is substituted acetyl. In certain embodiments,  $R^{1b}$  is substituted alkyl. In certain embodiments,  $R^{1b}$  is unsubstituted alkyl. In certain embodiments,  $R^{1b}$  is C<sub>1-6</sub> alkyl. In certain embodiments,  $R^{1b}$  is methyl. In certain embodiments,  $R^{1b}$  is ethyl. In certain embodiments,  $R^{1b}$  is propyl. In certain embodiments,  $R^{1b}$  is butyl. In certain embodiments,  $R^{1b}$  is substituted alkenyl. In certain embodiments,  $R^{1b}$  is unsubstituted alkenyl. In certain embodiments,  $R^{1b}$  is vinyl. In certain embodiments,  $R^{1b}$  is substituted alkynyl. In certain embodiments,  $R^{1b}$  is unsubstituted alkynyl. In certain embodiments,  $R^{1b}$  is substituted carbocyclyl. In certain embodiments,  $R^{1b}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{1b}$  is substituted aryl. In certain embodiments,  $R^{1b}$  is unsubstituted aryl. In certain embodiments,  $R^{1b}$  is substituted phenyl. In certain embodiments,  $R^{1b}$  is unsubstituted phenyl. In certain embodiments,  $R^{1b}$  is substituted heteroaryl. In certain embodiments,  $R^{1b}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{1b}$  is substituted

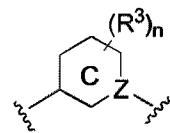
pyridyl. In certain embodiments,  $R^{1b}$  is unsubstituted pyridyl. In certain embodiments,  $R^{1b}$  is  $-CN$ . In certain embodiments,  $R^{1b}$  is  $-OR^{B1a}$ . In certain embodiments,  $R^{1b}$  is  $-N(R^{B1b})_2$  (e.g.,  $-NMe_2$ ). In certain embodiments,  $R^{1b}$  is  $-SR^{B1a}$ . In certain embodiments,  $R^{1b}$  is hydrogen, halogen, substituted or unsubstituted C<sub>1-6</sub> alkyl,  $-CN$ ,  $-OR^{B1a}$ , or  $-N(R^{B1b})_2$ . In certain embodiments,  $R^{1b}$  is hydrogen, halogen,  $-CN$ ,  $-OR^{B1a}$ ,  $-N(R^{B1b})_2$ , unsubstituted C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or more halogen, wherein each instance of  $R^{B1a}$  is independently hydrogen, unsubstituted C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> alkyl substituted with one or more halogen; and each occurrence of  $R^{B1b}$  is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group.

[00140] In certain embodiments, when  $R^{B1b}$  is  $-OR^{B1a}$  or  $-SR^{B1a}$ ,  $R^{B1a}$  is H. In certain embodiments,  $R^{B1a}$  is substituted acyl. In certain embodiments,  $R^{B1a}$  is unsubstituted acyl. In certain embodiments,  $R^{B1a}$  is acetyl. In certain embodiments,  $R^{B1a}$  is substituted acetyl. In certain embodiments,  $R^{B1a}$  is substituted alkyl. In certain embodiments,  $R^{B1a}$  is unsubstituted alkyl. In certain embodiments,  $R^{B1a}$  is C<sub>1-6</sub> alkyl. In certain embodiments,  $R^{B1a}$  is methyl. In certain embodiments,  $R^{B1a}$  is ethyl. In certain embodiments,  $R^{B1a}$  is propyl. In certain embodiments,  $R^{B1a}$  is butyl. In certain embodiments,  $R^{B1a}$  is substituted alkenyl. In certain embodiments,  $R^{B1a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{B1a}$  is vinyl. In certain embodiments,  $R^{B1a}$  is substituted alkynyl. In certain embodiments,  $R^{B1a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{B1a}$  is ethynyl. In certain embodiments,  $R^{B1a}$  is substituted carbocyclyl. In certain embodiments,  $R^{B1a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{B1a}$  is substituted heterocyclyl. In certain embodiments,  $R^{B1a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{B1a}$  is substituted aryl. In certain embodiments,  $R^{B1a}$  is unsubstituted aryl. In certain embodiments,  $R^{B1a}$  is substituted phenyl. In certain embodiments,  $R^{B1a}$  is unsubstituted phenyl. In certain embodiments,  $R^{B1a}$  is substituted or unsubstituted heteroaryl. In certain embodiments,  $R^{B1a}$  is substituted or unsubstituted pyridyl. In certain embodiments,  $R^{B1a}$  is an oxygen protecting group when attached to an oxygen atom. In certain embodiments,  $R^{B1a}$  is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments,  $R^{B1a}$  is a sulfur protecting group when attached to a sulfur atom. In certain embodiments,  $R^{B1a}$  is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

**[00141]** In certain embodiments,  $R^{1b}$  is  $-N(R^{B1b})_2$ . In certain embodiments, at least one instance of  $R^{B1b}$  is substituted acyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted acyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted or unsubstituted acetyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted alkyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted alkyl. In certain embodiments, at least one instance of  $R^{B1b}$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one instance of  $R^{B1b}$  is methyl. In certain embodiments, at least one instance of  $R^{B1b}$  is ethyl. In certain embodiments, at least one instance of  $R^{B1b}$  is propyl. In certain embodiments, at least one instance of  $R^{B1b}$  is butyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted alkenyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted alkenyl. In certain embodiments,  $R^{B1b}$  is vinyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted alkynyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted alkynyl. In certain embodiments, at least one instance of  $R^{B1b}$  is ethynyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted carbocyclyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted carbocyclyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted heterocyclyl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted heterocyclyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted aryl. In certain embodiments, at least one instance of  $R^{B1b}$  is unsubstituted aryl. In certain embodiments,  $R^{B1b}$  is substituted phenyl. In certain embodiments,  $R^{B1b}$  is unsubstituted phenyl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted or unsubstituted heteroaryl. In certain embodiments, at least one instance of  $R^{B1b}$  is substituted or unsubstituted pyridyl. In certain embodiments, at least one instance of  $R^{B1b}$  is a nitrogen protecting group when attached to a nitrogen atom (e.g., Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, two instances of  $R^{B1b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

**[00142]** As generally defined herein, in Formulae (I') and (II),  $R^2$  is a divalent linker moiety connecting Ring B and Ring C. In certain embodiments,  $R^2$  is  $-O-$ . In certain embodiments,  $R^2$  is  $-S-$ . In certain embodiments,  $R^2$  is  $-N(R^6)-$ , wherein each  $R^6$  is independently selected from hydrogen and  $-C_1-C_6$  alkyl. In certain embodiments,  $R^2$  is  $-NH-$ . In certain embodiments,  $R^2$  is  $-N(C_1-C_6$  alkyl)- (e.g.,  $-N(Me)$ ). In certain embodiments,  $R^2$  is an optionally substituted  $C_1-C_4$  alkylene, wherein one or more methylene units of the alkylene are optionally and independently replaced with  $-O-$ ,  $-S-$ , or  $-N(R^6)-$ . In certain embodiments,

$R^2$  is an optionally substituted  $C_2$  hydrocarbon chain, optionally wherein one or two carbon units of the hydrocarbon chain is replaced with  $-O-$ ,  $-S-$ , or  $-NR^6-$ . In certain embodiments,  $R^2$  is an optionally substituted  $C_3$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain is replaced with  $-O-$ ,  $-S-$ , or  $-NR^6-$ . In certain embodiments,  $R^2$  is an optionally substituted  $C_4$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain is replaced with  $-O-$ ,  $-S-$ , or  $-NR^6-$ . In certain embodiments, at least one carbon unit of the  $C_{1-4}$  hydrocarbon chain is substituted with one or more substituents independently selected from the group consisting of  $-O-$ ,  $-S-$ , or  $-NR^6-$  (e.g.,  $-NH-$  or  $-NMe-$ ).



[00143] Formulae (I') and (II) include Ring C of the formula: . In certain embodiments,  $Z$  is  $-CH-$ . In certain embodiments,  $Z$  is  $N$ . In certain embodiments, Ring C is

of formula: , (e.g., ). In certain embodiments, Ring C is of formula:

, , or . In certain embodiments, Ring C is of formula:

. In certain embodiments, Ring C is of formula: . In certain

embodiments, Ring C is of formula: , , or . In certain

embodiments, Ring C is of formula: . In certain embodiments, Ring C is of

formula: . In certain embodiments, Ring C is of formula: ,

, or . Ring C may include one or more instances of substituent  $R^3$ .

In certain embodiments,  $n$  is 0. In certain embodiments,  $n$  is 1. In certain embodiments,  $n$  is 2.

In certain embodiments, n is 3. In certain embodiments, n is 4. In certain embodiments, n is 5.

In certain embodiments, n is 6.

[00144] In certain embodiments, at least one instance of R<sup>3</sup> is halogen (e.g., F, Cl, Br, or I).

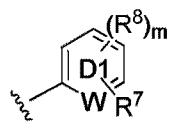
In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted acyl (e.g., -C(=O)Me). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted alkyl (e.g., substituted or unsubstituted C<sub>1-6</sub> alkyl). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted alkenyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkenyl). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted alkynyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkynyl). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R<sup>3</sup> is benzyl. In certain embodiments, at least one instance of R<sup>3</sup> is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R<sup>A1</sup> is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>3</sup> is -OR<sup>C1</sup> (e.g., -OH or -OMe). In certain embodiments, at least one instance of R<sup>3</sup> is -N(R<sup>C1a</sup>)<sub>2</sub> (e.g., -NMe<sub>2</sub>). In certain embodiments, at least one instance of R<sup>3</sup> is -SR<sup>C1</sup> (e.g., -SMe). In certain embodiments, two R<sup>3</sup> groups bound to the same ring carbon atom are taken together to form =O. In certain embodiments, two R<sup>3</sup> groups bound to the same or different ring carbon atoms are joined to form an optionally substituted carbocyclyl ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, two R<sup>3</sup> groups bound to the same or different ring carbon

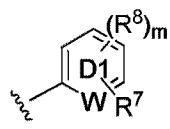
atoms are joined to form an optionally substituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, two R<sup>3</sup> groups bound to the same or different ring carbon atoms are joined to form an optionally substituted aryl. In certain embodiments, two R<sup>3</sup> groups bound to the same or different ring carbon atoms are joined to form an optionally substituted heteroaryl ring (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

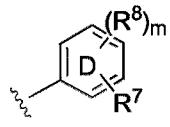
[00145] In certain embodiments, each occurrence of R<sup>C1</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom. In certain embodiments, each occurrence of R<sup>C1a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of R<sup>C1a</sup> are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

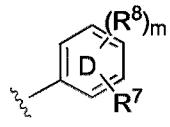
[00146] As generally defined herein, in Formula (I'), R<sup>4</sup> is a divalent linker moiety connecting Ring C and Ring D1. As generally defined herein, in Formula (I), R<sup>4</sup> is a divalent linker moiety connecting Ring C and Ring D. In certain embodiments, R<sup>4</sup> is a bond. In certain embodiments, R<sup>4</sup> is a single bond. In certain embodiments, R<sup>4</sup> is -C(=O)-. In certain embodiments, R<sup>4</sup> is -O-. In certain embodiments, R<sup>4</sup> is -S-. In certain embodiments, R<sup>4</sup> is -N(R<sup>6</sup>)- (e.g., -NH-). In certain embodiments, R<sup>4</sup> is -S(=O)<sub>2</sub>- . In certain embodiments, R<sup>4</sup> is an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkylene, wherein: one or more methylene units of the alkylene other than a methylene unit bound to a nitrogen atom is optionally and independently replaced with -C(=O)-, -O-, -S-, -N(R<sup>6</sup>)-, or -S(=O)<sub>2</sub>- . In certain embodiments, R<sup>4</sup> is an optionally substituted C<sub>2</sub> hydrocarbon chain, optionally wherein one

or two carbon units of the hydrocarbon chain is replaced with  $-O-$ ,  $-S-$ ,  $-NR^6-$ , or  $-S(=O)2-$ . In certain embodiments,  $R^4$  is  $-NR^6C(=O)-$ ,  $-C(=O)NR^6-$ ,  $-NR^6S(=O)2-$ ,  $-S(=O)2NR^6-$ ,  $-NR^6(C_{1-2}$  alkylene) $-$ , or  $-(C_{1-2}$  alkylene) $NR^6-$ . In certain embodiments,  $R^4$  is  $-NR^6C(=O)-$ ,  $-C(=O)NR^6-$ ,  $-NR^6S(=O)2-$ ,  $-S(=O)2NR^6-$ ,  $-NR^6(C_{1-2}$  alkylene) $-$ . In certain embodiments,  $R^4$  is  $-NHC(=O)-$ ,  $-C(=O)NH-$ ,  $-NHS(=O)2-$ ,  $-N(C(O)OC(CH_3)_3)-$ ,  $-N(Boc)-CH_2-$ ,  $-NH-$ ,  $-NHCH_2-$ ,  $-NMeCH_2-$ , or  $-OCH_2-$ . In certain embodiments,  $R^4$  is an optionally substituted  $C_4$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain is replaced with  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-N(R^6)-$ , or  $-S(=O)2-$ . In certain embodiments, at least one carbon unit of the  $C_{1-4}$  hydrocarbon chain is substituted with one or more substituents independently selected from the group consisting of  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-N(R^6)-$ , or  $-S(=O)2-$ .

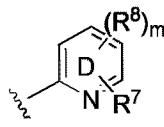
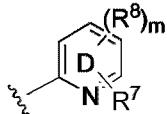


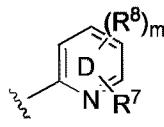
**[00147]** Formula (I') includes Ring D1 of the formula:  , wherein  $W$  is  $-CR^{D1}=$  or  $-N=$ , and  $R^{D1}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally



substituted heteroaryl. In certain embodiments, Ring D1 is  . In certain embodiments,  $W$  is  $-CH=$ . In certain embodiments,  $W$  is  $-C(Me)-$ . In certain embodiments,  $W$  is  $-N=$ .

**[00148]** In certain embodiments, Ring D1 is a compound of Ring D of the formula:

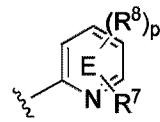


**[00149]** Formula (I) includes Ring D of the formula:  . Ring D includes zero or more instances of substituent  $R^8$ . In certain embodiments,  $m$  is 0. In certain embodiments,  $m$  is 1. In certain embodiments,  $m$  is 2. In certain embodiments,  $m$  is 3. In certain embodiments,  $m$  is 4. In certain embodiments, at least one instance of  $R^8$  is hydrogen, halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of  $R^8$  is F. In certain embodiments, at least one instance of  $R^8$  is Cl. In certain embodiments, at least one instance of  $R^8$  is Br. In certain embodiments, at least one instance of  $R^8$  is I (iodine). In certain embodiments, at least

one instance of R<sup>8</sup> is substituted or unsubstituted acyl (e.g., -C(=O)Me). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkyl (e.g., substituted or unsubstituted C<sub>1-6</sub> alkyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted C<sub>1-6</sub> alkyl. In certain embodiments, at least one instance of R<sup>8</sup> is unsubstituted C<sub>1-6</sub> alkyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is unsubstituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkenyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkenyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkynyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkynyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R<sup>8</sup> is benzyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>8</sup> is -OR<sup>D1</sup> (e.g., -OH or -OMe). In certain embodiments, at least one instance of R<sup>8</sup> is -OH. In certain embodiments, at least one instance of R<sup>8</sup> is -OMe. In certain embodiments, at least one instance of R<sup>8</sup> is -O(C<sub>1-6</sub> alkyl). In certain embodiments, at least one instance of R<sup>8</sup> is -N(R<sup>D1a</sup>)<sub>2</sub> (e.g., -NMe<sub>2</sub>). In certain embodiments, at least one instance of R<sup>8</sup> is -NMe<sub>2</sub>. In certain embodiments, at least one instance of R<sup>8</sup> is -SR<sup>D1</sup> (e.g., -SMe). In certain embodiments, at least one instance of R<sup>8</sup> is halogen, -O(alkyl), or optionally substituted alkyl. In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally

substituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted aryl ring (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted heteroaryl ring (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00150] In certain embodiments, each occurrence of R<sup>D1</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom. In certain embodiments, each occurrence of R<sup>D1a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of R<sup>D1a</sup> are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.



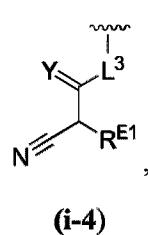
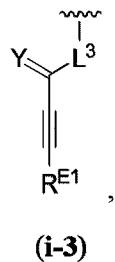
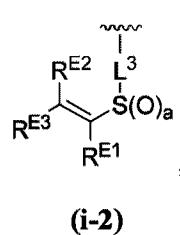
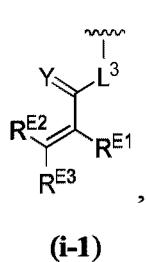
[00151] Formula (III) includes Ring E of the formula: . Ring E includes zero or more instances of substituent R<sup>8</sup>. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, m is 3. In certain embodiments, p is 4. In certain embodiments, p is 5. In certain embodiments, at least one instance of R<sup>8</sup> is hydrogen. In certain embodiments, at least one instance of R<sup>8</sup> is halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of R<sup>8</sup> is F. In certain embodiments, at least one instance of R<sup>8</sup> is Cl. In certain embodiments, at least one instance of R<sup>8</sup> is Br. In certain embodiments, at least one instance of R<sup>8</sup> is I (iodine). In certain embodiments, at least one

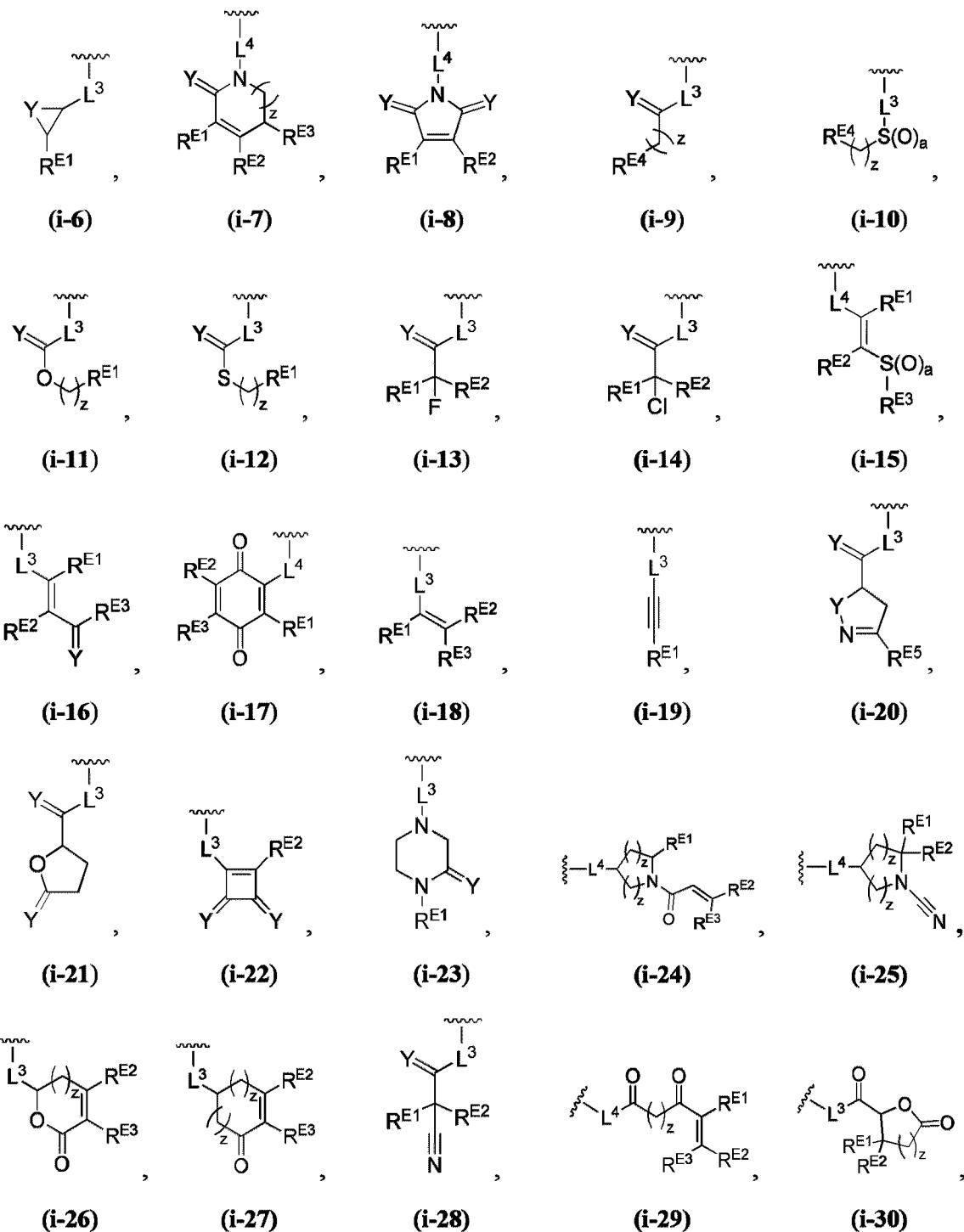
instance of R<sup>8</sup> is substituted or unsubstituted acyl (e.g., -C(=O)Me). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkyl (e.g., substituted or unsubstituted C<sub>1-6</sub> alkyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted C<sub>1-6</sub> alkyl. In certain embodiments, at least one instance of R<sup>8</sup> is unsubstituted C<sub>1-6</sub> alkyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is unsubstituted methyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted ethyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted propyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkenyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkenyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted alkynyl (e.g., substituted or unsubstituted C<sub>2-6</sub> alkynyl). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R<sup>8</sup> is benzyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R<sup>8</sup> is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R<sup>8</sup> is -OR<sup>D1</sup> (e.g., -OH or -OMe). In certain embodiments, at least one instance of R<sup>8</sup> is -OH. In certain embodiments, at least one instance of R<sup>8</sup> is -OMe. In certain embodiments, at least one instance of R<sup>8</sup> is -O(C<sub>1-6</sub> alkyl). In certain embodiments, at least one instance of R<sup>8</sup> is -N(R<sup>D1a</sup>)<sub>2</sub> (e.g., -NMe<sub>2</sub>). In certain embodiments, at least one instance of R<sup>8</sup> is -NMe<sub>2</sub>. In certain embodiments, at least one instance of R<sup>8</sup> is -SR<sup>D1</sup> (e.g., -SMe). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the

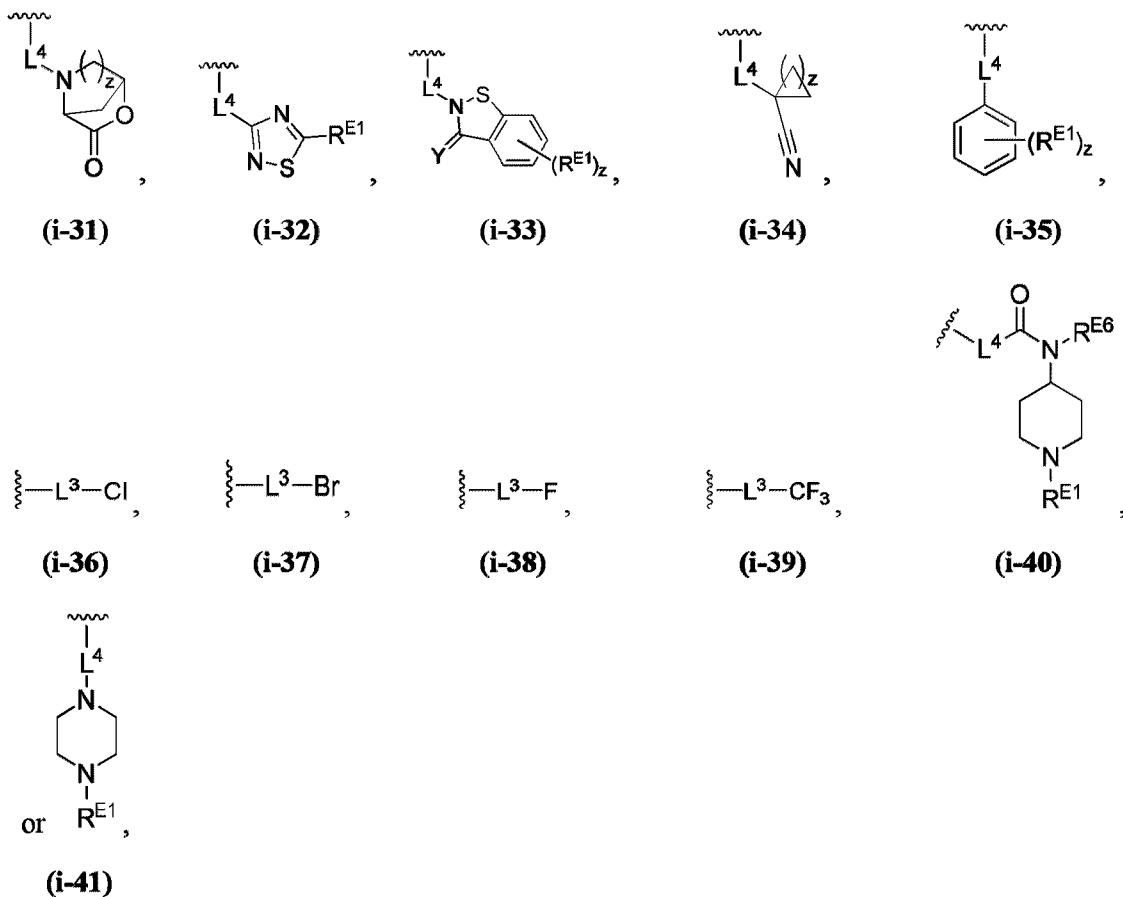
carbocyclic ring system). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted heterocyclyl (e.g., substituted or unsubstituted, 5- to 10-membered monocyclic or bicyclic heterocyclic ring, wherein one or two atoms in the heterocyclic ring are independently nitrogen, oxygen, or sulfur). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted aryl ring (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, two R<sup>8</sup> groups are joined to form an optionally substituted heteroaryl ring (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur; or substituted or unsubstituted, 9- to 10-membered, bicyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00152] In certain embodiments, each occurrence of R<sup>D1</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom. In certain embodiments, each occurrence of R<sup>D1a</sup> is independently selected from hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, a nitrogen protecting group, or optionally two instances of R<sup>D1a</sup> are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

[00153] As generally defined herein, Formulae (I') and (II) include substituent R<sup>7</sup>, wherein R<sup>7</sup> is a warhead of formula:





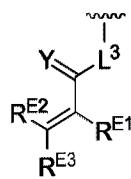


wherein:

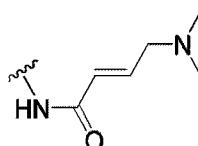
$L^3$  is a bond or an optionally substituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-\text{C=O}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}^{L3a}-$ ,  $-\text{NR}^{L3a}\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^{L3a}-$ ,  $-\text{SC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{S}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{NR}^{L3a}\text{C}(=\text{S})-$ ,  $-\text{C}(=\text{S})\text{NR}^{L3a}-$ ,  $-\text{trans-}CR^{L3b}=\text{CR}^{L3b}-$ ,  $-\text{cis-}CR^{L3b}=\text{CR}^{L3b}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})\text{O}-$ ,  $-\text{OS}(=\text{O})-$ ,  $-\text{S}(=\text{O})\text{NR}^{L3a}-$ ,  $-\text{NR}^{L3a}\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{O}-$ ,  $-\text{OS}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{NR}^{L3a}-$ , or  $-\text{NR}^{L3a}\text{S}(=\text{O})_2-$ , wherein  $R^{L3a}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group, and wherein each occurrence of  $R^{L3b}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{L3b}$  groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;  $L^4$  is a bond or an optionally substituted, branched or unbranched  $C_{1-6}$  hydrocarbon chain; each of  $R^{E1}$ ,  $R^{E2}$ , and  $R^{E3}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally

substituted aryl, optionally substituted heteroaryl,  $-\text{CN}$ ,  $-\text{CH}_2\text{OR}^{\text{EE}}$ ,  $-\text{CH}_2\text{N}(\text{R}^{\text{EE}})_2$ ,  $-\text{CH}_2\text{SR}^{\text{EE}}$ ,  $-\text{OR}^{\text{EE}}$ ,  $-\text{N}(\text{R}^{\text{EE}})_2$ ,  $-\text{Si}(\text{R}^{\text{EE}})_3$ , or  $-\text{SR}^{\text{EE}}$ , wherein each instance of  $\text{R}^{\text{EE}}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $\text{R}^{\text{EE}}$  groups are joined to form an optionally substituted heterocyclic ring; or  $\text{R}^{\text{E}1}$  and  $\text{R}^{\text{E}3}$ , or  $\text{R}^{\text{E}2}$  and  $\text{R}^{\text{E}3}$ , or  $\text{R}^{\text{E}1}$  and  $\text{R}^{\text{E}2}$  are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;  $\text{R}^{\text{E}4}$  is a leaving group;  $\text{R}^{\text{E}5}$  is halogen;  $\text{R}^{\text{E}6}$  is hydrogen, substituted or unsubstituted  $\text{C}_{1-6}$  alkyl, or a nitrogen protecting group; each instance of  $\text{Y}$  is independently  $\text{O}$ ,  $\text{S}$ , or  $\text{NR}^{\text{E}7}$ , wherein  $\text{R}^{\text{E}7}$  is hydrogen, substituted or unsubstituted  $\text{C}_{1-6}$  alkyl, or a nitrogen protecting group;  $\text{a}$  is 1 or 2; and each instance of  $\text{z}$  is independently 0, 1, 2, 3, 4, 5, or 6, as valency permits.

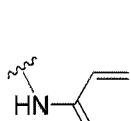
[00154] In certain embodiments,  $\text{R}^7$  is a warhead of formula (i-1) through (i-41). In certain



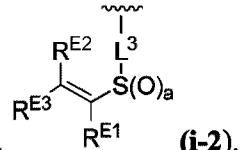
embodiments, the warhead is of formula (i-1). In certain embodiments,  $\text{R}^7$  is a



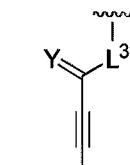
warhead is of formula (i-2). In certain embodiments,  $\text{R}^7$  is a warhead is of



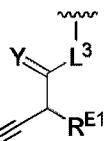
formula (i-3). In certain embodiments, the warhead is of formula

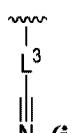


In certain embodiments, the warhead is of formula (i-4). In certain embodiments, the warhead is of formula

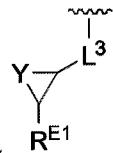


warhead is of formula (i-5). In certain embodiments, the warhead is of formula

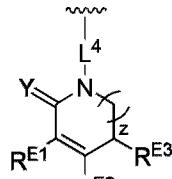




(i-5). In certain embodiments, the warhead is of formula

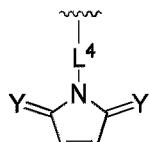


(i-6). In certain

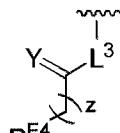


embodiments, the warhead is of formula

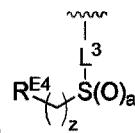
(i-7). In certain embodiments, the



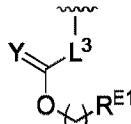
warhead is of formula (i-8). In certain embodiments, the warhead is of formula



(i-9). In certain embodiments, the warhead is of formula

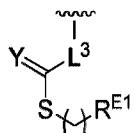


(i-10). In



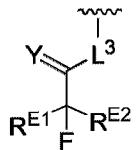
certain embodiments, the warhead is

(i-11). In certain embodiments, the warhead

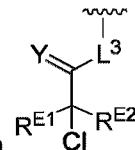


is of formula

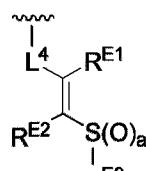
(i-12). In certain embodiments, the warhead is of formula



(i-13). In certain embodiments, the warhead is of formula

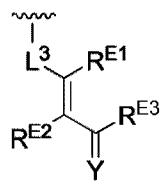


(i-14). In



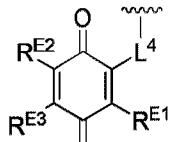
certain embodiments, the warhead is of formula

(i-15).



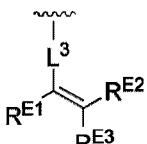
[00155] In certain embodiments, the warhead is of formula

(i-16). In certain



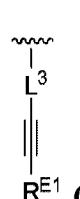
embodiments, the warhead is of formula

(i-17). In certain embodiments, the

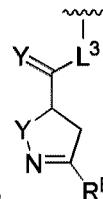


warhead is of formula

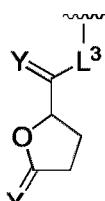
(i-18). In certain embodiments, the warhead is of formula



(i-19). In certain embodiments, the warhead is of formula

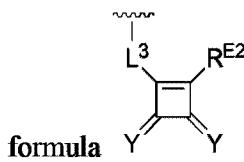


(i-20). In certain



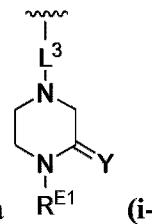
embodiments, the warhead is

(i-21). In certain embodiments, the warhead is of

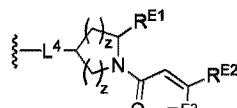


formula

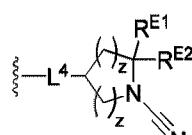
(i-22). In certain embodiments, the warhead is of formula



(i-23). In certain embodiments, the warhead is of formula

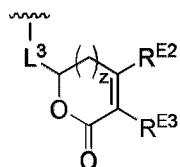


(i-24). In certain



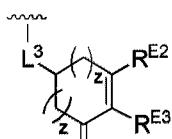
embodiments, the warhead is of formula

(i-25). In certain embodiments, the



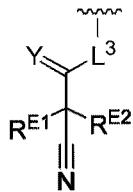
warhead is of formula

(i-26). In certain embodiments, the warhead is of

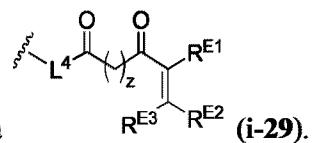


formula

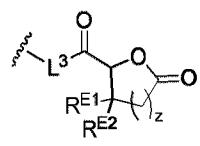
(i-27). In certain embodiments, the warhead is of formula



(i-28). In certain embodiments, the warhead is of formula

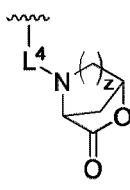


[00156] In certain embodiments, the warhead is of formula



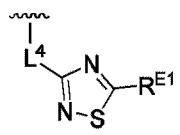
(i-29).

embodiments, the warhead is of formula



(i-30). In certain

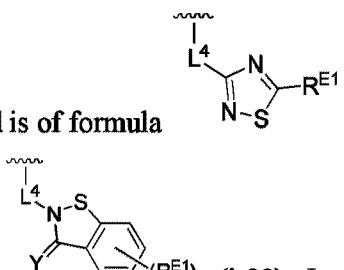
warhead is of formula



(i-31). In certain embodiments, the

(i-32). In certain embodiments, the warhead is of

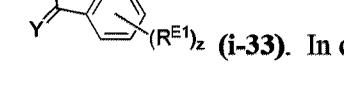
formula



(i-32). In certain embodiments, the warhead is of

(i-33). In certain embodiments, the warhead is of formula

formula

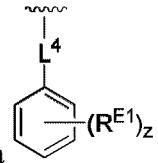


(i-33). In certain embodiments, the warhead is of

(i-34). In certain embodiments, the warhead is of formula

(i-34). In certain embodiments, the warhead is of formula

(i-34). In certain embodiments, the warhead is of formula



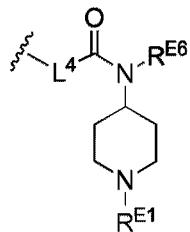
(i-34). In certain

certain embodiments, the warhead is of formula

(i-36). In certain embodiments, the warhead is of formula

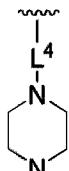
(i-37). In certain embodiments, the warhead is of formula

(i-38). In certain embodiments, the warhead is of formula



39). In certain embodiments, the warhead is of formula

(i-40). In certain



embodiments, the warhead is of formula (i-41).

[00157] In certain embodiments, L<sup>3</sup> is a bond (e.g., a single bond, a double bond, or a triple bond). In certain embodiments, L<sup>3</sup> is a single bond. In certain embodiments, L<sup>3</sup> is a double bond. In certain embodiments, L<sup>3</sup> is a triple bond. In certain embodiments, L<sup>3</sup> is an optionally substituted C<sub>1-4</sub> hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with –C=O–, –O–, –S–, –NR<sup>L3a</sup>–, –NR<sup>L3a</sup>C(=O)–, –C(=O)NR<sup>L3a</sup>–, –SC(=O)–, –C(=O)S–, –OC(=O)–, –C(=O)O–, –NR<sup>L3a</sup>C(=S)–, –C(=S)NR<sup>L3a</sup>–, *trans*–CR<sup>L3b</sup>=CR<sup>L3b</sup>–, *cis*–CR<sup>L3b</sup>=CR<sup>L3b</sup>–, –C≡C–, –S(=O)–, –S(=O)O–, –OS(=O)–, –S(=O)NR<sup>L3a</sup>–, –NR<sup>L3a</sup>S(=O)–, –S(=O)<sub>2</sub>–, –S(=O)<sub>2</sub>O–, –OS(=O)<sub>2</sub>–, –S(=O)<sub>2</sub>NR<sup>L3a</sup>–, or –NR<sup>L3a</sup>S(=O)<sub>2</sub>–, wherein R<sup>L3a</sup> is hydrogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, or a nitrogen protecting group, and wherein each occurrence of R<sup>L3b</sup> is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two R<sup>L3b</sup> groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring. In certain embodiments, L<sup>4</sup> is a bond (e.g., a single bond, a double bond, or a triple bond). In certain embodiments, L<sup>4</sup> is an optionally substituted branched C<sub>1-6</sub> hydrocarbon chain (e.g., i-Pr). In certain embodiments, L<sup>4</sup> is an optionally substituted unbranched C<sub>1-6</sub> hydrocarbon chain (e.g., n-Pr, or n-Bu). In certain embodiments, at least one instance of R<sup>E1</sup> is H. In certain embodiments, at least one instance of R<sup>E1</sup> is halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of R<sup>E1</sup> is optionally substituted alkyl (e.g., Me, or Et). In certain embodiments, at least one instance of R<sup>E1</sup> is optionally substituted alkenyl (e.g., optionally substituted vinyl). In certain embodiments, at least one instance of R<sup>E1</sup> is optionally substituted alkynyl. In certain embodiments, at least one instance of R<sup>E1</sup> is substituted or unsubstituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered,

monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of  $R^{E1}$  is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E1}$  is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of  $R^{E1}$  is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of  $R^{E1}$  is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E1}$  is  $-CN$ . In certain embodiments, at least one instance of  $R^{E1}$  is  $-CH_2OR^{EE}$ , wherein each instance of  $R^{EE}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one instance of  $R^{E1}$  is  $-CH_2N(R^{EF})_2$  or  $N(R^{EF})_2$ , wherein each instance of  $R^{EF}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, optionally wherein two  $R^{EF}$  groups are joined to form an optionally substituted heterocyclic ring. In certain embodiments, at least one instance of  $R^{E1}$  is  $-CH_2SR^{EE}$  or  $-SR^{EE}$  (e.g.,  $-CH_2SMe$  or  $-SMe$ ). In certain embodiments, at least one instance of  $R^{E1}$  is  $-OR^{EE}$  (e.g.,  $-OMe$ ). In certain embodiments, at least one instance of  $R^{E1}$  is  $-Si(R^{EG})_3$ , wherein each instance of  $R^{EG}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl (e.g.,  $-Si(Me)_3$ ).

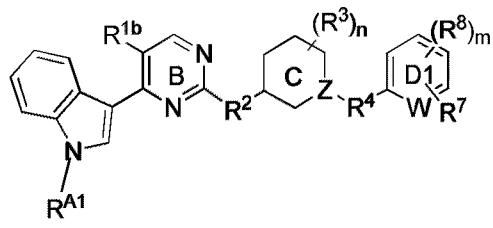
[00158] In certain embodiments, at least one instance of  $R^{E2}$  is H. In certain embodiments, at least one instance of  $R^{E2}$  is halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of  $R^{E2}$  is optionally substituted alkyl (e.g., Me, or Et). In certain embodiments, at least one instance of  $R^{E2}$  is optionally substituted alkenyl (e.g., optionally substituted vinyl). In certain embodiments, at least one instance of  $R^{E2}$  is optionally substituted alkynyl. In certain embodiments, at least one instance of  $R^{E2}$  is substituted or unsubstituted carbocyclyl

(e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of  $R^{E2}$  is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E2}$  is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of  $R^{E2}$  is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of  $R^{E2}$  is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E2}$  is  $-CN$ . In certain embodiments, at least one instance of  $R^{E2}$  is  $-CH_2OR^{EE}$ , wherein each instance of  $R^{EE}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one instance of  $R^{E2}$  is  $-CH_2N(R^{EF})_2$  or  $N(R^{EF})_2$ , wherein each instance of  $R^{EF}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally substituted aryl, or optionally substituted heteroaryl, optionally wherein two  $R^{EF}$  groups are joined to form an optionally substituted heterocyclic ring. In certain embodiments, at least one instance of  $R^{E2}$  is  $-CH_2SR^{EE}$  or  $-SR^{EE}$  (e.g.,  $-CH_2SMe$  or  $-SMe$ ). In certain embodiments, at least one instance of  $R^{E2}$  is  $-OR^{EE}$  (e.g.,  $-OMe$ ). In certain embodiments, at least one instance of  $R^{E2}$  is  $-Si(R^{EG})_3$ , wherein each instance of  $R^{EG}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl (e.g.,  $-Si(Me)_3$ ). In certain embodiments, at least one instance of  $R^{E3}$  is H. In certain embodiments, at least one instance of  $R^{E3}$  is halogen (e.g., F, Cl, Br, or I). In certain embodiments, at least one instance of  $R^{E3}$  is optionally substituted alkyl (e.g., Me, or Et). In certain embodiments, at least one instance of  $R^{E3}$  is optionally substituted alkenyl (e.g., optionally substituted vinyl). In certain embodiments, at least one instance of  $R^{E3}$  is optionally substituted alkynyl. In certain embodiments, at least one instance of  $R^{E3}$  is

substituted or unsubstituted carbocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of  $R^{E3}$  is substituted or unsubstituted heterocyclyl (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E3}$  is substituted or unsubstituted aryl (e.g., substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of  $R^{E3}$  is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of  $R^{E3}$  is substituted or unsubstituted heteroaryl (e.g., substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of  $R^{E3}$  is  $-CN$ . In certain embodiments, at least one instance of  $R^{E3}$  is  $-CH_2OR^{EE}$ , wherein each instance of  $R^{EE}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one instance of  $R^{E3}$  is  $-CH_2N(R^{EF})_2$  or  $N(R^{EF})_2$ , wherein each instance of  $R^{EF}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or optionally where two  $R^{EF}$  groups are joined to form an optionally substituted heterocyclic ring. In certain embodiments, at least one instance of  $R^{E3}$  is  $-CH_2SR^{EE}$  or  $-SR^{EE}$  (e.g.,  $-CH_2SMe$  or  $-SMe$ ). In certain embodiments, at least one instance of  $R^{E3}$  is  $-OR^{EE}$  (e.g.,  $-OMe$ ). In certain embodiments, at least one instance of  $R^{E3}$  is  $-Si(R^{EG})_3$ , wherein each instance of  $R^{EG}$  is independently hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl (e.g.,  $-Si(Me)_3$ ). In certain embodiments,  $R^{E1}$  and  $R^{E3}$  are joined to form an optionally substituted carbocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments,  $R^{E1}$  and  $R^{E3}$  are joined to form an optionally substituted heterocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system).

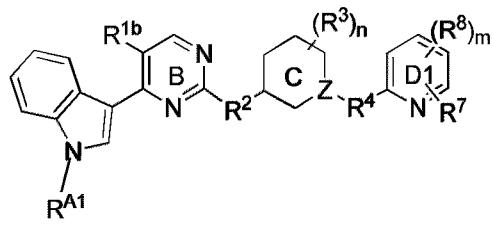
heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments,  $R^{E2}$  and  $R^{E3}$  are joined to form an optionally substituted carbocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments,  $R^{E2}$  and  $R^{E3}$  are joined to form an optionally substituted heterocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments,  $R^{E1}$  and  $R^{E2}$  are joined to form an optionally substituted carbocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments,  $R^{E1}$  and  $R^{E2}$  are joined to form an optionally substituted heterocyclic ring (e.g., substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments,  $R^{E4}$  is a leaving group (e.g., halogen, or a sulfonic acid ester, e.g.,  $-O(tosylate)$  or  $-O(mesylate)$ ). In certain embodiments,  $R^{E5}$  is halogen (e.g., F, Cl, Br, or I). In certain embodiments,  $R^{E6}$  is H. In certain embodiments,  $R^{E6}$  is substituted or unsubstituted C<sub>1-6</sub> alkyl (e.g., Me, is  $-CF_3$ , Bn, Et, perfluoroethyl, Pr, perfluoropropyl, Bu, or perfluorobutyl). In certain embodiments,  $R^{E6}$  is a nitrogen protecting group (e.g., Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, at least one instance of Y is O. In certain embodiments, at least one instance of Y is S. In certain embodiments, at least one instance of Y is  $NR^{E7}$ , wherein  $R^{E7}$  is hydrogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, or a nitrogen protecting group (e.g., NMe). In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, at least one instance of z is 0. In certain embodiments, at least one instance of z is 1. In certain embodiments, at least one instance of z is 2. In certain embodiments, at least one instance of z is 3. In certain embodiments, at least one instance of z is 4. In certain embodiments, at least one instance of z is 5. In certain embodiments, at least one instance of z is 6.

[00159] In certain embodiments, the compound of Formula (I') is of formula:



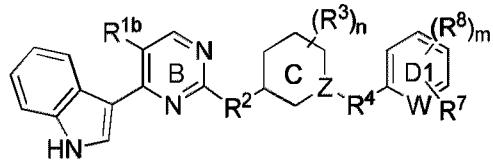
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00160] In certain embodiments, the compound of Formula (I) is of formula:



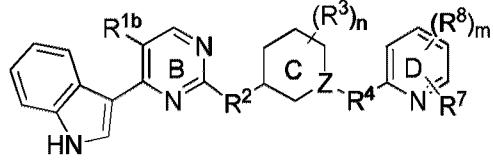
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00161] In certain embodiments, the compound of Formula (I') is of formula:



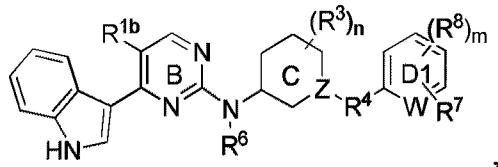
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00162] In certain embodiments, the compound of Formula (I) is of formula:



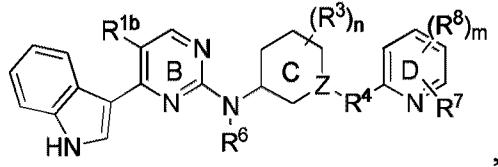
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00163] In certain embodiments, the compound of Formula (I') is of formula:



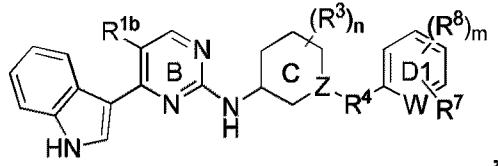
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00164] In certain embodiments, the compound of Formula (I) is of formula:



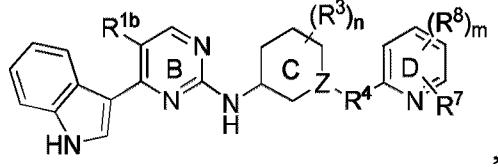
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00165] In certain embodiments, the compound of Formula (I') is of formula:



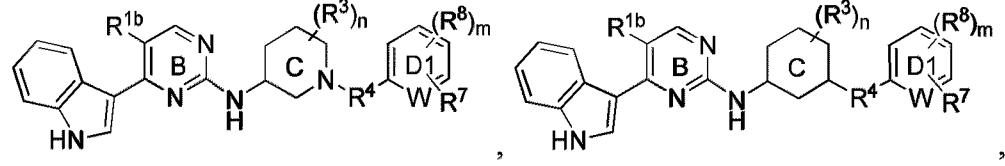
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00166] In certain embodiments, the compound of Formula (I) is of formula:



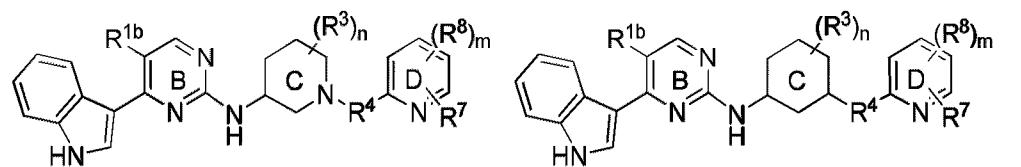
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00167] In certain embodiments, the compound of Formula (I') is of formula:



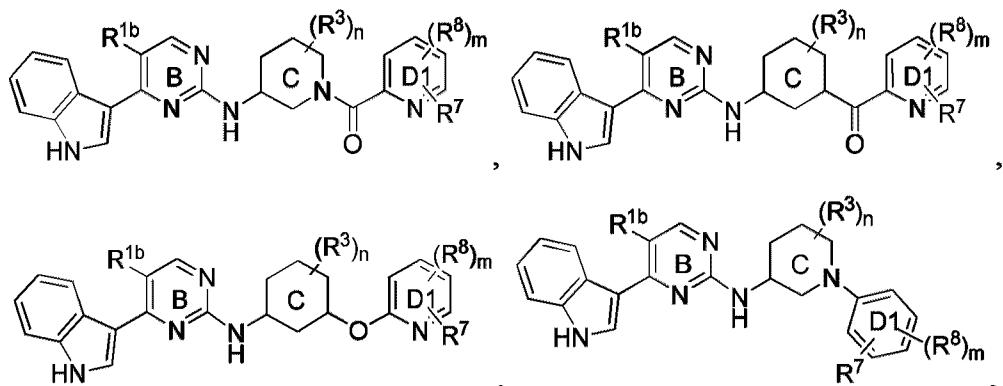
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00168] In certain embodiments, the compound of Formula (I) is of formula:



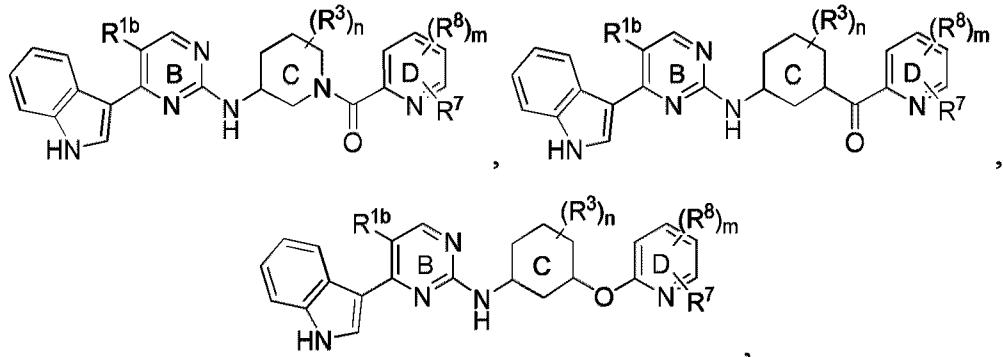
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00169] In certain embodiments, the compound of Formula (I') is of formula:



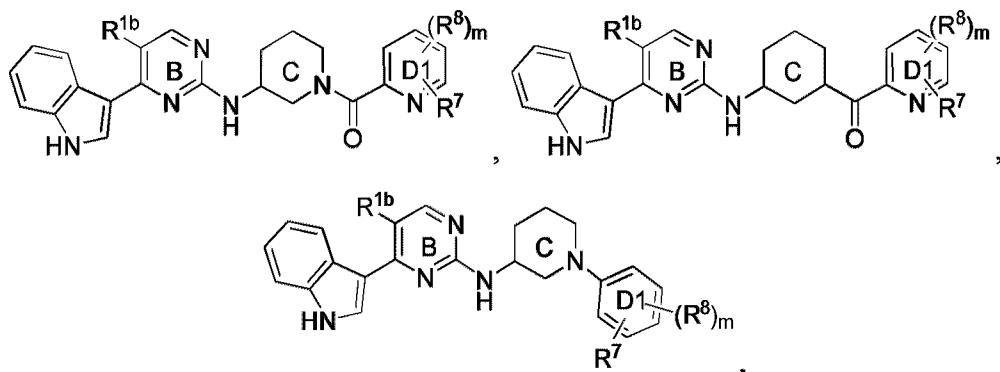
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00170] In certain embodiments, the compound of Formula (I) is of formula:



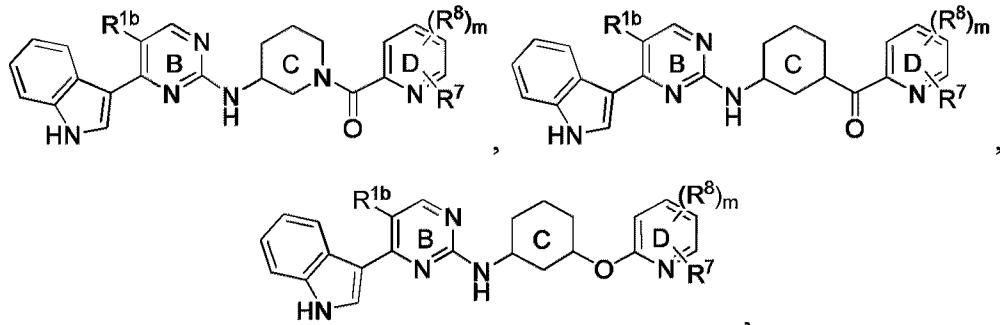
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00171] In certain embodiments, the compound of Formula (I') is of formula:



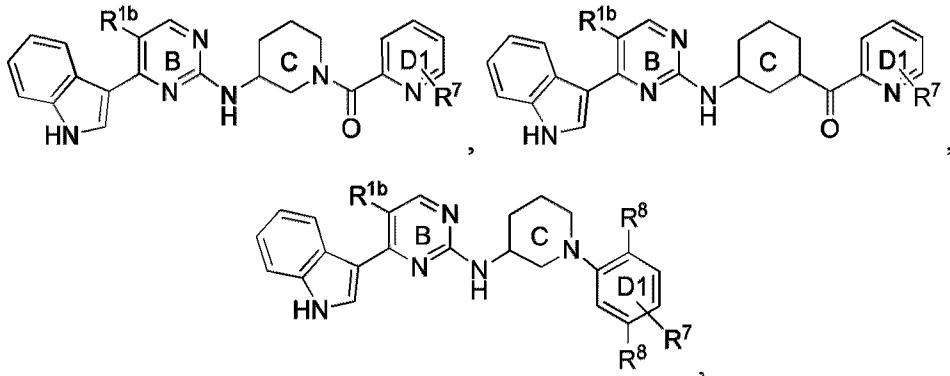
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00172] In certain embodiments, the compound of Formula (I) is of formula:



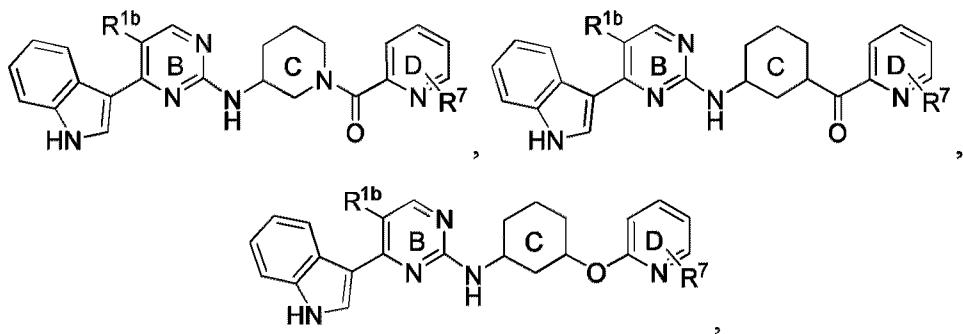
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00173] In certain embodiments, the compound of Formula (I') is of formula:



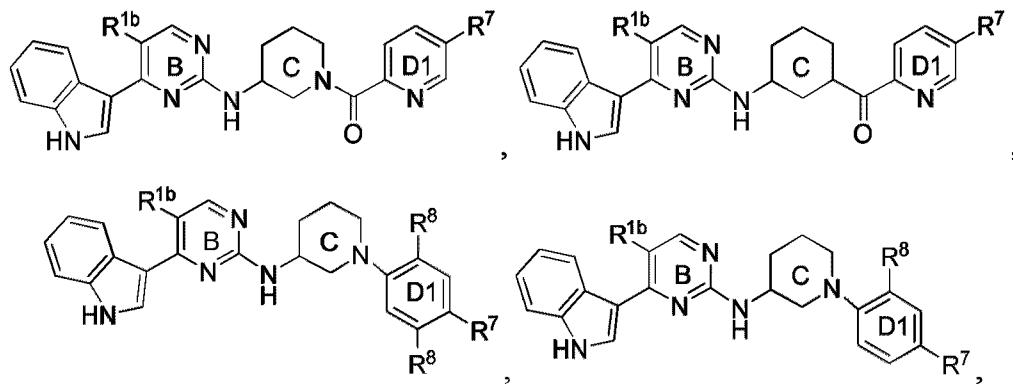
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00174] In certain embodiments, the compound of Formula (I) is of formula:



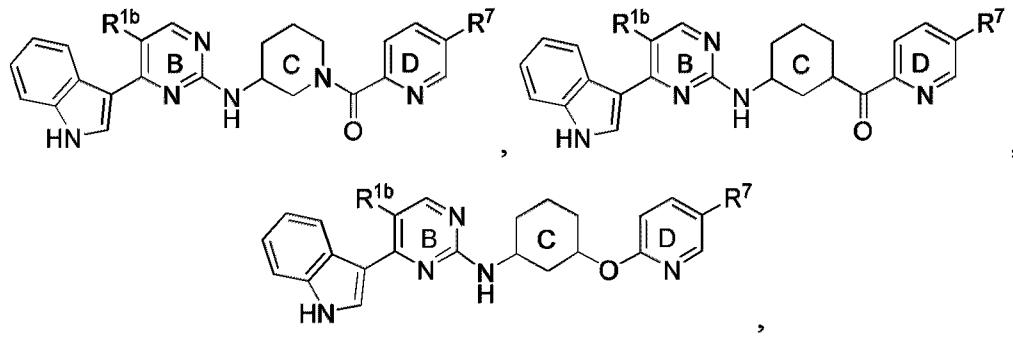
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00175] In certain embodiments, the compound of Formula (I') is of formula:



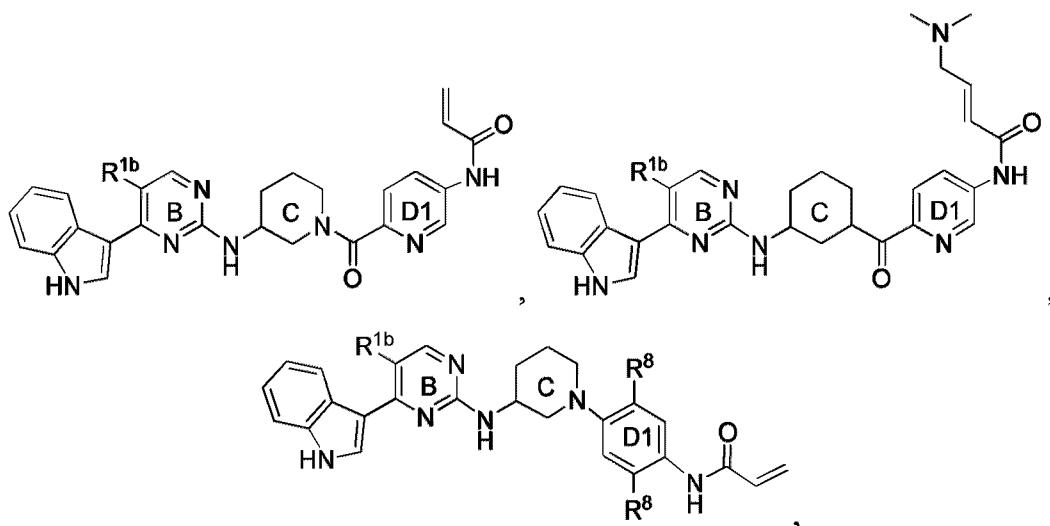
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00176] In certain embodiments, the compound of Formula (I) is of formula:



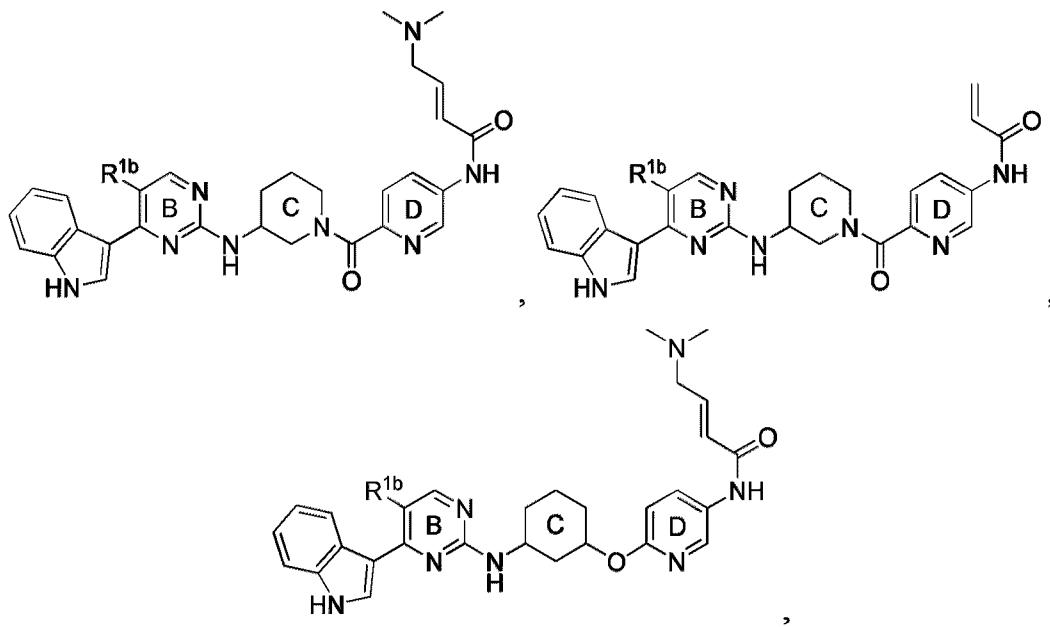
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00177] In certain embodiments, the compound of Formula (I') is of formula:



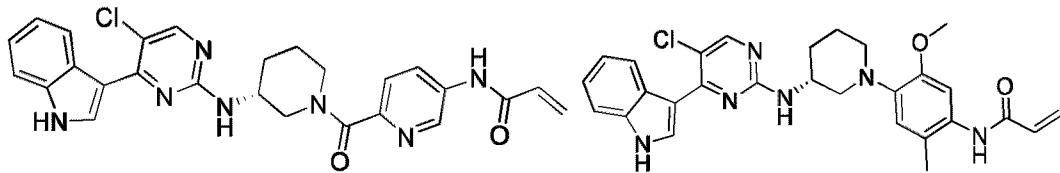
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

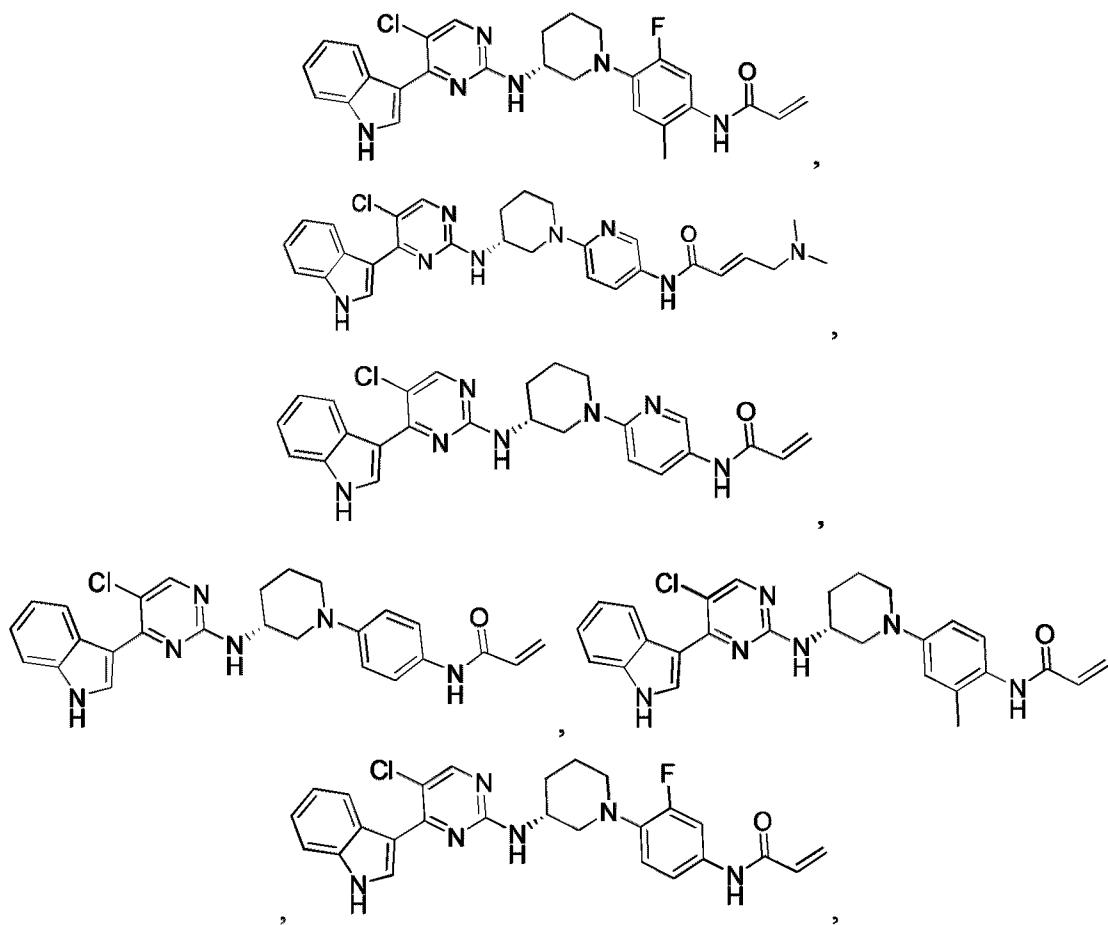
[00178] In certain embodiments, the compound of Formula (I) is of formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

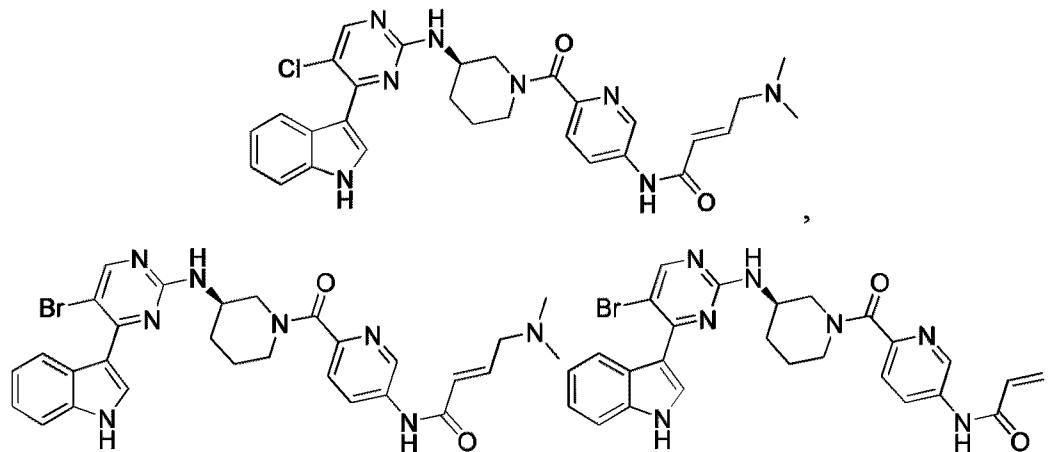
[00179] Exemplary compounds of Formula (I') include, but are not limited to:

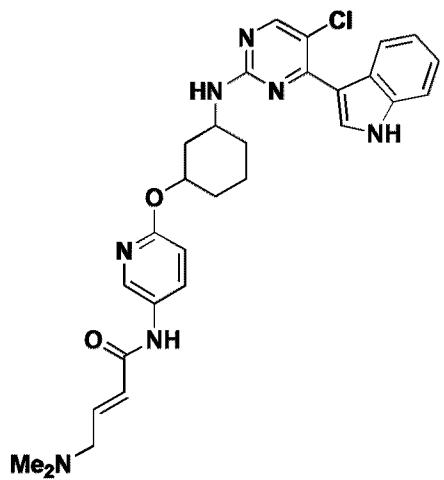




and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

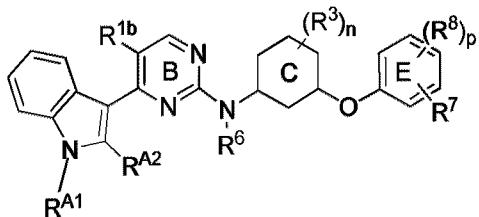
**[00180]** Exemplary compounds of Formula (I) include, but are not limited to:





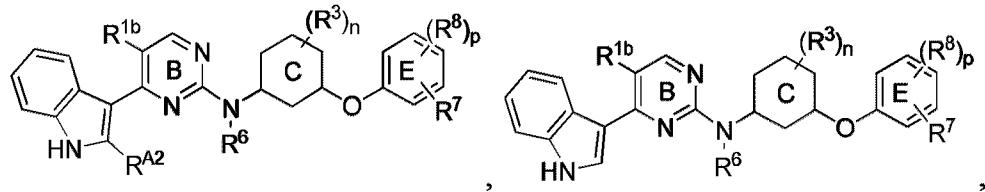
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

[00181] In another aspect, the present disclosure provides compounds of Formula (II):



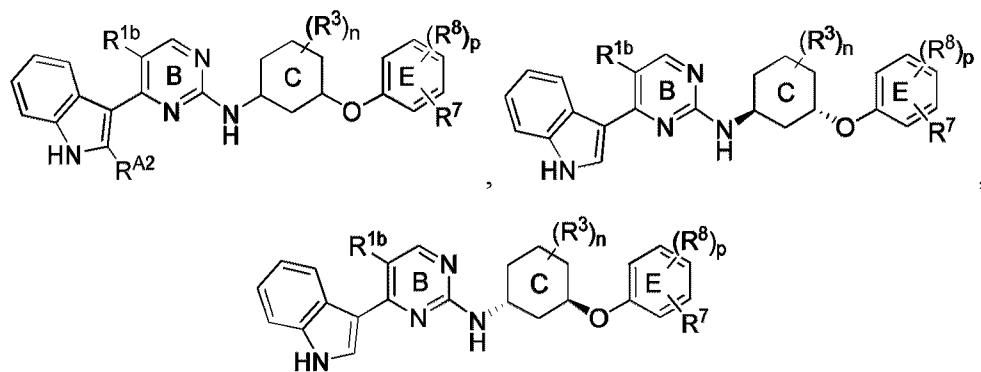
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00182] In certain embodiments, the compound of Formula (II) is of formula:



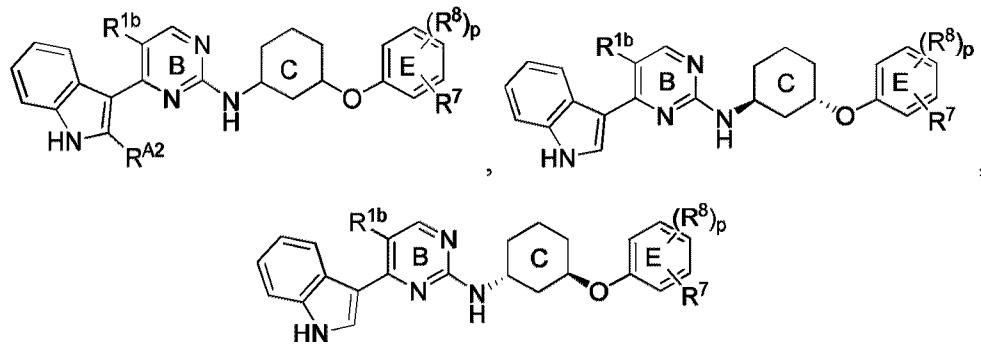
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00183] In certain embodiments, the compound of Formula (II) is of formula:



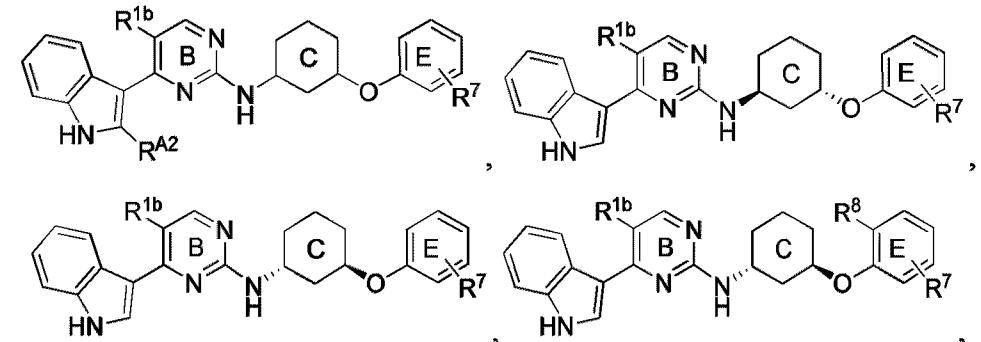
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00184] In certain embodiments, the compound of Formula (II) is of formula:



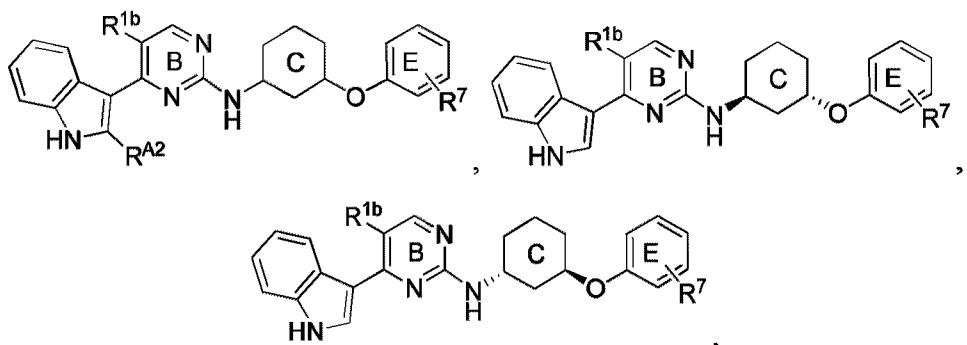
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00185] In certain embodiments, the compound of Formula (II) is of formula:



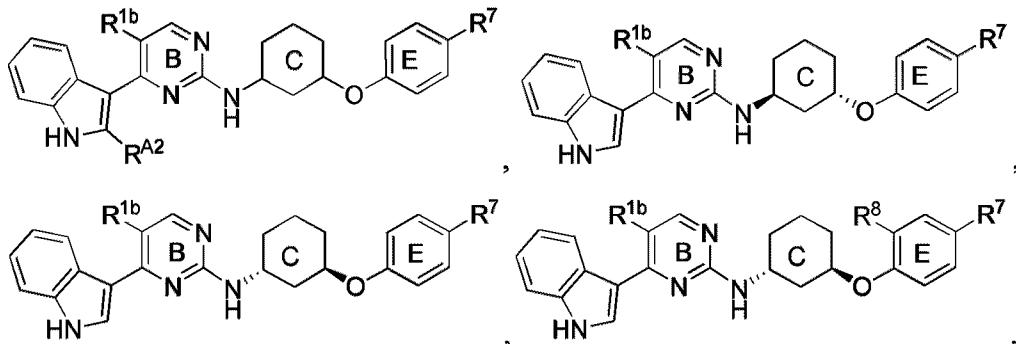
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00186] In certain embodiments, the compound of Formula (II) is of formula:



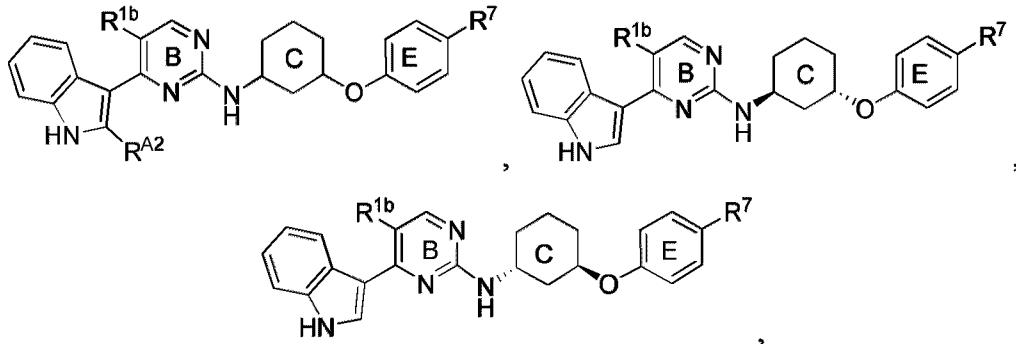
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00187] In certain embodiments, the compound of Formula (II) is of formula:



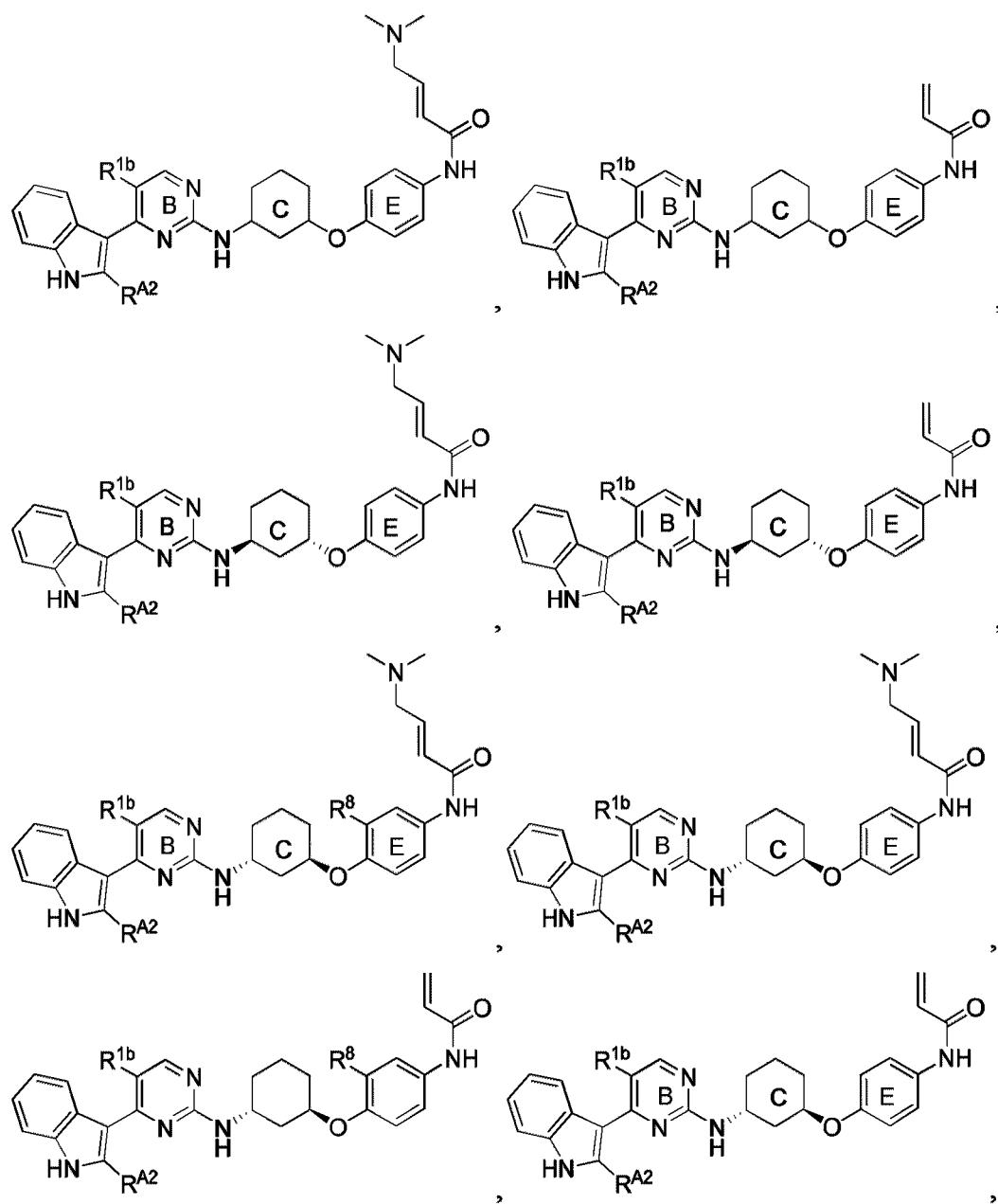
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00188] In certain embodiments, the compound of Formula (II) is of formula:



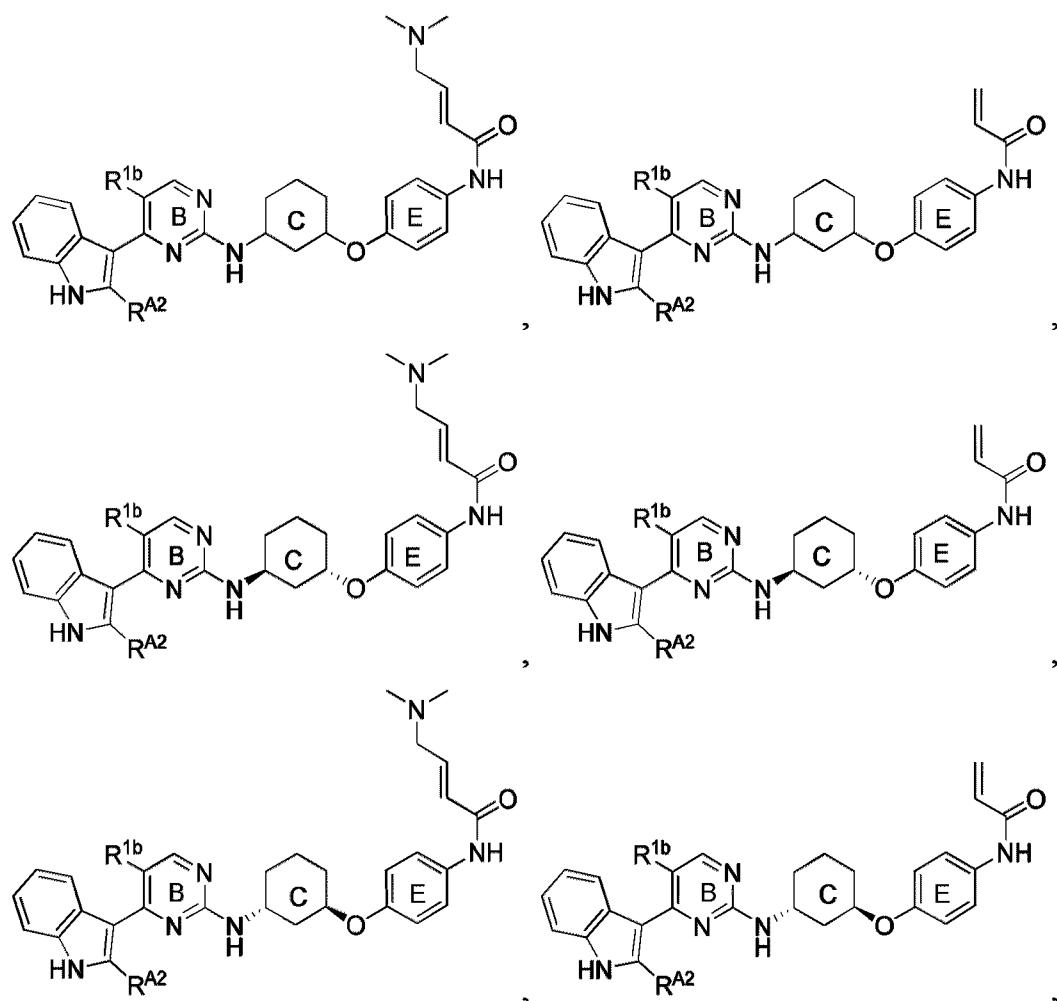
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00189] In certain embodiments, the compound of Formula (II) is of formula:



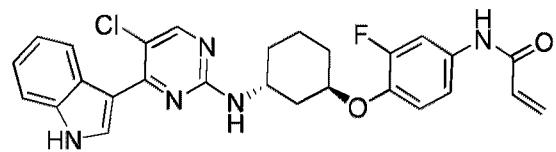
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

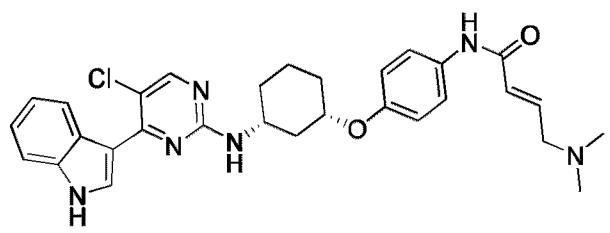
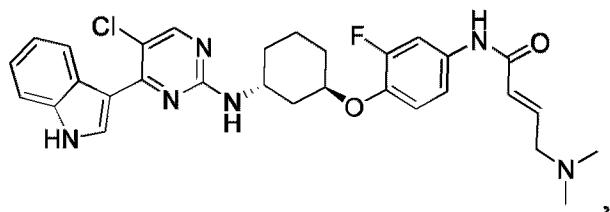
[00190] In certain embodiments, the compound of Formula (II) is of formula:



or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

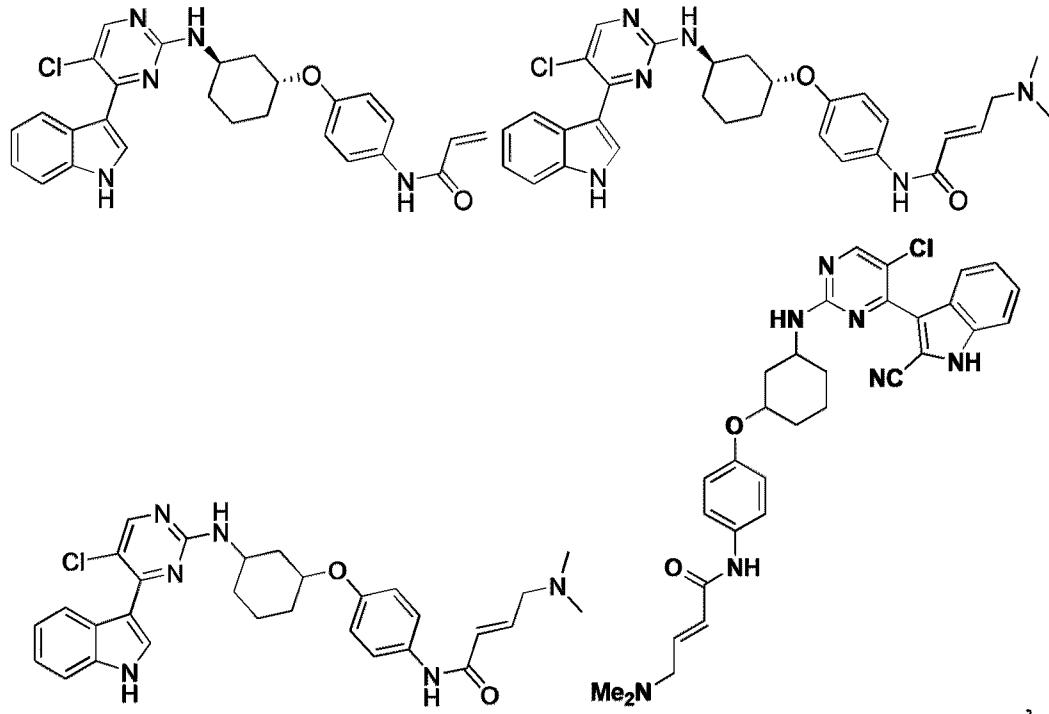
[00191] Exemplary compounds of Formula (II) include, but are not limited to:





and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

**[00192]** Exemplary compounds of Formula (II) include, but are not limited to:



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof.

#### *Pharmaceutical Compositions, Kits, and Administration*

**[00193]** The present disclosure also provides pharmaceutical compositions comprising a compound described herein and optionally a pharmaceutically acceptable excipient. In certain

embodiments, a compound described herein is a compound of Formula (I') or (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

**[00194]** In certain embodiments, the compound described herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, a therapeutically effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12). In certain embodiments, a therapeutically effective amount is an amount effective for treating a disease (e.g., a disease associated with aberrant activity of a CDK (e.g., proliferative disease)). In certain embodiments, a therapeutically effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12) and treating a disease (e.g., a disease associated with aberrant activity of a CDK (e.g., proliferative disease)). In certain embodiments, a therapeutically effective amount is an amount effective for inducing apoptosis in a cell. In certain embodiments, a therapeutically effective amount is an amount effective for affecting cell cycle control. In certain embodiments, a therapeutically effective amount is an amount effective for affecting DNA repair or DNA damage response. In certain embodiments, a prophylactically effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12). In certain embodiments, a prophylactically effective amount is an amount effective for preventing or keeping a subject in need thereof in remission of a disease (e.g., a disease associated with aberrant activity of a CDK (e.g., proliferative disease)). In certain embodiments, a prophylactically effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12, or a mutant form of CDK12), and preventing or keeping a subject in need thereof in remission of a disease (e.g., a disease associated with the activity of a CDK (e.g., proliferative disease)). In certain embodiments, a prophylactically effective amount is an amount effective for inducing apoptosis in a cell.

**[00195]** In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12) by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a CDK (e.g., CDK12) by not more than 10%, not more than 20%, not more than 30%, not more than 40%, not more than 50%, not more than 60%, not more than 70%, not more than 80%, not more than 90%, not more than 95%, or not more than 98%.

[00196] In certain embodiments, the subject is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject described herein is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal, such as a rodent (e.g., mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (e.g., transgenic mice and transgenic pigs). In certain embodiments, the subject is a fish or reptile.

[00197] In certain embodiments, the cell being contacted with a compound or composition described herein is *in vitro*. In certain embodiments, the cell being contacted with a compound or composition described herein is *in vivo*.

[00198] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the “active ingredient”) into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[00199] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[00200] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00201] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives,

buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00202] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00203] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00204] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (e.g., acacia, agar, alginic acid, sodium alginate, tragacanth, chondrus, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g., bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (e.g., stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carboomers (e.g., carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g., carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g., polyoxyethylene sorbitan monolaurate (Tween<sup>®</sup> 20), polyoxyethylene sorbitan (Tween<sup>®</sup> 60), polyoxyethylene sorbitan monooleate (Tween<sup>®</sup> 80), sorbitan monopalmitate (Span<sup>®</sup> 40), sorbitan monostearate (Span<sup>®</sup> 60), sorbitan tristearate (Span<sup>®</sup> 65), glyceryl monooleate, sorbitan monooleate (Span<sup>®</sup> 80), polyoxyethylene esters (e.g., polyoxyethylene monostearate (Myrij<sup>®</sup> 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol<sup>®</sup>), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g., Cremophor<sup>®</sup>), polyoxyethylene ethers, (e.g., polyoxyethylene lauryl ether (Brij<sup>®</sup> 30))), poly(vinyl-pyrrolidone), diethylene glycol

monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic® F-68, poloxamer P-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00205] Exemplary binding agents include starch (e.g., cornstarch and starch paste), gelatin, sugars (e.g., sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, etc.), natural and synthetic gums (e.g., acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00206] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[00207] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00208] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (e.g., sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (e.g., citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00209] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00210] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00211] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00212] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® II, Neolone®, Kathon®, and Euxyl®.

[00213] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00214] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00215] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macadamia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic

oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00216] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates described herein are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00217] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00218] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00219] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may

depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form may be accomplished by dissolving or suspending the drug in an oil vehicle.

[00220] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00221] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[00222] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00223] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and

granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings, and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

**[00224]** Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

**[00225]** Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid formulations to the dermis *via* a liquid jet injector and/or *via* a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable.

**[00226]** Formulations suitable for topical administration include, but are not limited to, liquid and/or semi-liquid preparations such as liniments, lotions, oil-in-water and/or water-in-oil emulsions such as creams, ointments, and/or pastes, and/or solutions and/or suspensions. Topically administrable formulations may, for example, comprise from about 1% to about

10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00227] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration *via* the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00228] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00229] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets

provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00230] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00231] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00232] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1-1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this disclosure.

[00233] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical

compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00234] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00235] The compounds and compositions provided herein can be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (e.g., systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (e.g., whether the subject is able to tolerate oral administration). In certain embodiments, the compound or pharmaceutical composition described herein is suitable for topical administration to the eye of a subject.

[00236] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (e.g., single oral dose) or multiple doses (e.g., multiple oral doses). In certain embodiments, when

multiple doses are administered to a subject or applied to a biological sample, tissue, or cell, any two doses of the multiple doses include different or substantially the same amounts of a compound described herein. In certain embodiments, when multiple doses are administered to a subject or applied to a biological sample, tissue, or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the biological sample, tissue, or cell is three doses a day, two doses a day, one dose a day, one dose every other day, one dose every third day, one dose every week, one dose every two weeks, one dose every three weeks, or one dose every four weeks. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the biological sample, tissue, or cell is one dose per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the biological sample, tissue, or cell is two doses per day. In certain embodiments, the frequency of administering the multiple doses to the subject or applying the multiple doses to the biological sample, tissue, or cell is three doses per day. In certain embodiments, when multiple doses are administered to a subject or applied to a biological sample, tissue, or cell, the duration between the first dose and last dose of the multiple doses is one day, two days, four days, one week, two weeks, three weeks, one month, two months, three months, four months, six months, nine months, one year, two years, three years, four years, five years, seven years, ten years, fifteen years, twenty years, or the lifetime of the subject, tissue, or cell. In certain embodiments, the duration between the first dose and last dose of the multiple doses is three months, six months, or one year. In certain embodiments, the duration between the first dose and last dose of the multiple doses is the lifetime of the subject, tissue, or cell. In certain embodiments, a dose (e.g., a single dose, or any dose of multiple doses) described herein includes independently between 0.1 µg and 1 µg, between 0.001 mg and 0.01 mg, between 0.01 mg and 0.1 mg, between 0.1 mg and 1 mg, between 1 mg and 3 mg, between 3 mg and 10 mg, between 10 mg and 30 mg, between 30 mg and 100 mg, between 100 mg and 300 mg, between 300 mg and 1,000 mg, or between 1 g and 10 g, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 1 mg and 3 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 3 mg and 10 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 10 mg and 30 mg, inclusive, of a compound described herein. In certain embodiments, a dose described herein includes independently between 30 mg and 100 mg, inclusive, of a compound described herein.

[00237] Dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00238] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (e.g., therapeutically and/or prophylactically active agents). The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (e.g., activity (e.g., potency and/or efficacy) in treating a disease in a subject in need thereof, in preventing a disease in a subject in need thereof, in inhibiting the activity of a protein kinase (e.g., CDK) in a subject, biological sample, tissue, or cell), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject, biological sample, tissue, or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both.

[00239] The compound or composition can be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, e.g., combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (e.g., compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful for treating and/or preventing a disease (e.g., proliferative disease, inflammatory disease, autoimmune disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder). Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional

pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

**[00240]** The additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-angiogenesis agents, anti-inflammatory agents, immunosuppressants, anti-bacterial agents, anti-viral agents, cardiovascular agents, cholesterol-lowering agents, anti-diabetic agents, anti-allergic agents, contraceptive agents, pain-relieving agents, and a combination thereof. In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent (e.g., anti-cancer agent). In certain embodiments, the additional pharmaceutical agent is an anti-leukemia agent. In certain embodiments, the additional pharmaceutical agent is ABITREXATE (methotrexate), ADE, Adriamycin RDF (doxorubicin hydrochloride), Ambochlorin (chlorambucil), ARRANON (nelarabine), ARZERRA (ofatumumab), BOSULIF (bosutinib), BUSULFEX (busulfan), CAMPATH (alemtuzumab), CERUBIDINE (daunorubicin hydrochloride), CLAFEN (cyclophosphamide), CLOFAREX (clofarabine), CLOLAR (clofarabine), CVP, CYTOSAR-U (cytarabine), CYTOXAN (cyclophosphamide), ERWINAZE (Asparaginase Erwinia Chrysanthemi), FLUDARA (fludarabine phosphate), FOLEX (methotrexate), FOLEX PFS (methotrexate), GAZYVA (obinutuzumab), GLEEVEC (imatinib mesylate), Hyper-CVAD, ICLUSIG (ponatinib hydrochloride), IMBRUVICA (ibrutinib), LEUKERAN (chlorambucil), LINFOLIZIN (chlorambucil), MARQIBO (vincristine sulfate liposome), METHOTREXATE LPF (methotrexate), MEXATE (methotrexate), MEXATE-AQ (methotrexate), mitoxantrone hydrochloride, MUSTARGEN (mechllorethamine hydrochloride), MYLERAN (busulfan), NEOSAR (cyclophosphamide), ONCASPAR (Pegasparagase), PURINETHOL (mercaptopurine), PURIXAN (mercaptopurine), Rubidomycin (daunorubicin hydrochloride), SPRYCEL (dasatinib), SYNRIBO (omacetaxine mepesuccinate), TARABINE PFS (cytarabine), TASIGNA (nilotinib), TREANDA (bendamustine hydrochloride), TRISENOX (arsenic trioxide), VINCASAR PFS (vincristine sulfate), ZYDELIG (idelalisib), or a combination thereof. In certain embodiments, the additional pharmaceutical agent is an anti-lymphoma agent. In certain embodiments, the additional pharmaceutical agent is

ABITREXATE (methotrexate), ABVD, ABVE, ABVE-PC, ADCETRIS (brentuximab vedotin), ADRIAMYCIN PFS (doxorubicin hydrochloride), ADRIAMYCIN RDF (doxorubicin hydrochloride), AMBOCHLORIN (chlorambucil), AMBOCLORIN (chlorambucil), ARRANON (nelarabine), BEACOPP, BECENUM (carmustine), BELEODAQ (belinostat), BEXXAR (tositumomab and iodine I 131 tositumomab), BICNU (carmustine), BLENOXANE (bleomycin), CARMUBRIS (carmustine), CHOP, CLAFEN (cyclophosphamide), COPP, COPP-ABV, CVP, CYTOXAN (cyclophosphamide), DEPOCYT (liposomal cytarabine), DTIC-DOME (dacarbazine), EPOCH, FOLEX (methotrexate), FOLEX PFS (methotrexate), FOLOTYN (pralatrexate), HYPER-CVAD, ICE, IMBRUVICA (ibrutinib), INTRON A (recombinant interferon alfa-2b), ISTODAX (romidepsin), LEUKERAN (chlorambucil), LINFOLIZIN (chlorambucil), Lomustine, MATULANE (procarbazine hydrochloride), METHOTREXATE LPF (methotrexate), MEXATE (methotrexate), MEXATE-AQ (methotrexate), MOPP, MOZOBIL (plerixafor), MUSTARGEN (mechlorethamine hydrochloride), NEOSAR (cyclophosphamide), OEPA, ONTAK (denileukin diftitox), OPPA, R-CHOP, REVLIMID (lenalidomide), RITUXAN (rituximab), STANFORD V, TREANDA (bendamustine hydrochloride), VAMP, VELBAN (vinblastine sulfate), VELCADE (bortezomib), VELSAR (vinblastine sulfate), VINCASAR PFS (vincristine sulfate), ZEVALIN (ibritumomab tiuxetan), ZOLINZA (vorinostat), ZYDELIG (idelalisib), or a combination thereof. In certain embodiments, the additional pharmaceutical agent is REVLIMID (lenalidomide), DACOGEN (decitabine), VIDAZA (azacitidine), CYTOSAR-U (cytarabine), IDAMYCIN (idarubicin), CERUBIDINE (daunorubicin), LEUKERAN (chlorambucil), NEOSAR (cyclophosphamide), FLUDARA (fludarabine), LEUSTATIN (cladribine), or a combination thereof. In certain embodiments, the additional pharmaceutical agent is ABITREXATE (methotrexate), ABRAXANE (paclitaxel albumin-stabilized nanoparticle formulation), AC, AC-T, ADE, ADRIAMYCIN PFS (doxorubicin hydrochloride), ADRUCIL (fluorouracil), AFINITOR (everolimus), AFINITOR DISPERZ (everolimus), ALDARA (imiquimod), ALIMTA (pemetrexed disodium), AREDIA (pamidronate disodium), ARIMIDEX (anastrozole), AROMASIN (exemestane), AVASTIN (bevacizumab), BECENUM (carmustine), BEP, BICNU (carmustine), BLENOXANE (bleomycin), CAF, CAMPTOSAR (irinotecan hydrochloride), CAPOX, CAPRELSA (vandetanib), CARBOPLATIN-TAXOL, CARMUBRIS (carmustine), CASODEX (bicalutamide), CEENU (lomustine), CERUBIDINE (daunorubicin hydrochloride), CERVARIX (recombinant HPV bivalent vaccine), CLAFEN (cyclophosphamide), CMF, COMETRIQ (cabozantinib-s-malate), COSMEGEN

(dactinomycin), CYFOS (ifosfamide), CYRAMZA (ramucirumab), CYTOSAR-U (cytarabine), CYTOXAN (cyclophosphamide), DACOGEN (decitabine), DEGARELIX, DOXIL (doxorubicin hydrochloride liposome), DOXORUBICIN HYDROCHLORIDE, DOX-SL (doxorubicin hydrochloride liposome), DTIC-DOME (dacarbazine), EFUDEX (fluorouracil), ELLENCE (epirubicin hydrochloride), ELOXATIN (oxaliplatin), ERBITUX (cetuximab), ERIVEDGE (vismodegib), ETOPOPHOS (etoposide phosphate), EVACET (doxorubicin hydrochloride liposome), FARESTON (toremifene), FASLODEX (fulvestrant), FEC, FEMARA (letrozole), FLUOROPLEX (fluorouracil), FOLEX (methotrexate), FOLEX PFS (methotrexate), FOLFIRI, FOLFIRI-BEVACIZUMAB, FOLFIRI-CETUXIMAB, FOLFIRINOX, FOLFOX, FU-LV, GARDASIL (recombinant human papillomavirus (HPV) quadrivalent vaccine), GEMCITABINE-CISPLATIN, GEMCITABINE-OXALIPLATIN, GEMZAR (gemcitabine hydrochloride), GILOTrif (afatinib dimaleate), GLEEVEC (imatinib mesylate), GLIADEL (carmustine implant), GLIADEL WAFER (carmustine implant), HERCEPTIN (trastuzumab), HYCAMTIN (topotecan hydrochloride), IFEX (ifosfamide), IFOSFAMIDUM (ifosfamide), INLYTA (axitinib), INTRON A (recombinant interferon alfa-2b), IRESSA (gefitinib), IXEMPRA (ixabepilone), JAKAFI (ruxolitinib phosphate), JEVITANA (cabazitaxel), KADCYLA (ado-trastuzumab emtansine), KEYTRUDA (pembrolizumab), KYPROLIS (carfilzomib), LIPODOX (doxorubicin hydrochloride liposome), LUPRON (leuprolide acetate), LUPRON DEPOT (leuprolide acetate), LUPRON DEPOT-3 MONTH (leuprolide acetate), LUPRON DEPOT-4 MONTH (leuprolide acetate), LUPRON DEPOT-PED (leuprolide acetate), MEGACE (megestrol acetate), MEKINIST (trametinib), METHAZOLASTONE (temozolomide), METHOTREXATE LPF (methotrexate), MEXATE (methotrexate), MEXATE-AQ (methotrexate), MITOXANTRONE HYDROCHLORIDE, MITOZYTREX (mitomycin c), MOZOBIL (plerixafor), MUSTARGEN (mechlorethamine hydrochloride), MUTAMYCIN (mitomycin c), MYLOSAR (azacitidine), NAVELBINE (vinorelbine tartrate), NEOSAR (cyclophosphamide), NEXAVAR (sorafenib tosylate), NOLVADEX (tamoxifen citrate), NOVALDEX (tamoxifen citrate), OFF, PAD, PARAPLAT (carboplatin), PARAPLATIN (carboplatin), PEG-INTRON (peginterferon alfa-2b), PEMETREXED DISODIUM, PERJETA (pertuzumab), PLATINOL (cisplatin), PLATINOL-AQ (cisplatin), POMALYST (pomalidomide), prednisone, PROLEUKIN (aldesleukin), PROLIA (denosumab), PROVENGE (sipuleucel-t), REVLIMID (lenalidomide), RUBIDOMYCIN (daunorubicin hydrochloride), SPRYCEL (dasatinib), STIVARGA (regorafenib), SUTENT (sunitinib malate), SYLATRON (peginterferon alfa-2b), SYLVANT (siltuximab), SYNOVIR

(thalidomide), TAC, TAFINLAR (dabrafenib), TARABINE PFS (cytarabine), TARCEVA (erlotinib hydrochloride), TASIGNA (nilotinib), TAXOL (paclitaxel), TAXOTERE (docetaxel), TEMODAR (temozolomide), THALOMID (thalidomide), TOPOSAR (etoposide), TORISEL (temsirolimus), TPF, TRISENOX (arsenic trioxide), TYKERB (lapatinib ditosylate), VECTIBIX (panitumumab), VEIP, VELBAN (vinblastine sulfate), VELCADE (bortezomib), VELSAR (vinblastine sulfate), VEPESID (etoposide), VIADUR (leuprolide acetate), VIDAZA (azacitidine), VINCASAR PFS (vincristine sulfate), VOTRIENT (pazopanib hydrochloride), WELLCOVORIN (leucovorin calcium), XALKORI (crizotinib), XELODA (capecitabine), XELOX, XGEVA (denosumab), XOFIGO (radium 223 dichloride), XTANDI (enzalutamide), YERVOY (ipilimumab), ZALTRAP (ziv-aflibercept), ZELBORAF (vemurafenib), ZOLADEX (goserelin acetate), ZOMETA (zoledronic acid), ZYKADIA (ceritinib), ZYTIGA (abiraterone acetate), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (e.g., bortezomib (Velcade)), mTOR inhibitors (e.g., rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Novartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, camptothecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin, aminopterin, and hexamethyl melamine, or a combination thereof. In certain embodiments, the additional pharmaceutical agent is a binder or inhibitor of a CDK (e.g., CDK12). In certain embodiments, the additional pharmaceutical agent is a protein kinase inhibitor (e.g., tyrosine protein kinase inhibitor). In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of epigenetic or transcriptional modulators (e.g., DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimitotic drugs (e.g., taxanes and vinca alkaloids), hormone receptor modulators (e.g., estrogen receptor modulators and androgen receptor modulators), cell signaling pathway inhibitors (e.g., tyrosine protein kinase inhibitors), modulators of protein stability (e.g., proteasome inhibitors), Hsp90 inhibitors, glucocorticoids, all-*trans* retinoic

acids, and other agents that promote differentiation. In certain embodiments, the compounds described herein or pharmaceutical compositions can be administered in combination with an anti-cancer therapy including, but not limited to, surgery, radiation therapy, transplantation (e.g., stem cell transplantation, bone marrow transplantation), immunotherapy, and chemotherapy.

[00241] Also encompassed by the disclosure are kits (e.g., pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (e.g., a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

[00242] Thus, in one aspect, provided are kits including a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, the kits are useful for treating a disease (e.g., proliferative disease, inflammatory disease, autoimmune disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for preventing a disease (e.g., proliferative disease, inflammatory disease, autoimmune disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits are useful for inhibiting the activity (e.g., aberrant activity, such as increased activity) of a protein kinase (e.g., CDK) in a subject, biological sample, tissue, or cell. In certain embodiments, the kits are useful for inducing apoptosis in a cell.

[00243] In certain embodiments, a kit described herein further includes instructions for using the compound or pharmaceutical composition included in the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a disease (e.g., proliferative disease, inflammatory disease, autoimmune disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for preventing a disease (e.g., proliferative disease, inflammatory

disease, autoimmune disease, genetic disease, hematological disease, neurological disease, painful condition, psychiatric disorder, or metabolic disorder) in a subject in need thereof. In certain embodiments, the kits and instructions provide for modulating (e.g., inhibiting) the activity (e.g., aberrant activity, such as increased activity) of a CDK in a subject, biological sample, tissue, or cell. In certain embodiments, the kits and instructions provide for inducing apoptosis in a cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

#### *Methods of Treatment and Uses*

[00244] The present disclosure provides methods of modulating (e.g., inhibiting or increasing) the activity (e.g., aberrant activity, such as increased or decreased activity) of a protein kinase (e.g., CDK). The present disclosure provides methods of modulating (e.g., inhibiting or increasing) the activity (e.g., aberrant activity, such as unwanted activity, increased activity, activity above normal levels, or decreased activity) of a CDK (e.g., CDK12) in a subject or cell. In certain embodiments, the CDK is a mutant form of CDK12. The present disclosure also provides methods for the treatment of a wide range of diseases, such as diseases associated with aberrant activity (e.g., increased activity) of a protein kinase, e.g., proliferative diseases, musculoskeletal diseases, genetic diseases, hematological diseases, neurological diseases, painful conditions, psychiatric disorders, metabolic disorders, benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases in a subject in need thereof. The present invention provides methods for the treatment or prevention of a proliferative disease (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

[00245] In another aspect, the present disclosure provides methods of modulating the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject or cell. In certain embodiments, provided are methods of inhibiting the activity of a protein kinase in a subject. In certain embodiments, the kinase is a mutant form of CDK12. In certain embodiments, provided are methods of inhibiting the activity of a protein kinase in a cell. In certain embodiments, provided are methods of increasing the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject. The compounds described herein may exhibit kinase inhibitory

activity; the ability to inhibit cyclin-dependent kinase (CDK); the ability to inhibit cyclin-dependent kinase 12 (CDK12); the ability to inhibit cyclin-dependent kinase 12 (CDK12), without inhibiting another cyclin-dependent kinase (CDK); a therapeutic effect and/or preventative effect in the treatment of cancers; a therapeutic effect and/or preventative effect in the treatment of Myc-dependent cancers; and/or a therapeutic profile (e.g., optimum safety and curative effect) that is superior to existing chemotherapeutic agents. In certain embodiments, provided are methods of inhibiting CDK12, without inhibiting another cyclin-dependent kinase (CDK7). In certain embodiments, provided are methods of inhibiting a mutant form of cyclin-dependent kinase 12 (CDK12), without inhibiting another cyclin-dependent kinase (CDK).

**[00246]** In certain embodiments, provided are methods of decreasing the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject or cell described herein by at least about 1%, at least about 3%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%. In certain embodiments, the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject or cell is decreased by a method described herein by at least about 1%, at least about 3%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%. In some embodiments, the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject or cell is selectively inhibited by the method. In some embodiments, the activity of a protein kinase (e.g., CDK, (e.g., CDK12)) in a subject or cell is selectively decreased by the method.

**[00247]** Without wishing to be bound by any particular theory, in certain embodiments the compounds described herein are able to bind (e.g., covalently modify) the protein kinase being inhibited. In certain embodiments, a compound described herein is able to bind (e.g., covalently modify) to the protein kinase. In certain embodiments, the compound described herein is able to covalently bind a cysteine residue of the protein kinase. In certain embodiments, the compound described herein is able to covalently bind residue Cys1039 of CDK12, without covalently binding other kinases. In certain embodiments, the compound described herein is able to covalently bind residue Cys1039 of CDK12, without covalently binding Cys312 of CDK7. In certain embodiments, the compound described herein is able to covalently bind residue Cys1039 of CDK12, without covalently binding other residues of CDK12. In certain embodiments, the compound is capable of covalently modifying CDK12 (e.g., Cys1039 of CDK12). In certain embodiments, the compound described herein is able to

covalently modify residue Cys1039 of CDK12. In certain embodiments, the compound described herein is able to covalently modify residue Cys1039 of CDK12, without covalently modifying other kinases. In certain embodiments, the compound described herein is able to covalently modify residue Cys1039 of CDK12, without covalently modifying Cys312 of CDK7. In certain embodiments, the compound described herein is able to covalently modify residue Cys1039 of CDK12, without covalently modifying other residues of CDK12.

[00248] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a subject, the methods comprising administering to the subject an effective amount (e.g., therapeutically effective amount) of a compound, or pharmaceutical composition thereof, as described herein. In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a biological sample, the methods comprising contacting the biological sample with an effective amount of a compound, or pharmaceutical composition thereof, as described herein. In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a tissue, the methods comprising contacting the tissue with an effective amount of a compound, or pharmaceutical composition thereof, as described herein.

[00249] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a cell, the methods comprising contacting the cell with an effective amount of a compound, or pharmaceutical composition thereof, as described herein.

[00250] In certain embodiments, the subject being treated is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

[00251] In certain embodiments, the biological sample being contacted with the compound or composition is breast tissue, bone marrow, lymph node, lymph tissue, spleen, or blood.

[00252] In certain embodiments, the cell being contacted with the compound or composition is present *in vitro*. In certain embodiments, the cell being contacted with the compound or composition is present *in vivo*. In certain embodiments, the cell being contacted with the compound or composition is present *ex vivo*. In certain embodiments, the cell being contacted with the compound or composition is a malignant cell (e.g., malignant blood cell). In certain

embodiments, the cell being contacted with the compound or composition is a malignant hematopoietic stem cell (e.g., malignant myeloid cell or malignant lymphoid cell). In certain embodiments, the cell being contacted with the compound or composition is a malignant lymphocyte (e.g., malignant T-cell or malignant B-cell). In certain embodiments, the cell being contacted with the compound or composition is a malignant red blood cell, malignant white blood cell, or malignant platelet. In certain embodiments, the cell being contacted with the compound or composition is a malignant neutrophil, malignant macrophage, or malignant plasma cell. In certain embodiments, the cell being contacted with the compound or composition is a carcinoma cell. In certain embodiments, the cell being contacted with the compound or composition is a carcinoma breast cell. In certain embodiments, the cell being contacted with the compound or composition is a sarcoma cell. In certain embodiments, the cell being contacted with the compound or composition is a sarcoma cell from breast tissue.

**[00253]** The proliferative disease to be treated or prevented using the compounds described herein may be associated with overexpression of a kinase, such as cyclin-dependent kinase (CDK). The process of eukaryotic cell division may be broadly divided into a series of sequential phases termed G1, S, G2, and M. Correct progression through the various phases of the cell cycle has been shown to be critically dependent upon the spatial and temporal regulation of a family of proteins known as cyclin dependent kinases (CDKs) and a diverse set of their cognate protein partners termed cyclins. CDKs are CDC2 (also known as CDK1) homologous serine-threonine kinase proteins that are able to utilize ATP as a substrate in the phosphorylation of diverse polypeptides in a sequence-dependent context. Cyclins are a family of proteins characterized by a homology region, containing approximately 100 amino acids, termed the “cyclin box” which is used in binding to, and defining selectivity for, specific CDK partner proteins.

**[00254]** Modulation of the expression levels, degradation rates, protein levels, and activity levels of various CDKs and cyclins throughout the cell cycle leads to the cyclical formation of a series of CDK/cyclin complexes, in which the CDKs are enzymatically active. The formation of these complexes controls passage through discrete cell cycle checkpoints and thereby enables the process of cell division to continue. Failure to satisfy the prerequisite biochemical criteria at a given cell cycle checkpoint, e.g., failure to form a required CDK/cyclin complex, can lead to cell cycle arrest and/or cellular apoptosis. Aberrant cellular proliferation can often be attributed to loss of correct cell cycle control. Inhibition of CDK enzymatic activity therefore provides a means by which abnormally dividing cells can have their division arrested and/or be killed. The diversity of CDKs, and CDK complexes, and

their critical roles in mediating the cell cycle, provides a broad spectrum of potential therapeutic targets selected on the basis of a defined biochemical rationale.

[00255] In certain embodiments, the proliferative disease to be treated or prevented using the compounds described herein may be associated with overexpression of a CDK (e.g., CDK12).

[00256] CDK12 and CDK13 are Cdc2-related proteins that share 92% identity in their kinase domains (Chen *et al.*, *Exp. Neurol.*, 2014, 261, 10-21). CDK12 plays a critical role in cell processes, for example, regulating transcription and splicing machinery by stabilizing the RNAPII and DNA interaction, and regulating DNA damage response (DDR) and maintenance of genomic stability by modulating the expression of DDR genes.

Overexpression of CDK12 has been found to correlate, both at the transcriptional and protein level, with pathological parameters of breast cancer disease.

[00257] A proliferative disease may be associated with aberrant activity of a CDK (e.g., CDK12). Aberrant activity of a CDK (e.g., CDK12) may be an elevated and/or an inappropriate activity of the CDK. Deregulation of cell cycle progression is a characteristic of a proliferative disease, and a majority of proliferative diseases have abnormalities in some component of CDK (e.g., CDK12) activity, frequently through elevated and/or inappropriate CDK activation. Inhibition of the catalytic activity of CDK12 would be expected to inhibit cell cycle progression by blocking the phosphorylation of cell cycle CDKs, and would additionally inhibit transcription of effectors of cell division. In certain embodiments, CDK12 is not overexpressed, but the activity of CDK12 is elevated and/or inappropriate. In certain embodiments, CDK12 is overexpressed, and the activity of CDK12 is elevated and/or inappropriate. The compounds described herein, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, may inhibit the activity of CDK7 and be useful in treating and/or preventing proliferative diseases. The compounds described herein, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, may inhibit the activity of CDK12 and be useful in treating and/or preventing proliferative diseases.

[00258] A proliferative disease may also be associated with inhibition of apoptosis of a cell in a biological sample or subject. All types of biological samples described herein or known in the art are contemplated as being within the scope of the invention. Apoptosis is the process of programmed cell death. Inhibition of apoptosis may result in uncontrolled cell

proliferation and, therefore, may cause proliferative diseases. The CycK/Cdk12 complex regulates phosphorylation of Ser2 in the C-terminal domain of RNA polymerase II and expression of a small subset of human genes, as revealed in expression microarrays. Through regulation of expression of DNA damage response genes (*i.e.* oncogenes), CycK/Cdk12 protects cells from genomic instability. In certain embodiments, the DNA damage response genes regulated by CDK12 are BRCA1, BRCA2, HER1, HER2, ATR, FANCI, or FANCD2. In certain embodiments, the DNA damage response genes regulated by CDK12 are BRCA1, HER2, ATR, FANCI, and FANCD2. In certain embodiments, the DNA damage response gene regulated by CDK12 is BRCA1. In certain embodiments, the DNA damage response gene regulated by CDK12 is HER2. In certain embodiments, the DNA damage response genes are down-regulated by CDK12.

[00259] In certain embodiments, the proliferative disease to be treated or prevented using the compounds described herein is cancer. All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the proliferative disease is a cancer associated with BCL-2 anti-apoptotic proteins (*e.g.*, MCL-1 and/or XIAP) (*e.g.*, cancer associated with dependence on BCL-2 anti-apoptotic proteins). In certain embodiments, the proliferative disease is a cancer associated with overexpression of MYC (a gene that codes for a transcription factor). In certain embodiments, the cancer is a MYC-dependent cancer. In certain embodiments, the proliferative disease is a cancer associated with the amplification of BRCA1. In certain embodiments, the proliferative disease is a cancer associated with the amplification of HER2. In certain embodiments, the proliferative disease is a hematological malignancy. In certain embodiments, the proliferative disease is a blood cancer. In certain embodiments, the proliferative disease is a hematological malignancy. In certain embodiments, the proliferative disease is a leukemia. In certain embodiments, the proliferative disease is chronic lymphocytic leukemia (CLL). In certain embodiments, the proliferative disease is acute lymphoblastic leukemia (ALL). In certain embodiments, the proliferative disease is T-cell acute lymphoblastic leukemia (T-ALL). In certain embodiments, the proliferative disease is chronic myelogenous leukemia (CML). In certain embodiments, the proliferative disease is acute myelogenous leukemia (AML). In certain embodiments, the proliferative disease is acute monocytic leukemia (AMoL). In certain embodiments, the proliferative disease is lymphoma. In some embodiments, the proliferative disease is Burkitt's lymphoma. In certain embodiments, the proliferative disease is a Hodgkin's lymphoma. In certain embodiments, the proliferative disease is a non-Hodgkin's lymphoma. In certain embodiments, the proliferative disease is multiple myeloma.

In certain embodiments, the proliferative disease is melanoma. In certain embodiments, the proliferative disease is colorectal cancer. In certain embodiments, the proliferative disease is breast cancer. In certain embodiments, the proliferative disease is recurring breast cancer. In certain embodiments, the proliferative disease is mutant breast cancer. In certain embodiments, the proliferative disease is HER2+ breast cancer. In certain embodiments, the proliferative disease is HER2- breast cancer. In certain embodiments, the proliferative disease is triple-negative breast cancer (TNBC). In certain embodiments, the proliferative disease is a bone cancer. In certain embodiments, the proliferative disease is osteosarcoma. In certain embodiments, the proliferative disease is Ewing's sarcoma. In some embodiments, the proliferative disease is a brain cancer. In some embodiments, the proliferative disease is neuroblastoma. In some embodiments, the proliferative disease is a lung cancer. In some embodiments, the proliferative disease is small cell lung cancer (SCLC). In some embodiments, the proliferative disease is non-small cell lung cancer. In some embodiments, the proliferative disease is a benign neoplasm. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is associated with angiogenesis. All types of angiogenesis disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the proliferative disease is an inflammatory disease. All types of inflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the inflammatory disease is rheumatoid arthritis.

**[00260]** In certain embodiments, the proliferative disease is an acute inflammatory disease. In certain embodiments, the acute inflammatory disease is rheumatoid arthritis, Crohn's disease, or fibrosis. In some embodiments, the proliferative disease is an autoinflammatory disease. All types of autoinflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is an autoimmune disease. All types of autoimmune diseases disclosed herein or known in the art are contemplated as being within the scope of the invention.

**[00261]** Another aspect of the invention relates to methods of inhibiting the activity of a kinase in a biological sample, tissue, cell, or subject. In certain embodiments, the kinase is a CDK. In certain embodiments, the kinase is CDK12. In certain embodiments, the kinase is a mutant form of CDK12. In certain embodiments, the activity of the kinase is aberrant or undesired activity of the kinase. In certain embodiments, the activity of the kinase is increased activity of the kinase. In certain embodiments, the inhibition of the activity of the

kinase is irreversible. In other embodiments, the inhibition of the activity of the kinase is reversible. In certain embodiments, the methods of inhibiting the activity of the kinase include covalently attaching a compound described herein to the kinase.

[00262] Also provided in the present invention are methods of inhibiting transcription of genes in a biological sample or subject. In certain embodiments, the transcription of genes regulated by the activity of CDK12 may be inhibited by a compound of the invention. In certain embodiments, the transcription of genes regulated by the activity of CDK12 may be inhibited by a compound of the invention. In certain embodiments, the genes which may have their transcription inhibited by the activity of CDK12 are one or more genes selected from the group consisting of BRCA1, FANCI, ATR, FANCD2, APEX1, NEK9, CHEK1, CHEK2, ATM, RAD51C, RAD51D, ORC3L, MDC1, TERF2, ERCC4, FANCF, PARP9, RUNX1, MYB, TAL1, MCL1, MYC, BCL2, ETS1, and EWS-FLI. In certain embodiments, administering a compound described herein to a subject in need thereof will up-regulate one or more genes selected from the group consisting of BRCA1, FANCI, ATR, FANCD2, APEX1, NEK9, CHEK1, CHEK2, ATM, RAD51C, RAD51D, ORC3L, MDC1, TERF2, ERCC4, FANCF, PARP9, RUNX1, MYB, TAL1, MCL1, MYC, BCL2, ETS1, and EWS-FLI. The present invention also provides methods of up-regulating one or more genes selected from the group consisting of BRCA1, FANCI, ATR, FANCD2, APEX1, NEK9, CHEK1, CHEK2, ATM, RAD51C, RAD51D, ORC3L, MDC1, TERF2, ERCC4, FANCF, PARP9, RUNX1, MYB, TAL1, MCL1, MYC, BCL2, ETS1, and EWS-FLI, the method comprising administering to a subject in need thereof a compound described herein. The present invention also provides uses of the compounds described herein, for up-regulating one or more genes selected from the group consisting of BRCA1, FANCI, ATR, FANCD2, APEX1, NEK9, CHEK1, CHEK2, ATM, RAD51C, RAD51D, ORC3L, MDC1, TERF2, ERCC4, FANCF, PARP9, RUNX1, MYB, TAL1, MCL1, MYC, BCL2, ETS1, and EWS-FLI, comprising administering to a subject in need thereof the compound described herein.

[00263] The present invention also provides methods of inhibiting cell growth in a biological sample, tissue, cell, or subject.

[00264] In still another aspect, the present invention provides methods of inducing apoptosis of a cell in a biological sample, tissue, cell, or subject.

[00265] In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a

pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the compound is contacted with a biological sample. In certain embodiments, the compound is administered to a subject. In certain embodiments, the compound is administered in combination with one or more additional pharmaceutical agents described herein. The additional pharmaceutical agent may be an anti-proliferative agent. In certain embodiments, the additional pharmaceutical agent is an anti-cancer agent. The additional pharmaceutical agent may also be a kinase inhibitor. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a CDK. In certain embodiments, the additional pharmaceutical agent is an inhibitor of CDK12. In certain embodiments, the additional pharmaceutical agent is a selective inhibitor of CDK12. In certain embodiments, the additional pharmaceutical agent is a nonselective inhibitor of CDK12. In certain embodiments, the additional pharmaceutical agent is an inhibitor of another CDK. In certain embodiments, the additional pharmaceutical agent is a selective inhibitor of another CDK. In certain embodiments, the additional pharmaceutical agent is a nonselective inhibitor of another CDK. In certain embodiments, the additional pharmaceutical agent is a selective inhibitor of another CDK. In certain embodiments, the additional pharmaceutical agent is a selective inhibitor of a mitogen-activated protein kinase (MAPK). In certain embodiments, the additional pharmaceutical agent is an inhibitor of a glycogen synthase kinase 3 (GSK3). In certain embodiments, the additional pharmaceutical agent is an inhibitor of an AGC kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a calmodulin-dependent kinase (CaM Kinase). In certain embodiments, the additional pharmaceutical agent is an inhibitor of a casein kinase 1. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a STE kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a tyrosine kinase.

[00266] In some embodiments, the additional pharmaceutical agent is a topoisomerase inhibitor, a MCL1 inhibitor, a BCL-2 inhibitor, a BCL-xL inhibitor, a BRD4 inhibitor, a BRCA1 inhibitor, BRCA2 inhibitor, HER1 inhibitor, HER2 inhibitor, a CDK9 inhibitor, a Jumonji histone demethylase inhibitor, or a DNA damage inducer. In some embodiments, the additional pharmaceutical agent is etoposide, obatoclax, navitoclax, JQ1, 4-(((5'-chloro-2'-((1*R*,4*R*)-4-(((*R*)-1-methoxypropan-2-yl)amino)cyclohexyl)amino)-[2,4'-bipyridin]-6-yl)amino)methyl)tetrahydro-2H-pyran-4-carbonitrile, JIB04, or cisplatin. In some

embodiments, the additional pharmaceutical agent is etoposide, obatoclax, or navitoclax, and the disease to be treated is breast cancer, *e.g.*, triple-negative breast cancer, HER2 positive breast cancer, HER2 negative breast cancer, ER-positive breast cancer, ER-negative breast cancer, or ER/PR-positive breast cancer. In some embodiments, the additional pharmaceutical agent is etoposide, JIB04, or cisplatin, and the disease to be treated is Ewing's sarcoma. In some embodiments, the additional pharmaceutical agent is JQ1 or NVP2, and the disease to be treated is leukemia, *e.g.*, acute myelogenous leukemia, myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia, monoblastic leukemia, or megakaryoblastic leukemia. In certain embodiments, a pharmaceutical composition described herein further comprises a combination of the additional pharmaceutical agents described herein.

[00267] The inventive compounds or compositions may synergistically augment inhibition of CDK12 induced by the additional pharmaceutical agent(s) in the biological sample or subject. Thus, the combination of the inventive compounds or compositions and the additional pharmaceutical agent(s) may be useful in treating proliferative diseases resistant to a treatment using the additional pharmaceutical agent(s) without the inventive compounds or compositions.

[00268] In some embodiments, the activity of a protein kinase is non-selectively inhibited by the compounds or pharmaceutical compositions described herein. In some embodiments, the activity of the protein kinase being inhibited is selectively inhibited by the compounds or pharmaceutical compositions described herein, compared to the activity of a different protein (*e.g.*, a different protein kinase). In certain embodiments, the activity of CDK (*e.g.*, CDK12) is selectively inhibited by a compound or pharmaceutical composition described herein, compared to the activity of a different protein. In certain embodiments, the activity of CDK12 is selectively inhibited by a compound or pharmaceutical composition described herein, compared to the activity of another CDK (*e.g.*, CDK7 or CDK13).

[00269] The selectivity of a compound or pharmaceutical composition described herein in inhibiting the activity of a protein kinase over a different protein (*e.g.*, a different protein kinase) may be measured by the quotient of the IC<sub>50</sub> value of the compound or pharmaceutical composition in inhibiting the activity of the different protein over the IC<sub>50</sub> value of the compound or pharmaceutical composition in inhibiting the activity of the protein kinase. The selectivity of a compound or pharmaceutical composition described herein for a protein kinase over a different protein may also be measured by the quotient of the K<sub>d</sub> value of an adduct of the compound or pharmaceutical composition and the different protein over

the  $K_d$  value of an adduct of the compound or pharmaceutical composition and the protein kinase. In certain embodiments, the selectivity is at least 2-fold, at least 3-fold, at least 5-fold, at least 10-fold, at least 30-fold, at least 100-fold, at least 300-fold, at least 1,000-fold, at least 3,000-fold, at least 10,000-fold, at least 30,000-fold, or at least 100,000-fold. In certain embodiments, the selectivity is not more than 100,000-fold, not more than 10,000-fold, not more than 1,000-fold, not more than 100-fold, not more than 10-fold, or not more than 2-fold. Combinations of the above-referenced ranges (e.g., at least 2-fold and not more than 10,000-fold) are also within the scope of the disclosure.

**[00270]** In certain embodiments, a kit described herein includes a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, a kit described herein is useful in treating a proliferative disease (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject in need thereof, preventing a proliferative disease in a subject in need thereof, inhibiting the activity of a protein kinase (e.g., CDK (e.g., CDK12)) in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell.

**[00271]** In certain embodiments, a kit described herein further includes instructions for using the compound or pharmaceutical composition included in the kit. A kit described herein may also include information as required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). In certain embodiments, the information included in the kits is prescribing information. In certain embodiments, the kits and instructions provide for treating a proliferative disease in a subject in need thereof, preventing a proliferative disease in a subject in need thereof, inhibiting the activity of a protein kinase (e.g., CDK (e.g., CDK12)) in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

#### **EXAMPLES**

**[00272]** In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

### Structure-activity Analyses for Selected Compounds

[00273] Select compounds described herein were evaluated for structure-activity analyses. Exemplary results of the IC<sub>50</sub> values of exemplary compound BSJ-01-175-1 on other CDK kinases from an Invitrogen biochemical assay are shown in Table 1. *In vitro* kinase assays were performed by Life Technologies in duplicate at an ATP concentration = K<sub>m</sub> for each kinase. The IC<sub>50</sub> on Jurkat cell is from an anti-proliferation assay; IC<sub>50</sub> on CDK2, CDK7 and CDK9 is from a biochemical kinase inhibition assay from Life technology. See *Table 1A* and *Table 1*.

*Table 1A.* IC<sub>50</sub> values of exemplary compounds described herein.

ID	IC <sub>50</sub> (nM) Jurkat Cell	IC <sub>50</sub> (nM)		
		CDK2/Cyclin A	CDK7/cyclin H/MNAT1	CDK9/ Cyclin T1
BSJ-01-033	139.8	>10000	587	585
BSJ-01-175	160.6	4510	121	367
BSJ-01-193				
BSJ-01-202	54.32	3870	402	658
BSJ-02-057		2040	272	505
BSJ-02-058		3740	251	734
BSJ-02-108		492	74	87.7
BSJ-02-109	11.22	1940	433	121
BSJ-02-139		3550	162	171
BSJ-03-005	131.7	266	118	230
BSJ-03-014	344	3360	403	522
BSJ-03-055		3390	919	530
BSJ-03-161	62.16	>10000	878	786
BSJ-03-162	154.3	3570	269	286

**Table 1.** IC<sub>50</sub> values of exemplary compounds described herein.

Invitrogen Technology: Kinase Tested	Invitrogen Technology: [ATP] Tested (uM)	Invitrogen Technology: IC <sub>50</sub> (nM)
CDK2/cyclin A	Km app	4510
CDK7/cyclin H/MNAT1	Km app	121
CDK9/cyclin T1	Km app	367

***Assay of anti-proliferation activity on Jurkat cells***

[00274] Jurkat cells were plated at 30,000 cells/well and treated with a titration of compounds indicated. Cells were allowed to grow for 72 hours. Cells were assayed using CELLTITER GLO (Promega) to determine cell viability by measuring the amount of ATP present, which is an indicator of cell metabolic activity. Results are graphedcalculated as relative as luminescence as compared to DMSOP=.cent values. Curves were generated using PRISM and an IC<sub>50</sub> value was determined. *See Table 1A.*

***Assay of Anti-Proliferative Activity for Selected Compounds***

[00275] Select compounds described herein were evaluated for anti-proliferative activity. Exemplary results of the assay for anti-proliferative activity (in nM) are shown in Table 2. HAP1 WT and CDK12 C1039S/ CDK13 C1017S double mutants cells were seeded at a density of 12,000 cells/ well in 96-well plates. Twenty-four hours later cells were then treated with compound BSJ-01-175-1 in a 10-pt dose escalation format from 1 nM to 10  $\mu$ M or DMSO control for 72 hrs. After 72 hrs, cells were assayed using CellTiter-Glo Luminescent Cell Viability Assay (Promega) to determine cell viability by measuring the amount of ATP present in each sample cell population, which is an indicator of cell metabolic activity. Results are graphed as fraction of the DMSO control at 72 hrs. All data points were performed in biological triplicate. HAP1 cells expressing putative inhibitor-refractory mutations in CDK12 (C1039S) and CDK13 (C1017S) are approximately half as sensitive to compound BSJ-01-175-1 as compared to control WT HAP1 cells. This result indicates that a portion of intracellular compound activity comes from covalent inhibition of CDK12 and/or CDK13 and mutation of the targeted cysteines (C1039 in CDK12 and C1017 in CDK13) to

less nucleophilic serines is sufficient to rescue some of compound BSJ-01-175-1's anti-proliferative activity. Compound BSJ-1-0175-1 anti-proliferative effects were found to be partially rescued by mutation of critical cysteines in CDK12 and CDK13.

**Table 2. Assay of Anti-Proliferative Activity for Selected Compounds**

ID	HAP1 (IC <sub>50</sub> , nM)	HAP1 CDK12/13 mutant (IC <sub>50</sub> , nM)
BSJ-01-175	313	670

***Pull-Down Assay for Selected Compounds***

[00276] Jurkat cells were treated with THZ1 (1  $\mu$ M), compound BSJ-01-175-1 (1  $\mu$ M), or DMSO vehicle control for 6 hrs. Clarified cellular lysates from each treatment condition were then incubated with either 1 $\mu$ M THZ1-biotin, a concentration that binds CDK7-cyclin H, CDK12-cyclin K, and CDK13-cyclin K complexes. Lysates were incubated with THZ1-biotin overnight at 4 degrees Celsius. Subsequent addition of streptavidin -coated beads permits the immunoprecipitation of the indicated protein complexes. Following washing of beads with lysis buffer, the immunoprecipitated proteins were eluted from the beads by boiling in SDS buffer. Western blotting for cyclin K was used to identify precipitated CDK12-cyclin K or CDK13-cyclin K complexes. Western blotting for cyclin H was used to identify precipitated CDK7-cyclin H complexes. As THZ1 and compound BSJ-01-175-1 bind to their intended targets covalently, pretreatment of cells with these compounds would be expected to block subsequent capture and immunoprecipitation of these protein complexes with THZ1-biotin. The western blot data indicates that THZ1 binds intracellular CDK12-cyclin K, CDK13-cyclin K and CDK7-cyclin H complexes, while compound BSJ-01-175-1 binds intracellular CDK12-cyclin K and CDK13-cyclin K complexes selectively (and not CDK7-cyclin H). *Figure 1* depicts the results of this pull-down assay of a Cyclin K pull down with THZ1-biotin probe. Indicating that exemplary compound BSJ-01-175-1 selectively binds intracellular CDK12/13-cyclin K complexes, and not CDK7-cyclin H complexes.

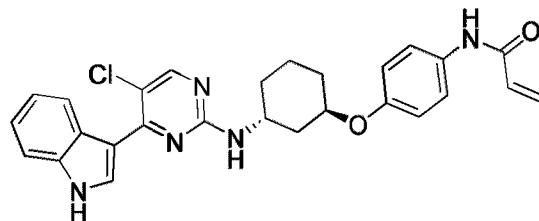
[00277] In another experiment, Jurkat cells were treated with DMSO or 1.0  $\mu$ M of the exemplary compounds BSJ-01-033, BSJ-01-175, BSJ-01-202, BSJ-02-139, BSJ-02-109 and BSJ-02-108. 6 hours after treatment, cells were washed and harvested by resuspending in lysis buffer (50 mM Hepes pH 7.4, 150 mM NaCl, 1% NP-40, 5 mM EDTA, protease and phosphatase inhibitors) and lysing on ice for 30 minutes. Lysates were cleared by centrifugation at 15,000 rpm for 30 minutes. Biotin-labeled THZ1 was added to 1  $\mu$ M to

lysates and rotated at 4 °C overnight. Streptavidin-agarose beads were washed and 30  $\mu$ L slurry was added to each lysate and rotated for 1 hour at 4 °C. Beads were washed 5 times with lysis buffer and 50  $\mu$ L 2X LDS buffer was added to each sample. Samples were boiled and equal volume of protein was loaded onto gel. Gel was transferred to nitrocellulose and blotted for Cyclin K and Cyclin H. *Figure 2* depicts the results of this pull-down assay.

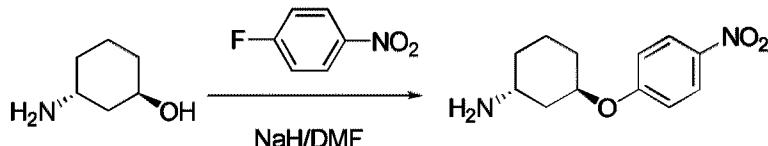
*Preparation of the compounds described herein*

**[00278]** The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. Where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

**Example 1. Synthesis of N-((1R,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyloxy)phenyl)acrylamide (BSJ-01-033)**

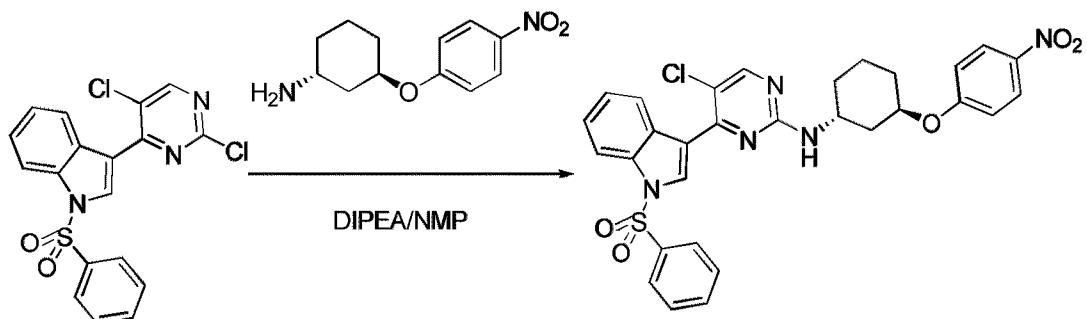


**(1R,3R)-3-(4-nitrophenoxy)cyclohexanamine**



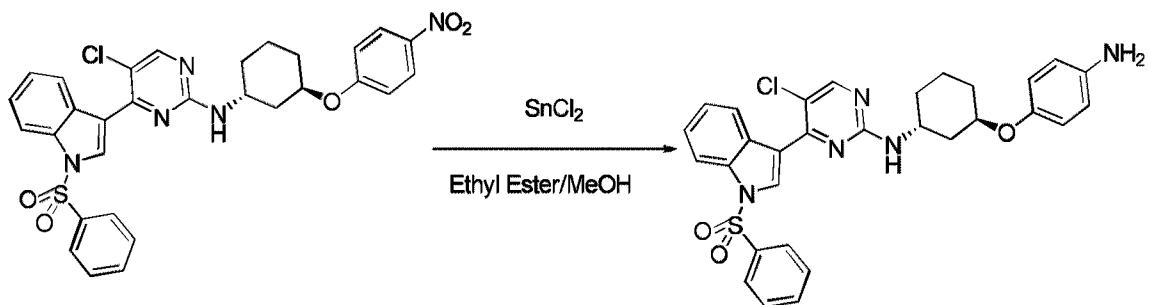
**[00279]** To a suspension of NaH (0.8g, 8.25 mmol) in 3.0 mL of anhydrous DMF was added (1R,3R)-3-aminocyclohexanol HCl salt (0.5g, 3.3 mmol) slowly at 0 °C and kept stirring for 0.5h, then 1-fluoro-4-nitrobenzene (0.465g, 3.3 mmol) was added. The reaction mixture was kept stirring at 0 °C for another 0.5h, then warm to room temperature and kept stirring for 2h. 1.0 mL of H<sub>2</sub>O was added dropwise to quench the reaction. The mixture was extracted with DCM (100mL), washed with brine (3X50 mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the title compound (623 mg, 80%) as a brown solid. LC-MS (m/z): 237 [M+H]<sup>+</sup>.

**5-chloro-N-((1R,3R)-3-(4-nitrophenoxy)cyclohexyl)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine**



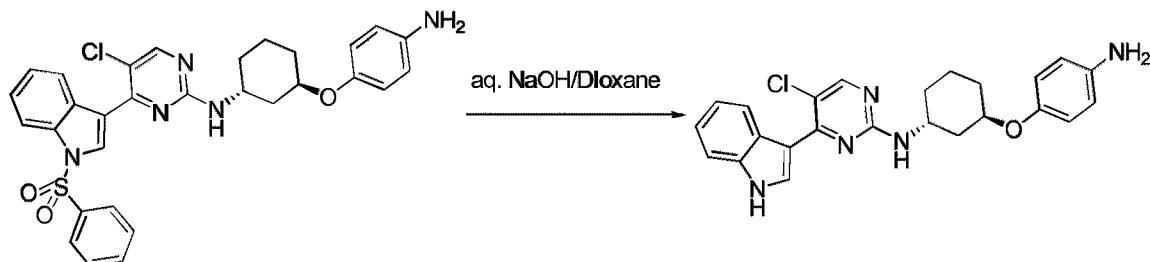
[00280] 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (50mg, 0.12 mmol) and (1R,3R)-3-(4-nitrophenoxy)cyclohexanamine (58mg, 0.25 mmol) were dissolved in 1.0 mL of NMP, 0.2 mL of DIPEA was added and the mixture was heated to 140 °C and kept stirring for 5h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20mL), washed with sat. NaHCO<sub>3</sub> (5mL), brine (5mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 604 [M+H]<sup>+</sup>.

**N-((1R,3R)-3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine**



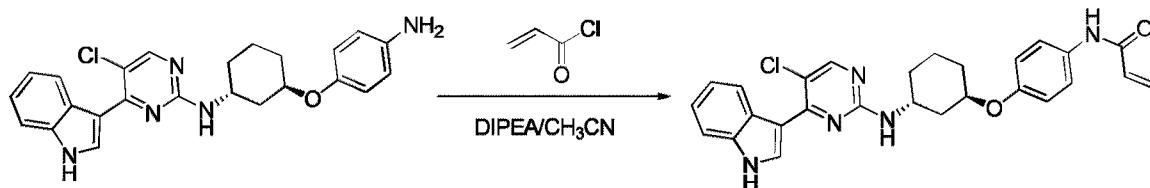
[00281] To a solution of 5-chloro-N-((1R,3R)-3-(4-nitrophenoxy)cyclohexyl)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine obtained from last step in 5.0 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL) was added SnCl<sub>2</sub> (230 mg, 1.2 mmol). The mixture was heated to 80 °C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat. NaHCO<sub>3</sub>, extracted with 200 mL of CHCl<sub>3</sub>/i-PrOH (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 574 [M+H]<sup>+</sup>.

**N-((1R,3R)-3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine**



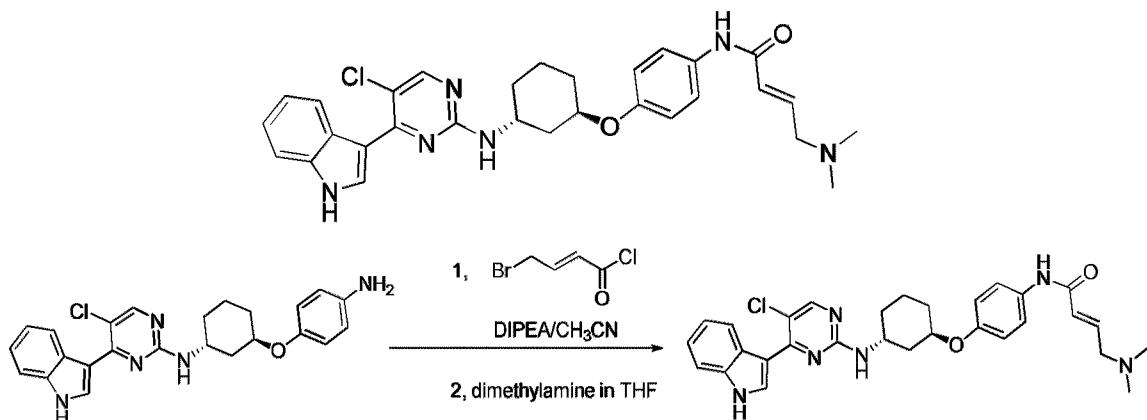
[00282] To a suspension of N-((1R,3R)-3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1-phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine obtained from last step in 2.0 mL of dioxane was added 2.0 mL of 1N of aqu. NaOH and stirred for 5h at room temperature. Then 2.0 mL of 1N HCl was added to quench the reaction and the solvent was evaporated under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (38.9 mg, 75% in 3 steps). LC-MS (m/z): 434 [M+H]<sup>+</sup>.

**N-(4-((1R,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyloxy)phenyl)acrylamide (BSJ-01-033)**



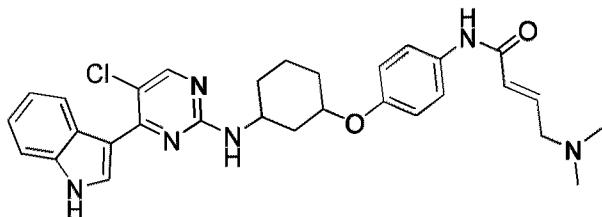
[00283] To a solution of N-((1R,3R)-3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added acryloyl chloride (3.46 mg, 0.038 mmol) in 1.0 mL of DCM dropwise, and stirred for 1h at 0°C. The reaction mixture was then concentrated and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (14.8 mg, 87%) as a light yellow solid after lyophilisation. LC-MS (m/z): 488 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d6) δ 10.99 (dd, J = 10.4, 5.6 Hz, 1H), 10.36 (s, 1H), 8.60 (d, J = 8.4 Hz, 2H), 8.36 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.49-7.31 (m, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.21 – 7.13 (m, 3H), 7.09-6.96 (m, 2H), 6.76 (dt, J = 14.7, 7.2 Hz, 1H), 6.48 (d, J = 15.3 Hz, 1H), 4.81 (s, 1H), 2.22 – 1.94 (m, 2H), 1.88 – 1.69 (m, 3H), 1.69 – 1.50 (m, 2H), 1.43 (d, J = 11.9 Hz, 2H).

**Example 2. Synthesis of (E)-N-(4-((1R,3R)-3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyloxy)phenyl)-4-(dimethylamino)but-2-enamide (BSJ-01-175)**

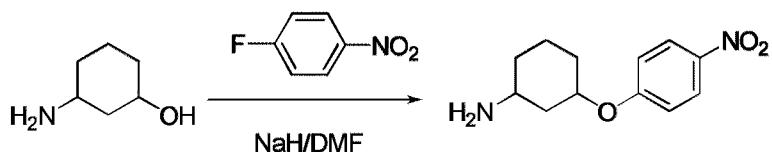


[00284] To a cold solution (0°C) of N-((1R,3R)-3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added a solution of (E)-4-bromobut-2-enoyl chloride (6.34 mg, 0.035 mmol) in 1.0 mL of DCM dropwise. After 0.5h at 0°C, a 2M solution of dimethylamine in THF (1.0 mL) was added and the mixture was stirred for 1h at 0°C. Then 1.5 mL of DMSO was added, followed by removal of the low boiling point solvents under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (11 mg, 58%) as a light yellow solid after lyophilisation. LC-MS (m/z): 545 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d6) δ 10.92 (dd, J = 10.4, 5.6 Hz, 1H), 10.38 (s, 1H), 8.65 (d, J = 8.4 Hz, 2H), 8.36 (s, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 50.9 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.21 – 7.13 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.76 (dt, J = 14.7, 7.2 Hz, 1H), 6.48 (d, J = 15.3 Hz, 1H), 4.81 (s, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.74 (s, 3H), 2.73 (s, 3H), 2.22 – 1.94 (m, 2H), 1.88 – 1.69 (m, 3H), 1.69 – 1.50 (m, 2H), 1.43 (d, J = 11.9 Hz, 2H).

**Example 3. Synthesis of (E)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyloxy)phenyl)-4-(dimethylamino)but-2-enamide (BSJ-01-193)**

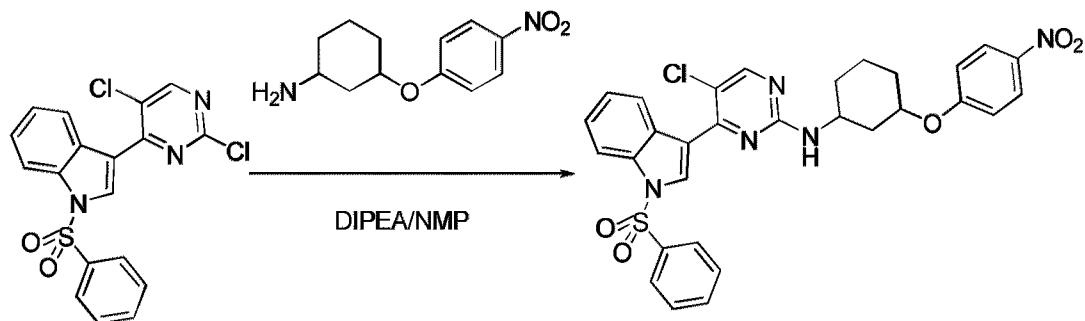


3-(4-nitrophenoxy)cyclohexanamine



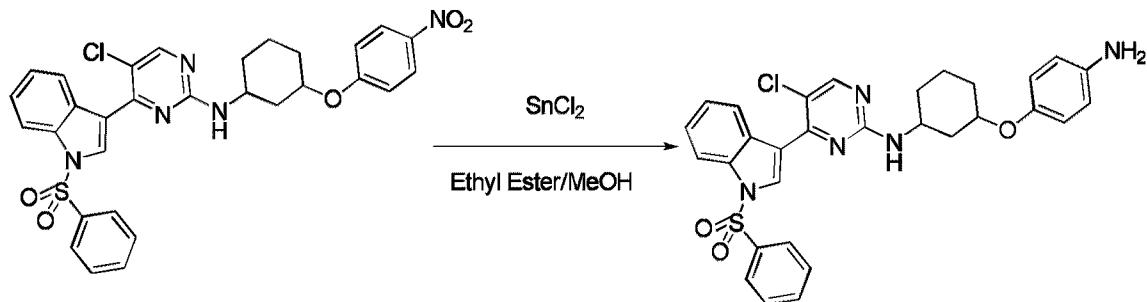
**[00285]** To a suspension of NaH (0.8g, 8.25 mmol) in 3.0 mL of anhydrous DMF was added 3-aminocyclohexanol HCl salt (0.5g, 3.3 mmol) slowly at 0 °C and kept stirring for 0.5h, then 1-fluoro-4-nitrobenzene (0.465g, 3.3 mmol) was added. The reaction mixture was kept stirring at 0 °C for another 0.5h, then warm to room temperature and kept stirring for 2h. 1.0 mL of H<sub>2</sub>O was added dropwise to quench the reaction. The mixture was extracted with DCM (100mL), washed with brine (3X50 mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the title compound (623 mg, 80%) as a brown solid. LC-MS (m/z): 237 [M+H]<sup>+</sup>.

**5-chloro-N-(3-(4-nitrophenoxy)cyclohexyl)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine**



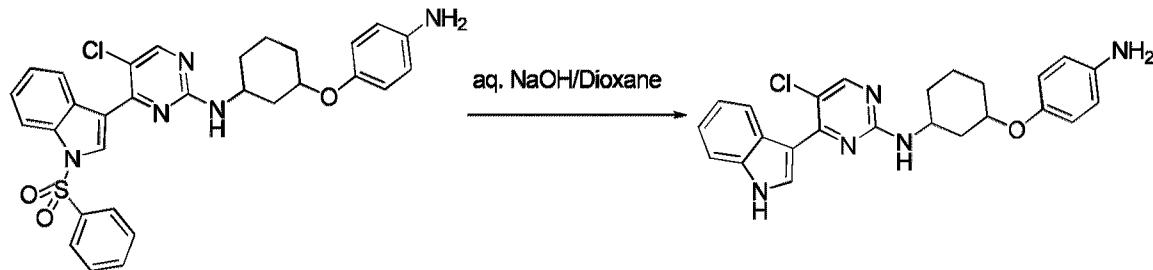
3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (50mg, 0.12 mmol) and 3-(4-nitrophenoxy)cyclohexanamine (58mg, 0.25 mmol) were dissolved in 1.0 mL of NMP, 0.2 mL of DIPEA was added and the mixture was heated to 140 °C and kept stirring for 5h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20mL), washed with sat. NaHCO<sub>3</sub> (5mL), brine (5mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 604 [M+H]<sup>+</sup>.

**N-(3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine**



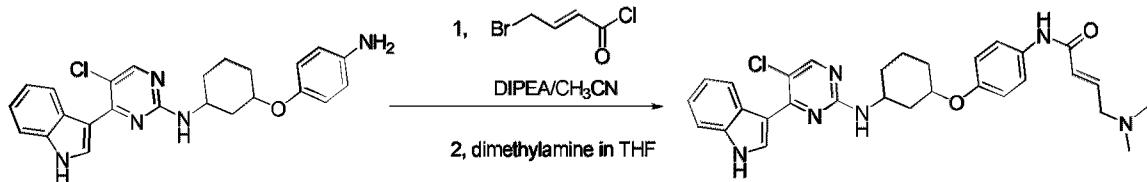
[00286] To a solution of 5-chloro-N-(3-(4-nitrophenoxy)cyclohexyl)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine obtained from last step in 5.0 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL) was added  $\text{SnCl}_2$  (230 mg, 1.2 mmol). The mixture was heated to 80 °C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat.  $\text{NaHCO}_3$ , extracted with 200 mL of  $\text{CHCl}_3/\text{i-PrOH}$  (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 574  $[\text{M}+\text{H}]^+$ .

**N-(3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine**



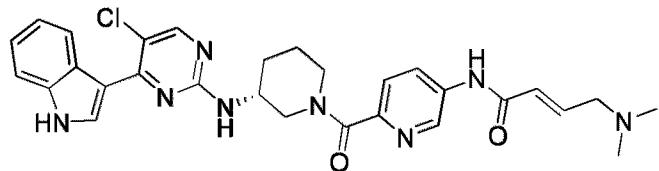
[00287] To a suspension of N-(3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-amine obtained from last step in 2.0 mL of dioxane was added 2.0 mL of 1N of aq. NaOH and stirred for 5h at room temperature. Then 2.0 mL of 1N HCl was added to quench the reaction and the solvent was evaporated under reduced pressure. The residue was purified by prep-HPLC ( $\text{MeOH}/\text{H}_2\text{O}$ , 0.05% TFA) to give the title compound (38.8 mg, 75% in 3 steps). LC-MS (m/z): 434  $[\text{M}+\text{H}]^+$ .

**(E)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)cyclohexyloxy)phenyl)-4-(dimethylamino)but-2-enamide**

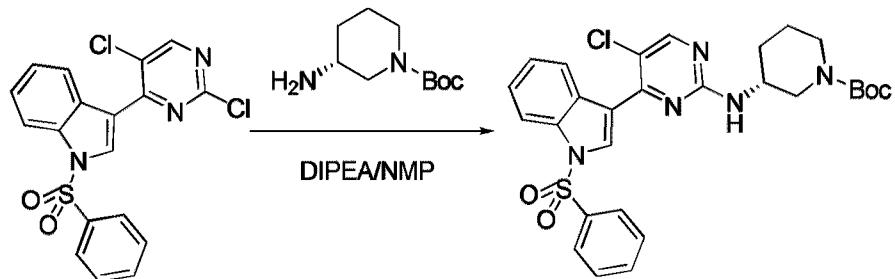


**[00288]** To a cold solution (0°C) of N-(3-(4-aminophenoxy)cyclohexyl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added a solution of (E)-4-bromobut-2-enoyl chloride (6.34 mg, 0.035 mmol) in 1.0 mL of DCM dropwise. After 0.5h at 0°C, a 2M solution of dimethylamine in THF (1.0 mL) was added and the mixture was stirred for 1h at 0°C. Then 1.5 mL of DMSO was added, followed by removal of the low boiling point solvents under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (11 mg, 58%) as a light yellow solid after lyophilisation. LC-MS (m/z): 545[M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d6) δ 10.92 (dd, J = 10.4, 5.6 Hz, 1H), 10.38 (s, 1H), 8.65 (d, J = 8.4 Hz, 2H), 8.36 (s, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 50.9 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.21 – 7.13 (m, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.76 (dt, J = 14.7, 7.2 Hz, 1H), 6.48 (d, J = 15.3 Hz, 1H), 4.81 (s, 1H), 3.89 (t, J = 6.1 Hz, 2H), 2.74 (s, 3H), 2.73 (s, 3H), 2.22 – 1.94 (m, 2H), 1.88 – 1.69 (m, 3H), 1.69 – 1.50 (m, 2H), 1.43 (d, J = 11.9 Hz, 2H).

**Example 4. Synthesis of (E)-N-(6-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (BSJ-01-202)**

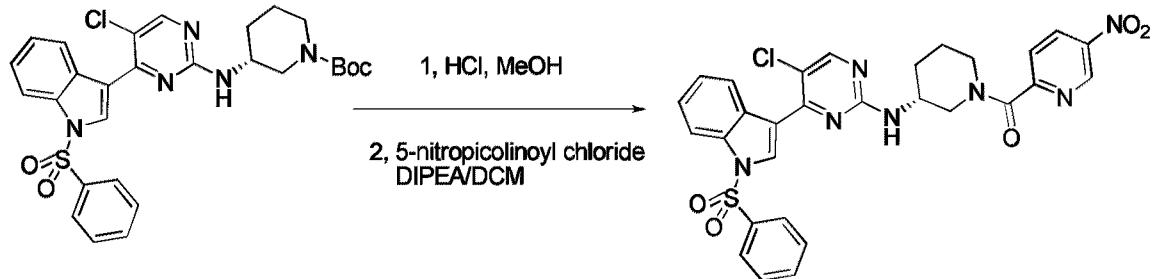


**(R)-*tert*-butyl 3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate**



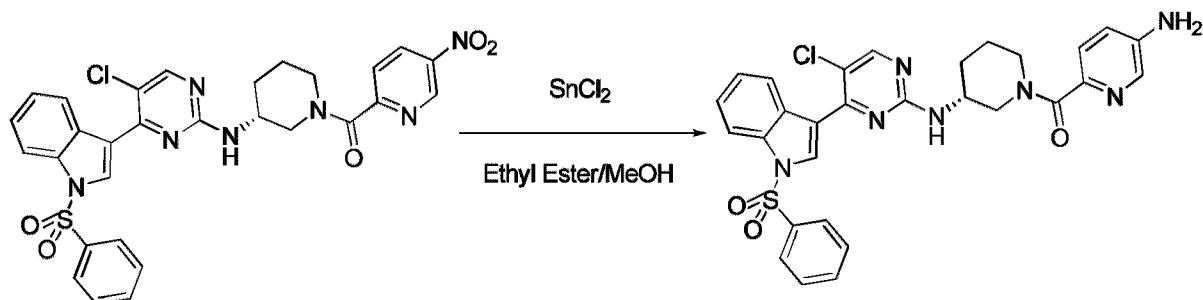
[00289] 3-(2,5-dichloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (500 mg, 1.2 mmol) and (R)-*tert*-butyl 3-aminopiperidine-1-carboxylate (480 mg, 2.4 mmol) were dissolved in 5.0 mL of NMP, 0.8 mL of DIPEA was added and the mixture was heated to 140 °C and kept stirring for 5h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20mL), washed with sat. NaHCO<sub>3</sub> (5mL), brine (5mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the title compound (620 mg, 91%). LC-MS (m/z): 568 [M+H]<sup>+</sup>.

**(R)-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)(5-nitropyridin-2-yl)methanone**



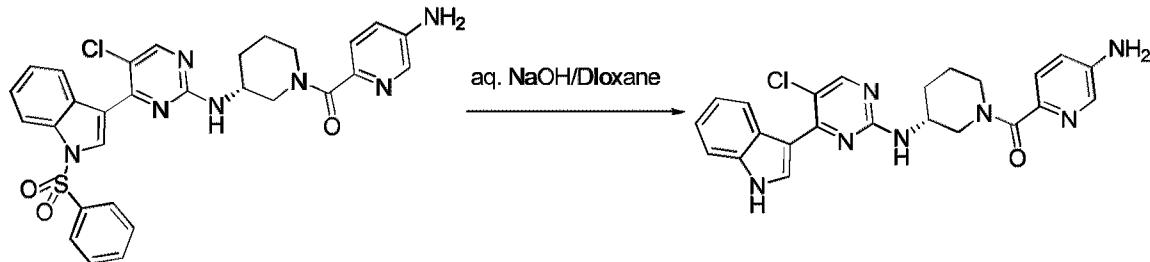
[00290] A solution of (R)-*tert*-butyl 3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (100 mg, 0.18 mmol) in 5 mL of MeOH was treated with 2.0 mL of 4N HCl in dioxane. The resulting mixture was stirred for 4h at room temperature before being evaporated to dryness. The residue was then dissolved in 5.0 mL of DCM, 0.5 mL of DIPEA was added and the mixture was cooled to 0°C. 5-nitropicolinoyl chloride (36.2 mg, 0.19 mmol) was added and the reaction mixture was kept stirring for 2h at room temperature before being evaporated to dryness. The residue was used directly for the next step without further purification. LC-MS (m/z): 618 [M+H]<sup>+</sup>.

**(R)-(5-aminopyridin-2-yl)(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone**



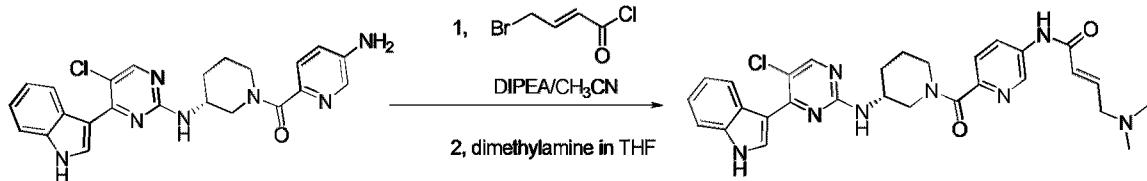
[00291] To a solution of (R)-(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)(5-nitropyridin-2-yl)methanone obtained from last step in 5 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL) was added  $\text{SnCl}_2$  (340.0 mg, 1.8 mmol). The mixture was heated to 80 °C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat.  $\text{NaHCO}_3$ , extracted with 200 mL of  $\text{CHCl}_3/\text{i-PrOH}$  (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 588  $[\text{M}+\text{H}]^+$ .

**(R)-(5-aminopyridin-2-yl)(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone**



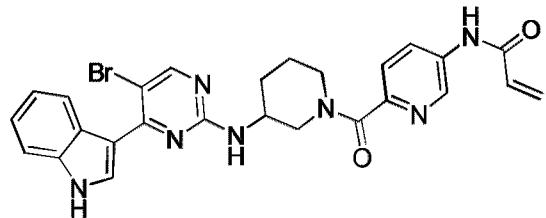
[00292] To a solution of (R)-(5-aminopyridin-2-yl)(3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone obtained from last step in 2.0 mL of dioxane was added 2.0 mL of 1N of aq. NaOH and stirred for 5h at room temperature. Then 2.0 mL of 1N HCl was added to quench the reaction and the solvent was evaporated under reduced pressure. The residue was purified by prep-HPLC ( $\text{MeOH}/\text{H}_2\text{O}$ , 0.05% TFA) to give the title compound (40 mg, 50% in 4 steps). LC-MS (m/z): 448  $[\text{M}+\text{H}]^+$ .

**(E)-N-(6-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-carbonyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide**

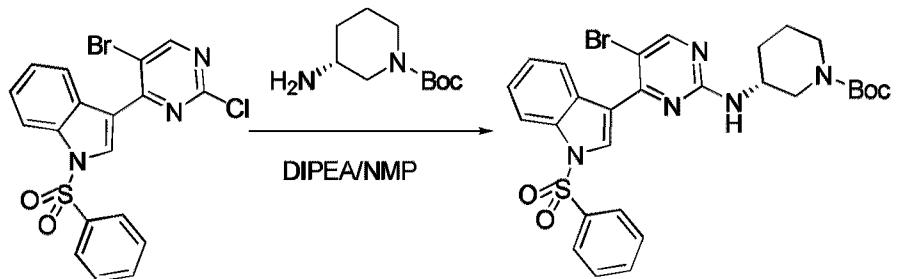


**[00293]** To a cold solution (0°C) of (R)-(5-aminopyridin-2-yl)(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone (16 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added a solution of (E)-4-bromobut-2-enoyl chloride (6.34 mg, 0.035 mmol) in 1.0 mL of DCM dropwise. After 0.5h at 0°C, a 2M solution of dimethylamine in THF (1.0 mL) was added and the mixture was stirred for 1h at 0°C. Then 1.5 mL of DMSO was added, followed by removal of the low boiling point solvents under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (12 mg, 61%) as a light yellow solid after lyophilisation. LC-MS (m/z): 559 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d6) δ 11.99 – 11.79 (m, 1H), 10.81-10.54 (M, 1H), 9.88 (s, 1H), 8.92 – 8.57 (m, 1H), 8.39-8.22 (m, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.55 – 7.29 (m, 2H), 7.25-7.17 (m, 1H), 7.16-7.05 (m, 1H), 6.91 – 6.68 (m, 1H), 6.56-6.39 (m, 1H), 3.96 (d, J = 9.2 Hz, 2H), 3.85 – 3.61 (m, 1H), 3.48 (s, 1H), 3.07 (s, 1H), 2.81 (s, 6H), 2.17-1.94 (m, 2H), 1.84 – 1.70 (m, 2H), 1.70 – 1.45 (m, 2H).

**Example 5. Synthesis of N-(6-(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)pyridin-3-yl)acrylamide (BSJ-02-057)**

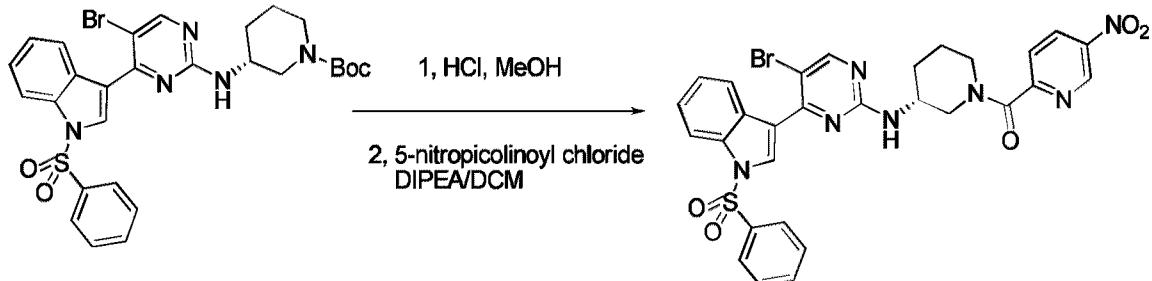


**(R)-tert-butyl 3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate**



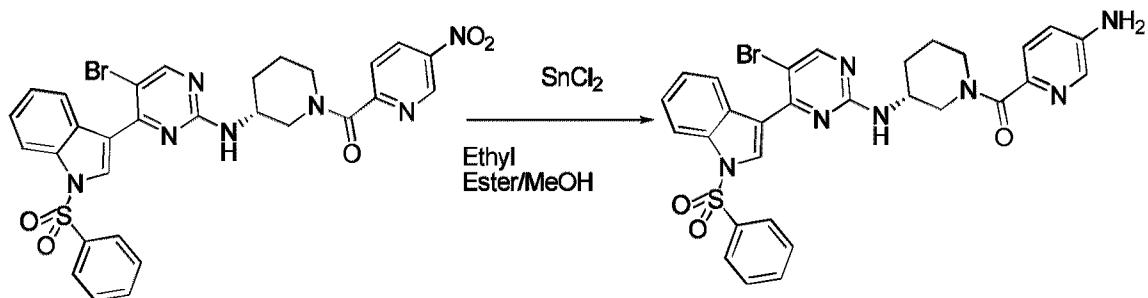
[00294] 3-(5-bromo-2-chloropyrimidin-4-yl)-1-(phenylsulfonyl)-1H-indole (536 mg, 1.2 mmol) and (R)-*tert*-butyl 3-aminopiperidine-1-carboxylate (480 mg, 2.4 mmol) were dissolved in 5.0 mL of NMP, 0.8 mL of DIPEA was added and the mixture was heated to 140 °C and kept stirring for 5h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20mL), washed with sat. NaHCO<sub>3</sub> (5mL), brine (5mL), dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the title compound (594 mg, 81%). LC-MS (m/z): 612 [M+H]<sup>+</sup>.

**(R)-(3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)(5-nitropyridin-2-yl)methanone**



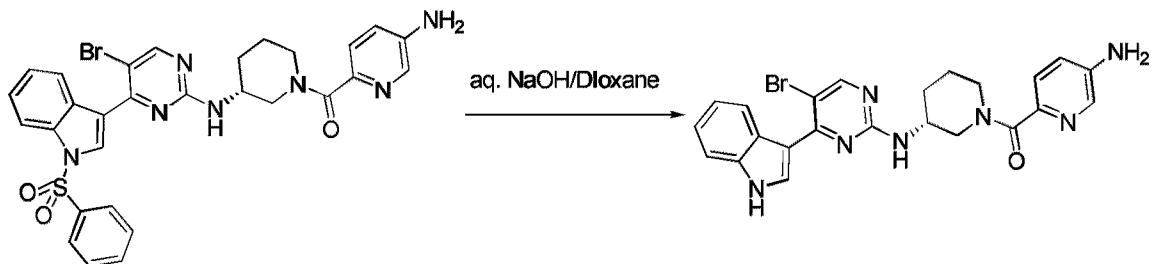
[00295] A solution of (R)-*tert*-butyl 3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (110 mg, 0.18 mmol) in 5 mL of MeOH was treated with 2.0 mL of 4N HCl in dioxane. The resulting mixture was stirred for 4h at room temperature before being evaporated to dryness. The residue was then dissolved in 5.0 mL of DCM, 0.5 mL of DIPEA was added and the mixture was cooled to 0°C. 5-nitropicolinoyl chloride (36.2 mg, 0.19 mmol) was added and the reaction mixture was kept stirring for 2h at room temperature before being evaporated to dryness. The residue was used directly for the next step without further purification. LC-MS (m/z): 662 [M+H]<sup>+</sup>.

**(R)-(5-aminopyridin-2-yl)(3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone**



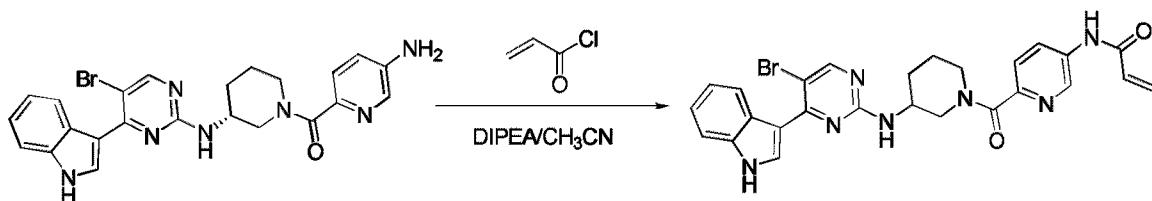
**[00296]** To a solution of (R)-(3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)(5-nitropyridin-2-yl)methanone obtained from last step in 5 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL) was added  $\text{SnCl}_2$  (340.0 mg, 1.8 mmol). The mixture was heated to 80 °C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat.  $\text{NaHCO}_3$ , extracted with 200 mL of  $\text{CHCl}_3/\text{i-PrOH}$  (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was used directly for the next step without further purification. LC-MS (m/z): 632  $[\text{M}+\text{H}]^+$ .

**(R)-(5-aminopyridin-2-yl)(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone**



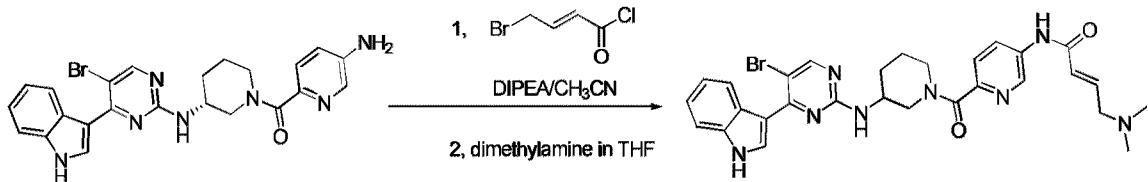
**[00297]** To a solution of (R)-(3-(5-bromo-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)(5-nitropyridin-2-yl)methanone obtained from last step in 2.0 mL of dioxane was added 2.0 mL of 1N of aq. NaOH and stirred for 5h at room temperature. Then 2.0 mL of 1N HCl was added to quench the reaction and the solvent was evaporated under reduced pressure. The residue was purified by prep-HPLC ( $\text{MeOH}/\text{H}_2\text{O}$ , 0.05% TFA) to give the title compound (51 mg, 51% in 4 steps). LC-MS (m/z): 492  $[\text{M}+\text{H}]^+$ .

**N-(6-(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-carbonyl)pyridin-3-yl)acrylamide**



**[00298]** To a solution of (R)-(5-aminopyridin-2-yl)(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone (17 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added acryloyl chloride (3.46 mg, 0.038 mmol) in 1.0 mL of DCM dropwise, and stirred for 1h at 0°C. The reaction mixture was then concentrated and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (17.2 mg, 90%) as a light yellow solid after lyophilisation. LC-MS (m/z): 546 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.94 – 11.70 (m, 1H), 10.69 – 10.25 (m, 1H), 8.94 – 8.69 (m, 1H), 8.65 – 8.34 (m, 1H), 8.34 – 7.93 (m, 1H), 7.81 – 7.56 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.44 – 7.29 (m, 2H), 7.19 (t, J = 7.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.45 (ddd, J = 21.8, 16.7, 10.0 Hz, 1H), 6.37 – 6.22 (m, 1H), 5.94-5.83 (m, 1H), 4.67-4.37 (m, 1H), 3.20 – 2.78 (m, 1H), 2.15 – 1.59 (m, 3H), 1.53 (qt, J = 8.1, 4.5 Hz, 1H), 1.42 (d, J = 6.5 Hz, 1H), 1.37 – 1.14 (m, 2H).

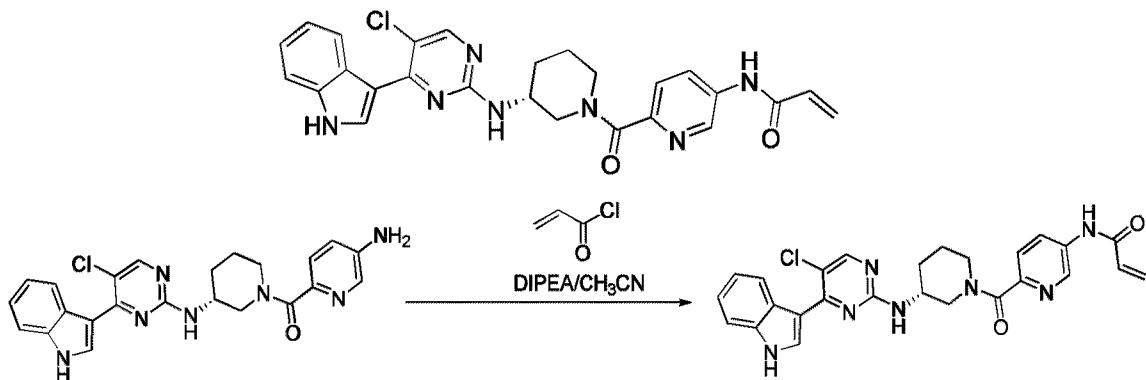
**Example 6. Synthesis of (E)-N-(6-(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carbonyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (BSJ-02-058)**



**[00299]** To a cold solution (0°C) of (R)-(5-aminopyridin-2-yl)(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)methanone (17 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added a solution of (E)-4-bromobut-2-enoyl chloride (6.34 mg, 0.035 mmol) in 1.0 mL of DCM dropwise. After 0.5h at 0°C, a 2M solution of dimethylamine in THF (1.0 mL) was added and the mixture was stirred for 1h at 0°C. Then 1.5 mL of DMSO was added, followed by removal of the low boiling point solvents under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (12 mg, 61%) as a light yellow solid after lyophilisation. LC-MS (m/z): 603 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.81 (dd, J =

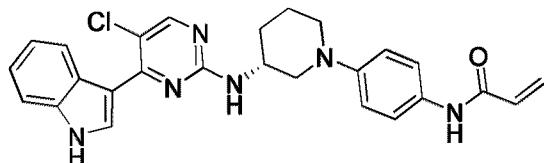
13.1, 3.1 Hz, 1H), 10.87-10.64 (m, 1H), 9.94 (s, 1H), 8.91-8.75 (m, 1H), 8.66 – 8.35 (m, 3H), 8.23 (dd,  $J$  = 8.5, 2.5 Hz, 1H), 8.17 – 7.91 (m, 1H), 7.76-7.61 (m, 2H), 7.44 – 7.24 (m, 2H), 7.21-7.02 (m, 2H), 6.80 (ddd,  $J$  = 15.2, 12.7, 7.2 Hz, 1H), 6.47 (dd,  $J$  = 24.4, 15.3 Hz, 1H), 4.54 (d,  $J$  = 12.3 Hz, 1H), 3.22 – 2.90 (m, 2H), 2.81 (s, 6H), 2.17 – 1.84 (m, 2H), 1.77 (d,  $J$  = 14.0 Hz, 1H), 1.70 – 1.46 (m, 2H), 1.32 – 1.14 (m, 1H).

**Example 7. Synthesis of (E)-N-(6-(3-(5-bromo-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-carbonyl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (BSJ-03-055)**

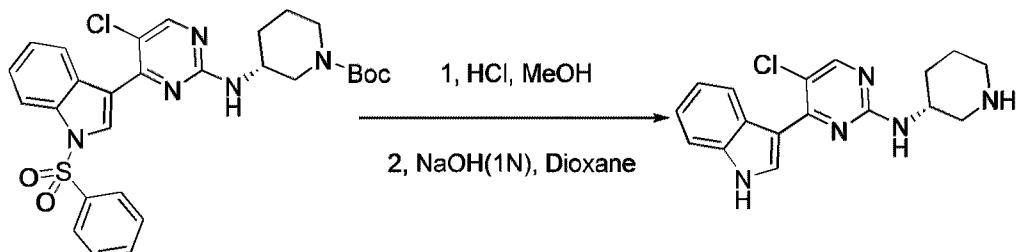


**[00300]** To a solution of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone (16 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added acryloyl chloride (3.46 mg, 0.038 mmol) in 1.0 mL of DCM dropwise, and stirred for 1h at 0°C. The reaction mixture was then concentrated and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (17.2 mg, 90%) as a light yellow solid after lyophilisation. LC-MS (m/z): 502 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d6)  $\delta$  11.80 (s, 1H), 10.66 (s, 1H), 9.78 (s, 1H), 8.98-8.67 (m, 1H), 8.39-8.22 (m, 1H), 8.10 (d,  $J$  = 8.6 Hz, 1H), 7.68 (d,  $J$  = 8.5 Hz, 1H), 7.55-7.29 (m, 2H), 7.25-7.17 (m, 1H), 7.16-7.05 (m, 1H), 6.85-6.61 (m, 1H), 6.56-6.39 (m, 1H), 3.86 (d,  $J$  = 9.0 Hz, 2H), 3.85-3.61 (m, 1H), 3.48 (s, 1H), 3.07 (s, 1H), 2.27-1.99 (m, 2H), 1.88-1.73 (m, 2H), 1.71-1.45 (m, 2H).

**Example 8. Synthesis of (R)-N-(4-(3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)phenyl)acrylamide (BSJ-02-139)**

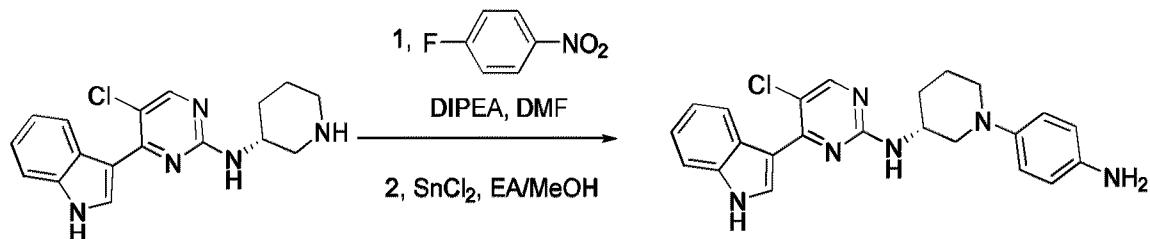


**(R)-5-chloro-4-(1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine**



**[00301]** To a solution of (R)-*tert*-butyl 3-(5-chloro-4-(1-(phenylsulfonyl)-1H-indol-3-yl)pyrimidin-2-ylamino)piperidine-1-carboxylate (100 mg, 0.18 mmol) in 5 mL of MeOH was treated with 2.0 mL of 4N HCl in dioxane. The resulting mixture was stirred for 4h at room temperature before being evaporated to dryness. The residue was then dissolved in 3 mL of dioxane, 3 mL of 1N aqueous NaOH was added and the mixture was stirred for 2h. Then 1N aqueous HCl was added to adjust the pH to 7. The resulting mixture was evaporated and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (54 mg, 92%) as a light yellow solid after lyophilisation. LC-MS (m/z): 328 [M+H]<sup>+</sup>.

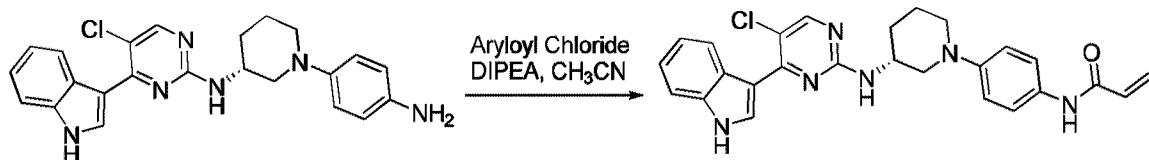
**(R)-N-(1-(4-aminophenyl)piperidin-3-yl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine**



**[00302]** To a solution of (R)-5-chloro-4-(1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine (54mg, 0.17 mmol) in 3 mL of DMF was added 0.1 mL of DIPEA and 1-fluoro-4-nitrobenzene (24 mg, 0.17 mmol). The mixture was heated to 70 °C and kept stirring for 8h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. The residue was re-dissolved in 5 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL), SnCl<sub>2</sub> (340.0 mg, 1.8 mmol) was added. The mixture was heated to 80°C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat. NaHCO<sub>3</sub>, extracted with 200

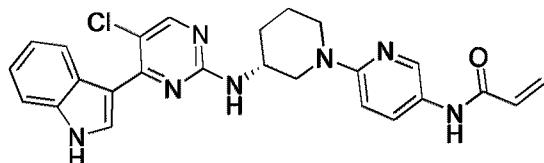
mL of  $\text{CHCl}_3/\text{i-PrOH}$  (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC ( $\text{MeOH}/\text{H}_2\text{O}$ , 0.05% TFA) to give the title compound (59 mg, 85%) as a grey solid after lyophilisation. LC-MS (m/z): 419  $[\text{M}+\text{H}]^+$ .

**(R)-N-(4-((3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)phenyl)acrylamide**

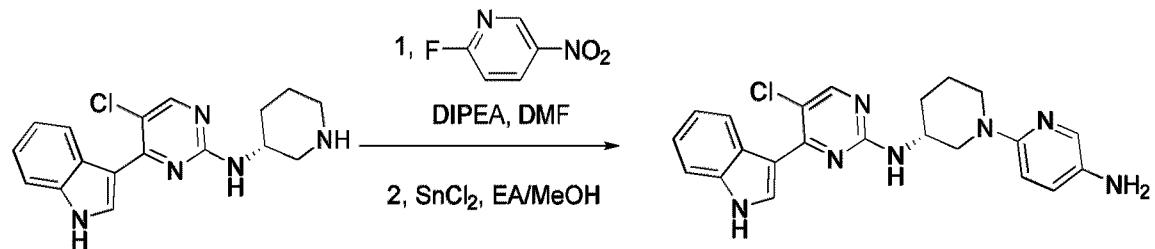


**[00303]** To a solution of (R)-N-(1-(4-aminophenyl)piperidin-3-yl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous  $\text{CH}_3\text{CN}$  was added acryloyl chloride (3.46 mg, 0.038 mmol) in 1.0 mL of DCM dropwise, and stirred for 1h at 0°C. The reaction mixture was then concentrated and the residue was purified by prep-HPLC ( $\text{MeOH}/\text{H}_2\text{O}$ , 0.05% TFA) to give the title compound (15 mg, 91%) as a light yellow solid after lyophilisation. LC-MS (m/z): 473  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ )  $\delta$  11.83 (s, 1H), 10.58 (s, 1H), 8.61 – 8.38 (m, 1H), 8.33 – 7.91 (m, 1H), 7.84 – 7.51 (m, 1H), 7.45 (d,  $J$  = 8.0 Hz, 1H), 7.49 – 7.25 (m, 2H), 7.13 (t,  $J$  = 7.2 Hz, 1H), 7.08 (t,  $J$  = 7.2 Hz, 1H), 6.59-6.42 (m, 1H), 6.34 – 6.20 (m, 1H), 5.90-5.85 (m, 1H), 4.67-4.36 (m, 1H), 3.22 – 2.80 (m, 1H), 2.05 – 1.62 (m, 3H), 1.60-1.49 (m, 1H), 1.48 (d,  $J$  = 6.3 Hz, 1H), 1.38 – 1.16 (m, 2H).

**Example 9. Synthesis of (R,E)-N-(4-((3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)phenyl)-4-(dimethylamino)but-2-enamide (BSJ-02-109)**

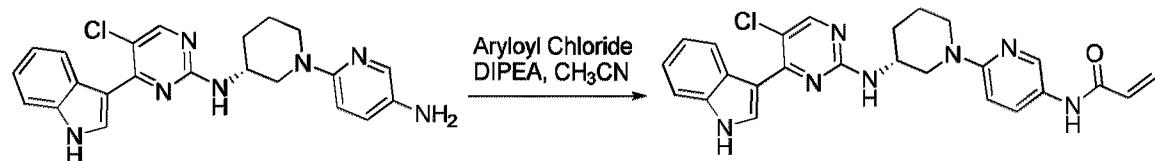


**(R)-N-(1-(5-aminopyridin-2-yl)piperidin-3-yl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine**



[00304] To a solution of (R)-5-chloro-4-(1H-indol-3-yl)-N-(piperidin-3-yl)pyrimidin-2-amine (54mg, 0.17 mmol) in 3 mL of DMF was added 0.1 mL of DIPEA and 2-fluoro-5-nitropyridine (24 mg, 0.17 mmol). The mixture was heated to 70 °C and kept stirring for 8h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. The residue was re-dissolved in 5 mL of ethyl ester (4.0 mL) and MeOH (1.0 mL),  $\text{SnCl}_2$  (340.0 mg, 1.8 mmol) was added. The mixture was heated to 80°C and kept stirring for 2h. Then the reaction mixture was cooled to room temperature and diluted with 100 mL of sat.  $\text{NaHCO}_3$ , extracted with 200 mL of  $\text{CHCl}_3$ /i-PrOH (v/v=4:1), washed with brine (3X100 mL), dried (anhydrous  $\text{Na}_2\text{SO}_4$ ), filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (61 mg, 85%) as a grey solid after lyophilisation. LC-MS (m/z): 420 [M+H]<sup>+</sup>.

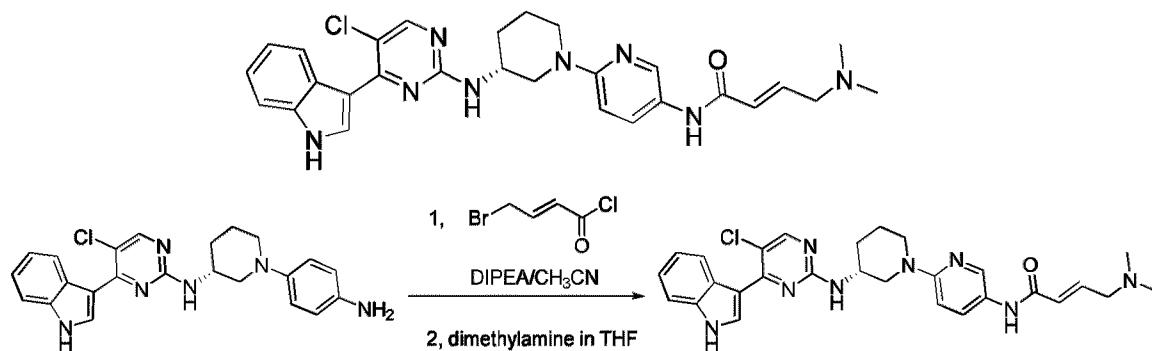
**(R)-N-(6-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)pyridin-3-yl)acrylamide**



[00305] To a solution of (R)-N-(1-(5-aminopyridin-2-yl)piperidin-3-yl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous  $\text{CH}_3\text{CN}$  was added acryloyl chloride (3.46 mg, 0.038 mmol) in 1.0 mL of DCM dropwise, and stirred for 1h at 0°C. The reaction mixture was then concentrated and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (14 mg, 91%) as a light yellow solid after lyophilisation. LC-MS (m/z): 474 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.87 (d,  $J$  = 3.1 Hz, 1H), 10.25 (s, 1H), 8.48 (d,  $J$  = 3.0 Hz, 1H), 8.39 (s, 2H), 8.32 (s, 1H), 7.85 (t,  $J$  = 21.2 Hz, 1H), 7.46 (t,  $J$  = 8.6 Hz, 2H), 7.19 (s, 2H), 6.38 (dd,  $J$  = 17.0, 10.1 Hz,

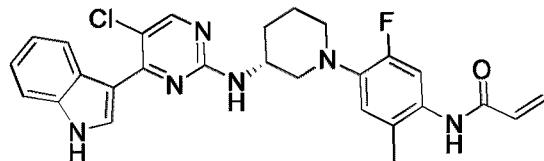
1H), 6.25 (dd,  $J = 17.0, 2.0$  Hz, 1H), 5.78 (dd,  $J = 10.0, 2.0$  Hz, 1H), 4.27 (s, 1H), 4.06 (d,  $J = 13.4$  Hz, 1H), 3.06 (dd,  $J = 24.8, 13.0$  Hz, 2H), 2.09 (s, 1H), 1.91 (s, 1H), 1.74–1.56 (m, 2H).

**Example 10. Synthesis of (R,E)-N-(6-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)pyridin-3-yl)-4-(dimethylamino)but-2-enamide (BSJ-02-108)**



**[00306]** To a cold solution (0°C) of (R)-N-(1-(5-aminopyridin-2-yl)piperidin-3-yl)-5-chloro-4-(1H-indol-3-yl)pyrimidin-2-amine (15 mg, 0.035 mmol) and 0.1 mL of DIPEA in 2.0 mL of anhydrous CH<sub>3</sub>CN was added a solution of (E)-4-bromobut-2-enoyl chloride (6.34 mg, 0.035 mmol) in 1.0 mL of DCM dropwise. After 0.5h at 0°C, a 2M solution of dimethylamine in THF (1.0 mL) was added and the mixture was stirred for 1h at 0°C. Then 1.5 mL of DMSO was added, followed by removal of the low boiling point solvents under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to give the title compound (16 mg, 86%) as a light yellow solid after lyophilisation. LC-MS (m/z): 531 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.91 (s, 1H), 10.20 (s, 1H), 8.68 (d,  $J = 3.0$  Hz, 1H), 8.39 (s, 2H), 8.30 (s, 1H), 7.9–7.66 (m, 1H), 7.46 (t,  $J = 8.6$  Hz, 2H), 7.11 (s, 2H), 6.45 (dd,  $J = 17.0, 10.1$  Hz, 1H), 6.22–6.03 (m, 1H), 5.78 (dd,  $J = 10.0, 2.0$  Hz, 1H), 4.27 (s, 1H), 4.16–3.99 (m, 3H), 3.26–3.08 (m, 2H), 2.84 (s, 6H), 2.19 (s, 1H), 1.90 (s, 1H), 1.76–1.51 (m, 2H).

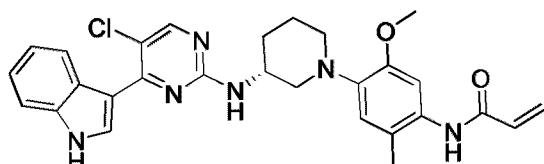
**Example 11. Synthesis of (R)-N-(4-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)-5-fluoro-2-methylphenylacrylamide (BSJ-03-005)**



**[00307]** Example 11 was synthesized via a procedure similar to Example 8. LC-MS (m/z): 505 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.87 (s, 1H), 9.38 (s, 1H), 8.49 (d,  $J = 3.1$  Hz, 1H), 8.28 (s, 1H), 7.47 (d,  $J = 8.1$  Hz, 1H), 7.35 (d,  $J = 14.1$  Hz, 2H), 7.19 (d,  $J = 14.8$

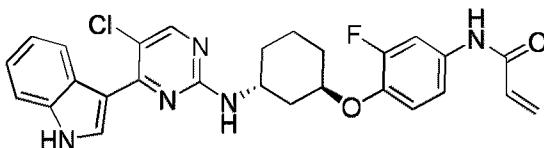
Hz, 1H), 6.92 (d,  $J$  = 9.5 Hz, 1H), 6.52 (dd,  $J$  = 17.0, 10.2 Hz, 1H), 6.22 (dd,  $J$  = 17.0, 2.1 Hz, 1H), 5.73 (dd,  $J$  = 10.2, 2.1 Hz, 1H), 3.31 (d,  $J$  = 11.7 Hz, 1H), 2.76 – 2.57 (m, 2H), 2.22 – 1.93 (m, 4H), 1.92 – 1.62 (m, 2H), 1.55 (qd,  $J$  = 11.9, 4.0 Hz, 1H).

**Example 12. (R)-N-(4-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)piperidin-1-yl)-5-methoxy-2-methylphenylacrylamide (BSJ-03-014)**



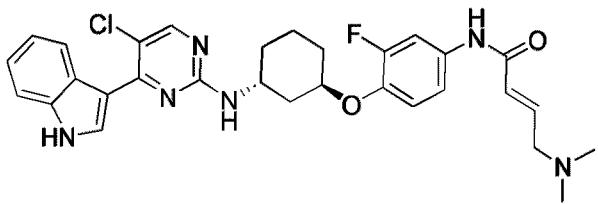
[00308] Example 12 was synthesized via a procedure similar to Example 8. LC-MS (m/z): 517 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.86 (s, 1H), 9.41 (s, 1H), 8.48 (d,  $J$  = 3.1 Hz, 1H), 8.29 (s, 1H), 7.48 (d,  $J$  = 8.2 Hz, 1H), 7.22 (d,  $J$  = 36.4 Hz, 3H), 6.52 (dd,  $J$  = 17.0, 10.2 Hz, 1H), 6.22 (dd,  $J$  = 17.0, 2.1 Hz, 1H), 5.72 (dd,  $J$  = 10.3, 2.1 Hz, 1H), 3.14 (qd,  $J$  = 7.4, 4.2 Hz, 2H), 2.11 (s, 3H), 1.96 – 1.51 (m, 3H), 1.26 (s, 7H).

**Example 13. N-((4-((1R,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)oxy)-3-fluorophenyl)acrylamide (BSJ-03-161)**



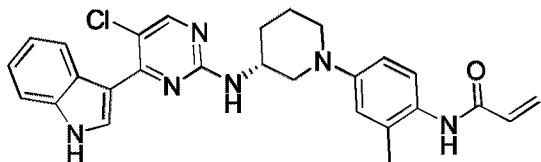
[00309] Example 13 was synthesized via a procedure similar to Example 1. LC-MS (m/z): 506 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.88 (s, 1H), 10.18 (s, 1H), 8.67 (d,  $J$  = 8.1 Hz, 1H), 8.52 (s, 1H), 8.26 (s, 1H), 7.69 (dd,  $J$  = 13.5, 2.5 Hz, 1H), 7.49 (d,  $J$  = 8.1 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.25 – 7.17 (m, 2H), 7.11 (s, 1H), 6.38 (dd,  $J$  = 16.9, 10.1 Hz, 1H), 6.24 (dd,  $J$  = 17.0, 2.0 Hz, 1H), 5.75 (dd,  $J$  = 10.1, 2.0 Hz, 1H), 4.78 (s, 1H), 3.17 (s, 1H), 2.17 (d,  $J$  = 13.2 Hz, 1H), 1.81 (d,  $J$  = 13.8 Hz, 3H), 1.67 – 1.46 (m, 2H), 1.46 – 1.20 (m, 1H).

**Example 14. (E)-N-((4-((1R,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)oxy)-3-fluorophenyl)-4-(dimethylamino)but-2-enamide (BSJ-03-162)**



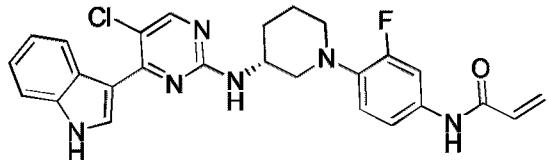
**[00310]** Example 14 was synthesized via a procedure similar to Example 2. LC-MS (m/z): 563 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 11.86 (s, 1H), 10.37 (s, 1H), 9.80 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.50 (s, 1H), 8.25 (d, *J* = 3.6 Hz, 1H), 7.69 (dd, *J* = 13.3, 2.5 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.09 (m, 4H), 6.73 (dt, *J* = 14.8, 7.2 Hz, 1H), 6.49 – 6.33 (m, 1H), 4.79 (s, 1H), 3.97 – 3.91 (m, 2H), 2.80 (s, 6H), 2.17 (d, *J* = 13.1 Hz, 1H), 1.81 (d, *J* = 14.2 Hz, 3H), 1.68 – 1.48 (m, 2H), 1.48 – 1.18 (m, 1H).

**Example 15. (R)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)-2-methylphenyl)acrylamide (BSJ-03-012)**



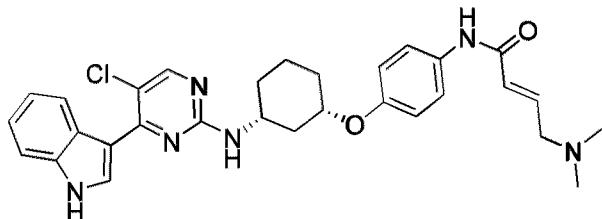
**[00311]** Example 15 was synthesized via a procedure similar to Example 8. LC-MS (m/z): 487 [M+H]<sup>+</sup>.

**Example 16. (R)-N-(4-(3-(5-chloro-4-(1H-indol-3-yl)pyrimidin-2-ylamino)piperidin-1-yl)-3-fluorophenyl)acrylamide (BSJ-03-018)**



**[00312]** Example 16 was synthesized via a procedure similar to Example 8. LC-MS (m/z): 491 [M+H]<sup>+</sup>.

**Example 17 (E)-N-(4-(((1S,3R)-3-((5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl)amino)cyclohexyl)oxy)phenyl)-4-(dimethylamino)but-2-enamide (BSJ-03-149)**



[00313] Example 17 was synthesized via a procedure similar to Example 2, LC-Mz (m/z) 546 [M+H]<sup>+</sup>.

#### EQUIVALENTS AND SCOPE

[00314] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00315] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, e.g., in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or

sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[00316] This application refers to various issued patents, published patent applications, journal articles, and other publications.

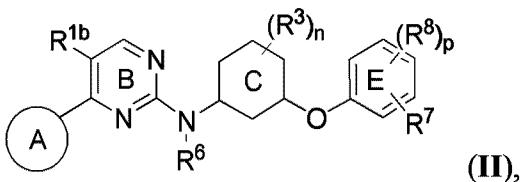
In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00317] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

## **CLAIMS**

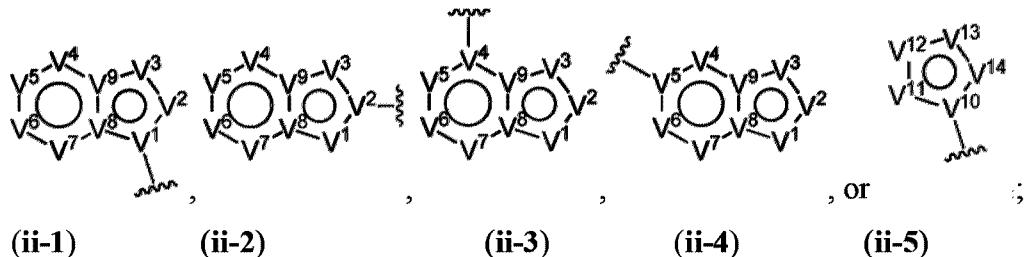
What is claimed is:

### 1. A compound of Formula (II):



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

Ring A is an optionally substituted heteroaryl ring of any one of Formulae (ii-1)-(ii-5):



or an optionally substituted 6-membered aryl or heteroaryl ring;

each instance of  $V^1, V^2, V^3, V^4, V^5, V^6, V^7, V^8, V^9, V^{10}, V^{11}, V^{12}, V^{13}$ , and  $V^{14}$  is independently  $O, S, N, N(R^{A1}), C$ , or  $C(R^{A2})$ ;

each instance of  $R^{A1}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

each instance of  $R^{A2}$  is independently hydrogen, halogen, -CN, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{A2a}$ ,  $-N(R^{A2b})_2$ , or  $-SR^{A2a}$ , wherein each instance of  $R^{A2a}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom;

wherein each occurrence of  $R^{A2b}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group, or optionally two instances of  $R^{A2b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

any two  $R^{A1}$ , any two  $R^{A2}$ , or one  $R^{A1}$  and one  $R^{A2}$  are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring;

$R^{1b}$  is independently hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-CN$ ,  $-OR^{B1a}$ ,  $-N(R^{B1b})_2$ , or  $-SR^{B1a}$ , wherein of  $R^{B1a}$  is hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom,

wherein each occurrence of  $R^{B1b}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group, or optionally two instances of  $R^{B1b}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

each instance of  $R^3$ , if present, is independently halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{C1}$ ,  $-N(R^{C1a})_2$ , or  $-SR^{C1}$ , wherein each occurrence of  $R^{C1}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,

an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom,

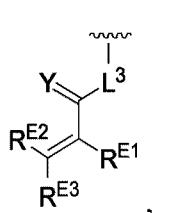
wherein each occurrence of  $R^{C1a}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group, or optionally two instances of  $R^{C1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^3$  groups bound to the same ring carbon atom are taken together to form  $=O$ , or

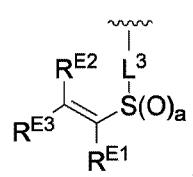
two  $R^3$  groups bound to the same or different ring carbon atoms are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

$R^6$  is hydrogen or  $-C_1-C_6$  alkyl;

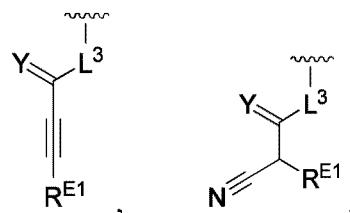
$R^7$  is a warhead of formula:



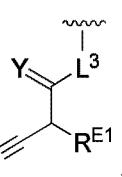
(i-1)



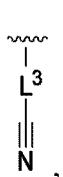
(i-2)



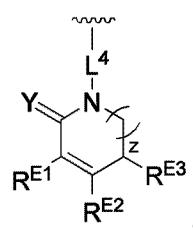
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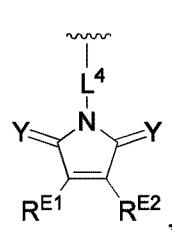
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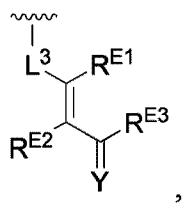
(i-5)



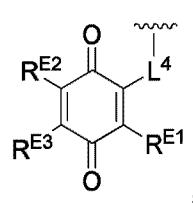
(i-7)



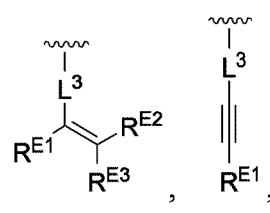
(i-8)



(i-16)



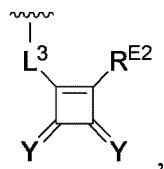
(i-17)



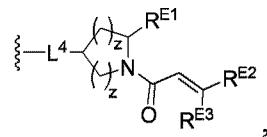
(i-18)



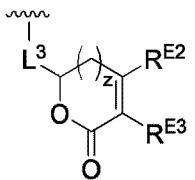
(i-19)



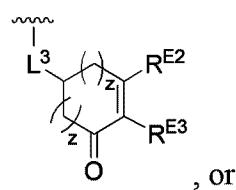
(i-22)



(i-24)

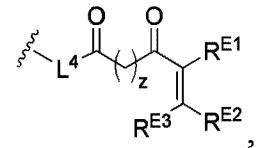


(i-26)



(i-27)

, or



(i-29)

wherein:

$L^3$  is a bond or an optionally substituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C=O-$ ,  $-O-$ ,  $-S-$ ,  $-NR^{L3a}-$ ,  $-NR^{L3a}C(=O)-$ ,  $-C(=O)NR^{L3a}-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-NR^{L3a}C(=S)-$ ,  $-C(=S)NR^{L3a}-$ ,  $trans-CR^{L3b}=CR^{L3b}-$ ,  $cis-CR^{L3b}=CR^{L3b}-$ ,  $-C\equiv C-$ ,  $-S(=O)-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^{L3a}-$ ,  $-NR^{L3a}S(=O)-$ ,  $-S(=O)_2-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^{L3a}-$ , or  $-NR^{L3a}S(=O)_2-$ , wherein each instance of  $R^{L3a}$  is independently hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group, and wherein each occurrence of  $R^{L3b}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{L3b}$  groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$L^4$  is a bond or an optionally substituted, branched or unbranched  $C_{1-6}$  hydrocarbon chain;

each instance of  $R^{E1}$ ,  $R^{E2}$ , and  $R^{E3}$  is independently hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-CN$ ,  $-CH_2OR^{EE}$ ,  $-CH_2N(R^{EE})_2$ ,  $-CH_2SR^{EE}$ ,  $-OR^{EE}$ ,  $-N(R^{EE})_2$ ,  $-Si(R^{EE})_3$ , or  $-SR^{EE}$ , wherein each instance of  $R^{EE}$  is independently hydrogen, optionally

substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl, or two  $R^{EE}$  groups are joined to form an optionally substituted heterocyclic ring; or  $R^{E1}$  and  $R^{E3}$ , or  $R^{E2}$  and  $R^{E3}$ , or  $R^{E1}$  and  $R^{E2}$  are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

each instance of Y is independently O, S, or  $NR^{E7}$ , wherein  $R^{E7}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

a is 1 or 2;

each instance of z is independently 0, 1, 2, 3, 4, 5, or 6, as valency permits; and

each instance of  $R^8$ , if present, is independently hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl,  $-OR^{D1}$ ,  $-N(R^{D1a})_2$ , or  $-SR^{D1}$ , wherein each occurrence of  $R^{D1}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted heteroaryl, or a nitrogen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom,

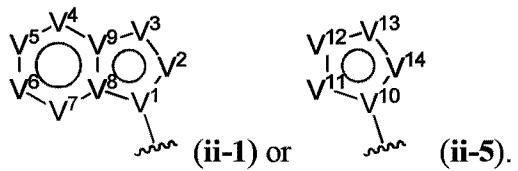
wherein each occurrence of  $R^{D1a}$  is independently hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a nitrogen protecting group, or optionally two instances of  $R^{D1a}$  are taken together with their intervening atoms to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring; or

two  $R^8$  groups are joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring;

n is 0, 1, 2, 3, 4, 5 or 6; and

p is 0, 1, 2, 3, 4, or 5.

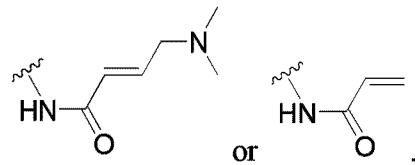
2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Ring A is of the formula:



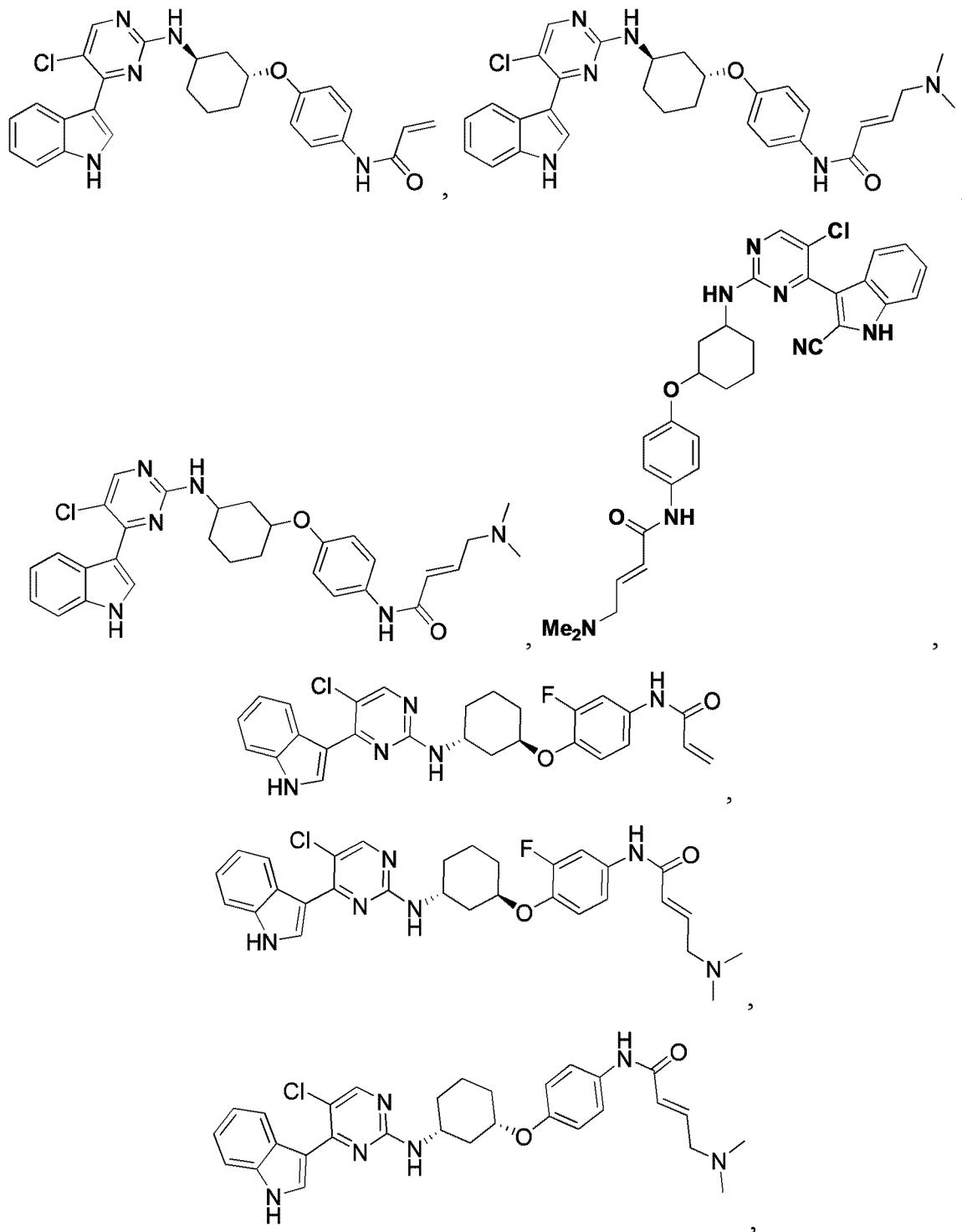
3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein R<sup>1b</sup> is halogen.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein at least one instance of R<sup>8</sup> is halogen, -O(alkyl), or optionally substituted alkyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein R<sup>7</sup> is of formula:



6. The compound of claim 1, wherein the compound is of formula:



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

7. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

8. Use of the compound of claim 1, or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof for treatment of a proliferative disease in a subject in need thereof.

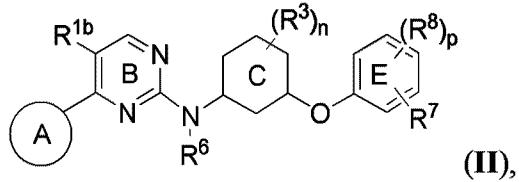
9. Use of the compound of claim 1, or the pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof for inhibition of the activity of a cyclin-dependent kinase (CDK) in a biological sample or subject.

10. Use of the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof for inhibition of transcription in a biological sample or subject.

11. Use of the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof for inhibition of cell growth in a biological sample or subject.

12. Use of the compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof for induction of apoptosis of a cell in a biological sample or subject.

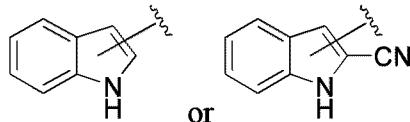
13. The compound of claim 1, wherein the compound is the compound of Formula (II):



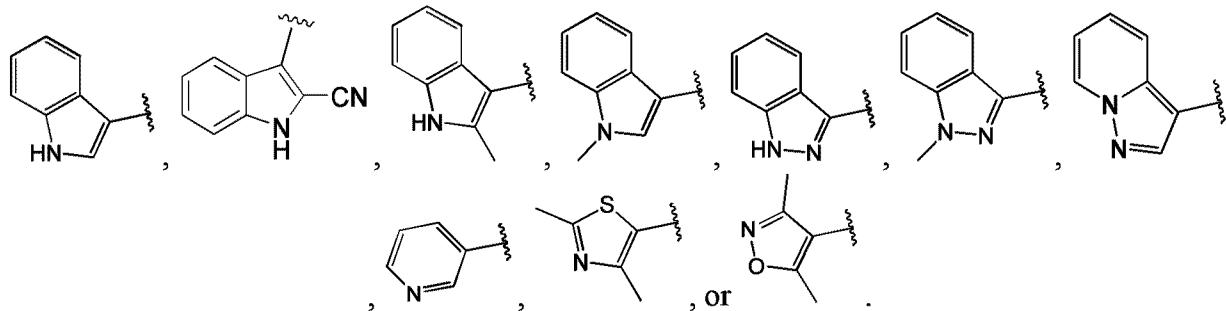
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein  $R^6$  is H.

15. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Ring A is of formula:



16. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Ring A is of formula:

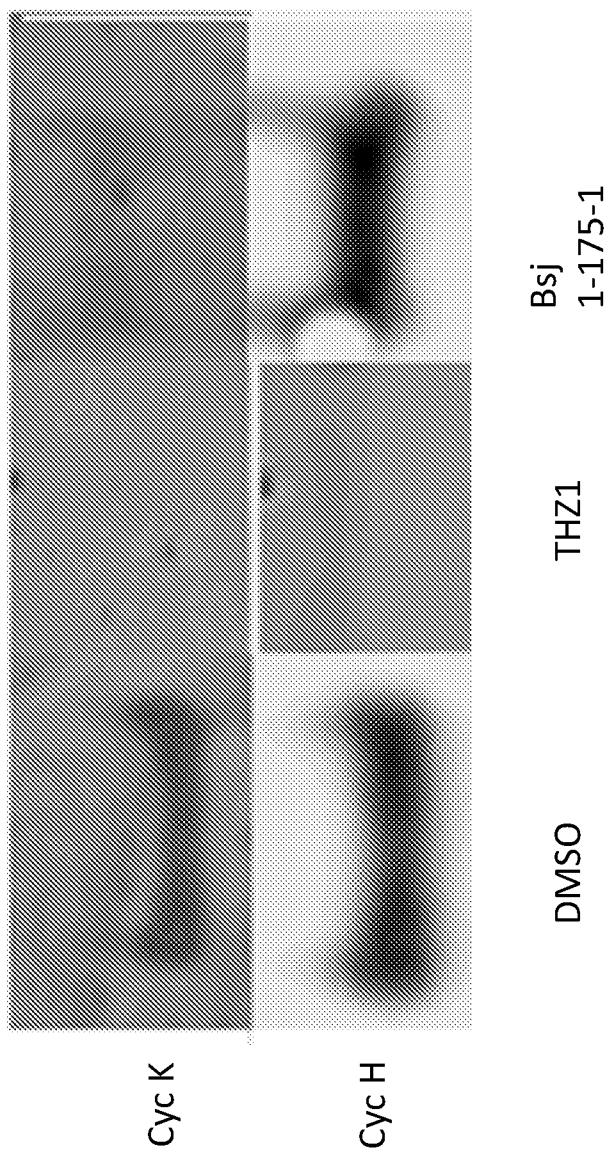


17. The compound of claim 3, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein R<sup>1b</sup> is Cl.

18. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein n is 0.

19. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein p is 0.

20. The compound of claim 3, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein R<sup>1b</sup> is Br.



**Figure 1**

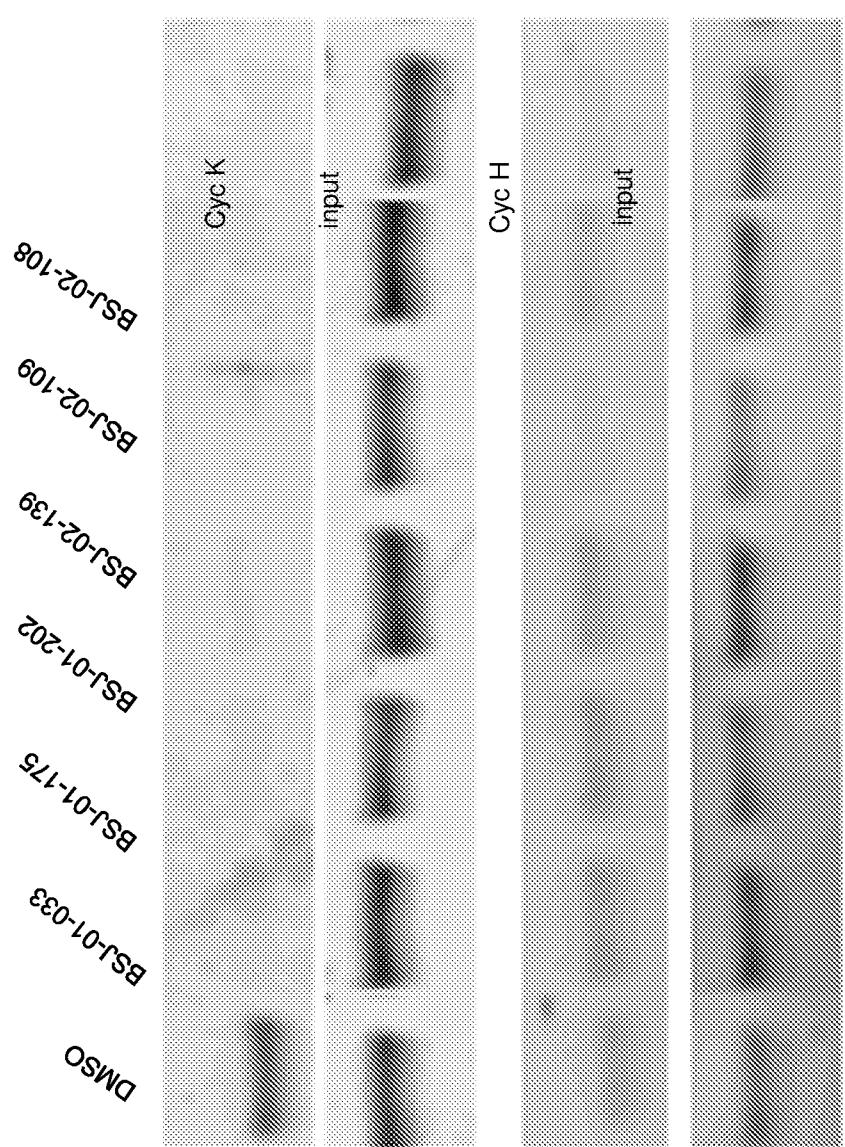
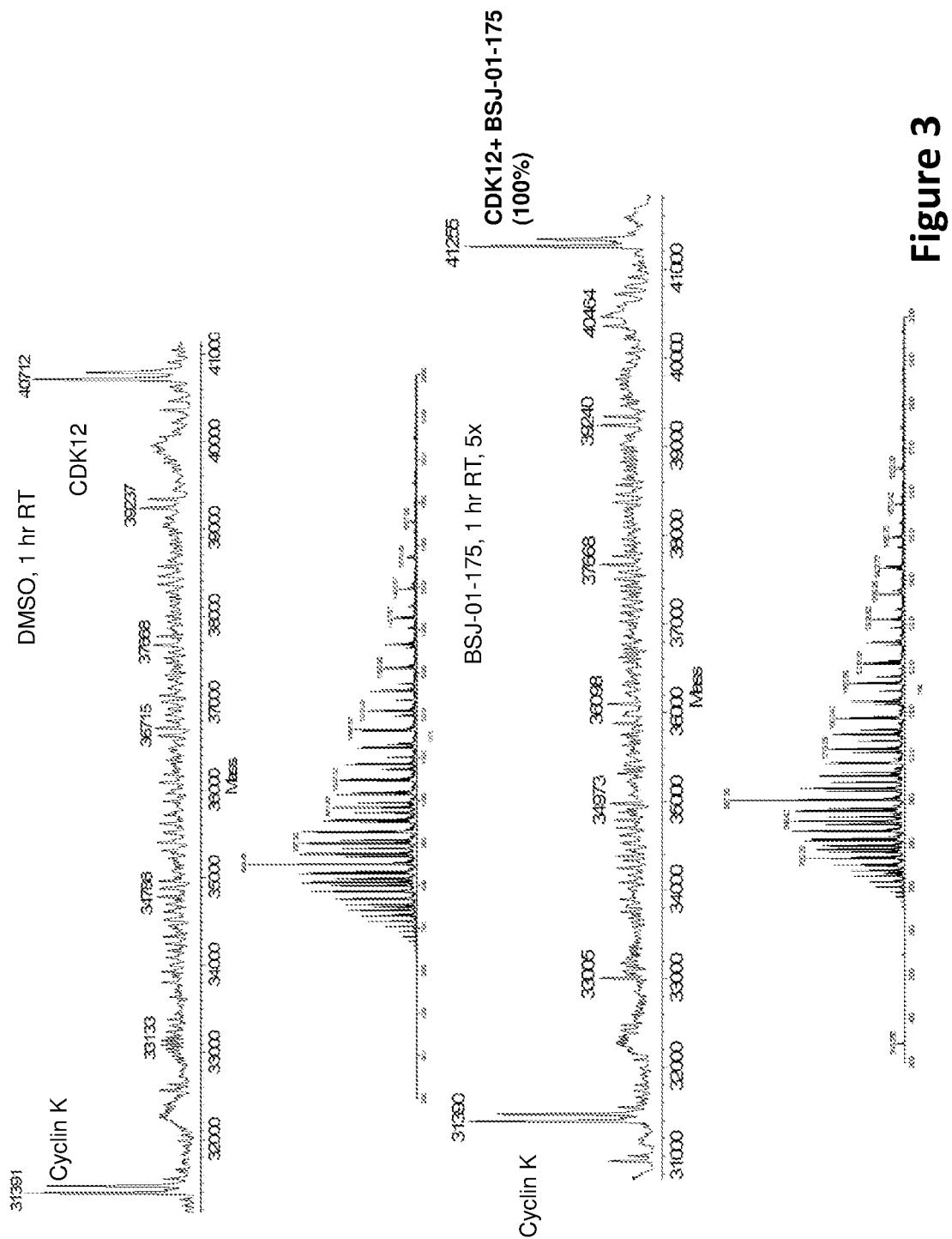


Figure 2

**Figure 3**

