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## (54) Title: FUSED BICYCLIC PYRIMIDINE DERIVATIVES AND USES THEREOF

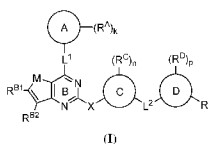
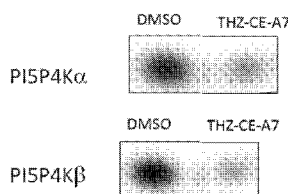


Figure 3A



(57) Abstract: The present invention provides novel compounds of Formula (I), 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 or preventing proliferative diseases (e.g., cancers (e.g., lung cancer, breast cancer, leukemia, lymphoma, melanoma, multiple myeloma, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma), benign neoplasms, 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 (e.g. a protein kinase (e.g. a cyclin-dependent kinase (CDK) (e.g. CDK7, CDK12, or CDK13) or a lipid kinase such as a phosphatidylinositol- 5 -phosphate 4- kinase (PIP4K) (e.g., PI5P4Kα, PI5P4Kβ, or PI5P4Kγ)) in the sub-

## **FUSED BICYCLIC PYRIMIDINE DERIVATIVES AND USES THEREOF**

### **RELATED APPLICATION**

**[0001]** The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional application, U.S.S.N. 62/185,366, filed June 26, 2015, which is incorporated herein by reference.

### **GOVERNMENT SUPPORT**

**[0002]** This invention was made with government support under grant number R01CA197329 awarded by The National Institutes of Health. The government has certain rights in the invention.

### **BACKGROUND OF THE INVENTION**

**[0003]** Lung cancer is the leading cancer killer worldwide accounting for 1.37 million deaths annually. In the United States, lung cancer causes more deaths than the next three most common cancers combined (colon, breast and pancreatic) and in 2014, an estimated 159,260 Americans will die from lung cancer. Lung cancer arises as a result of environmental exposures, such as smoking, combined with genetic alterations such as deregulation of oncoproteins, including Myc and RAS, and loss of tumor suppressors, such as p53. The vast majority of patients that develop lung cancer will have non-small cell lung cancer (NSCLC), and 50% of patients will initially present with advanced NSCLC, which is incurable using currently available therapies. The median survival of patients with advanced NSCLC treated with chemotherapy is 8-10 months.

**[0004]** A major therapeutic goal in lung cancer is to identify agents against targets that are critical to the growth of lung cancers. This has been clinically achieved for patients that harbor activating mutations in EGFR or chromosomal translocations such as EML4-ALK using selective ATP-competitive kinase inhibitors. Unfortunately the duration of response to targeted kinase inhibitors is typically less than 2 years, and most lung tumors do not express an oncogene that is targeted by an available drug. For example, loss of p53 is a common event in lung cancer, but there are currently limited drugs that can exploit its loss.

**[0005]** Phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) is a membrane bound lipid molecule with the ability to affect a wide array of signaling pathways that regulate different cellular

processes (Camilli *et al.*, *Science*, 1996, 271: 1533-1539). PIP<sub>2</sub> is used as a precursor to generate the second messengers PIP<sub>3</sub>, DAG, and IP<sub>3</sub>, indispensable molecules for signaling events generated by membrane receptors. However, PIP<sub>2</sub> can also directly regulate a vast array of proteins and is emerging as a crucial messenger with the potential to distinctly modulate biological processes critical for both normal and pathogenic cell physiology (Martin, T. F. J. (1998) *Annu.Rev.Cell Dev.Biol.* 14, 231-264). PIP<sub>2</sub> directly associates with effector proteins via unique phosphoinositide binding domains, altering their localization and/or enzymatic activity. The spatial and temporal generation of PIP<sub>2</sub> synthesized by the phosphatidylinositol phosphate kinases (PIPKs) tightly regulates the activation of receptor signaling pathways, endocytosis and vesicle trafficking, cell polarity, focal adhesion dynamics, actin assembly, and 3' mRNA processing (Balla *et al.*, *Phosphoinositides I: Enzymes of Synthesis and Degradation*, 2012, Chapter 2, PIP Kinases from the Cell Membrane to the Nucleus, p 25). Two types of PIP kinases have been identified, type I and type II PI(4)P 5-kinases (Fruman *et al.*, *Annu.Rev.Biochem.*, 1998, 67: 481-507). Type I phosphorylates PI(4)P at the 5-position to make PI(4,5)P<sub>2</sub> and type II can phosphorylate PI(5)P and PI(3)P at the 4-position to make PI(4,5)P<sub>2</sub> and PI(3,4)P<sub>2</sub>.

**[0006]** Recently, it has been discovered that RNAi-mediated depletion of two type II PIP kinases, PIP4K2A and PIP4K2B, selectively inhibited the proliferation of TP53 mutant breast cancer cell line (BT474 cells) while cells that were wild-type for TP53 were unaffected (Emerling *et al.*, *Cell*, 2013, 155: 844-857). These kinases phosphorylate the lipid phosphatidylinositol-5-phosphate (PI-5-P) at the 4-position of the inositol ring to generate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P<sub>2</sub>) and are in the same kinase family as the PI3 kinases which are now targeted by a number of clinical stage drugs. Genetic studies in mice demonstrate that homozygous germline deletion of PIP4K2B results in healthy mice with a normal life span, while combined deletion of PIP4K2B and TP53 results in early embryonic lethality (Figure 1) (Rameh *et al.*, *Nature*, 1997, 390: 192-196). Mice expressing one allele of PIP4K2B and homozygous deletion of PIP4K2A and TP53 are viable and exhibit a dramatic reduction in cancers and an extended lifespan compared to their littermates that were TP53 deleted with wild type PIP4K2A. These studies suggest that PIP4K2A/B becomes essential when TP53 function is lost. Therefore, small molecule inhibitors of PIP4K2A/B may hold promise as a therapeutic agent for treating cancer.

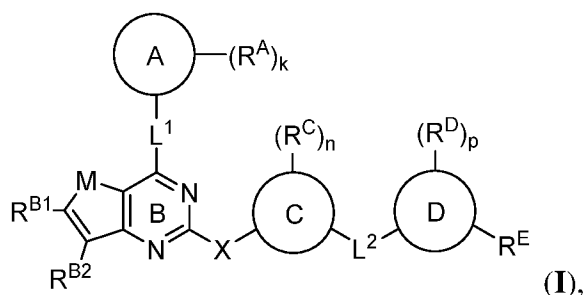
## SUMMARY OF THE INVENTION

**[0007]** The phosphoinositide family of lipids includes seven derivatives of phosphatidylinositol (PI) that are formed through the phosphorylation of the 3-, 4-, and 5-positions on the inositol ring (Emerling *et al.*, *Cell*, 2013, 155: 844-857). Phosphoinositides have distinct biological roles and regulate many cellular processes, including proliferation survival, glucose uptake, and migration. Phosphoinositide kinases, phosphatases and phospholipases, spatially and temporally regulate the generation of the different phosphoinositide species, which localize to different subcellular compartments. phosphorylation of lipid phosphatidylinositol-5-phosphate (PI-5-P) at the 4-position to generate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P<sub>2</sub>) is catalyzed by the enzymes PIP4K2A, B and C. Germ line deletion of PIP4K2A and PIP4K2B in mice suppresses tumor formation in the context of TP53 deletion (Rameh *et al.*, *Nature*, 1997, 390: 192-196). Loss or mutations in the tumor suppressor gene TP53 (encoding p53) is one of the most frequent events in cancer. Clinical and functional studies have unequivocally validated the functional importance of the loss of p53 in cancer. Therefore, it is advantageous to develop PIP4K2A and/or PIP4K2B inhibitors to provide therapeutic benefit in cancers, for example, TP53-deleted tumors.

**[0008]** The present invention provides compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. The compounds of Formula (I), 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 protein kinase. In certain embodiments, the protein kinase is a CDK (*e.g.*, cyclin-dependent kinases (CDKs)). In certain embodiments, the kinase is a lipid kinase. In certain embodiments, the lipid kinase is a phosphatidylinositol phosphate kinase (PIPK). In certain embodiments, the PIPK is PIP4K, catalyzing phosphorylation of lipid phosphatidylinositol-5-phosphate (PI-5-P) at the 4-position to generate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P<sub>2</sub>). In some embodiments, the PIP4K is class I PIP4K, *i.e.*, PIP4K1. In some embodiments, the PIP4K is class II PIP4K, *i.e.*, PIP4K2. In some embodiments, the PIP4K2 is PIP4K2A protein. In some embodiments, the PIP4K2 is PIP4K2B protein. In some embodiments, the PIP4K2 is PIP4K2C protein. In certain embodiments, the compound of Formula (I) is selective for a lipid kinase compared to other kinases. In certain embodiments, the compound of Formula (I) is selective for PIP4K compared to other kinases.

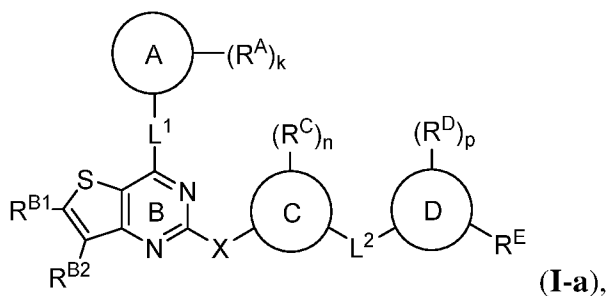
**[0009]** The present invention further provides methods of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, to study the inhibition of a kinase (*e.g.*, PIP4K) and as therapeutics for the prevention and/or treatment of diseases associated with overexpression and/or aberrant activity of a kinase (*e.g.*, PIP4K). In certain embodiments, the inventive compounds are used for the prevention and/or treatment of proliferative diseases (*e.g.*, cancers (*e.g.*, lung cancer, breast cancer, leukemia, lymphoma, melanoma, multiple myeloma, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma), benign neoplasms, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) in a subject.

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



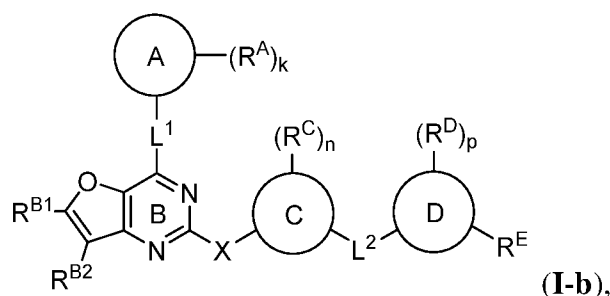
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring A, L<sup>1</sup>, L<sup>2</sup>, R<sup>B1</sup>, R<sup>B2</sup>, M, X, R<sup>A</sup>, R<sup>C</sup>, R<sup>D</sup>, R<sup>E</sup>, n, and p are as defined herein.

**[0011]** In certain embodiments, a compound of Formula (I) is of Formula (I-a):



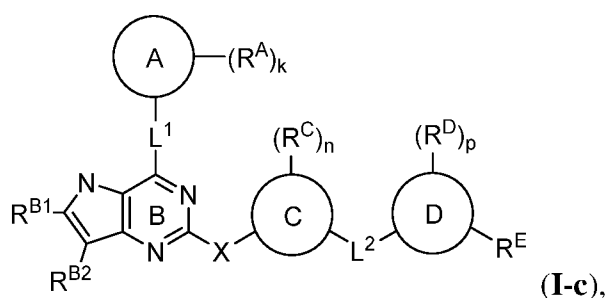
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[0012] In certain embodiments, a compound of Formula (I) is Formula (I-b):



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

[0013] In certain embodiments, a compound of Formula (I) is Formula (I-c):



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

[0014] In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. The pharmaceutical composition may be useful for treating and/or preventing a proliferative disease (*e.g.*, cancer) or an infectious disease.

[0015] In another aspect, the present invention provides methods for treating and/or preventing proliferative diseases. Exemplary proliferative diseases include cancer (*e.g.*, lung cancer, breast cancer, leukemia, lymphoma, melanoma, multiple myeloma, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases. In certain embodiments, the cancer has one or more mutations. In certain embodiments, the cancer is TP53-deleted

cancer. In other embodiments, the present invention provides methods for treating and/or preventing an infectious disease (*e.g.*, a viral infection).

**[0016]** Another aspect of the invention relates to methods of modulating the activity of a kinase (*e.g.*, PIP4K (*e.g.*, PIP4K2) enzyme) in a biological sample or subject. In certain embodiments, the method involves the selective inhibition of the PIP4K enzyme over other kinases. In certain embodiments, the method involves the selective inhibition of the PIP4K2 enzyme over other kinases.

**[0017]** The present invention also provides methods of inhibiting cell growth in a biological sample or subject.

**[0018]** Another aspect of the invention relates to methods of screening a library of compounds (*e.g.*, compounds of Formula (I)) to identify one or more compounds useful in the treatment of a proliferative disease (*e.g.*, cancer (*e.g.*, lung cancer, breast cancer, leukemia, lymphoma, melanoma, multiple myeloma, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) or an infectious disease (*e.g.*, viral infection) in a subject, in inhibiting a kinase (*e.g.*, PIP4K enzyme), or in inhibiting cell growth.

**[0019]** In yet another aspect, the present invention provides compounds of Formula (I), 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 proliferative disease in a subject.

**[0020]** In yet another aspect, the present invention provides compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof, for use in the treatment or prevention of an infectious disease in a subject. In certain embodiments, the infectious disease is a viral infection.

**[0021]** Another aspect of the present invention relates to kits comprising a container with a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. The kits of the invention may include a single dose or multiple doses of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. The provided kits may be useful for the treatment and/or prevention of a proliferative disease (*e.g.*, cancer (*e.g.*,

lung cancer, breast cancer, leukemia, lymphoma, melanoma, multiple myeloma, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma), benign neoplasm, angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases) or an infectious disease in a subject. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or the pharmaceutical composition thereof.

**[0022]** The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Examples, and the Claims.

### DEFINITIONS

**[0023]** 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.

**[0024]** 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 disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

**[0025]** 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>.

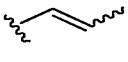
**[0026]** The term “aliphatic” includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are substituted or unsubstituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “aliphatic” is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. Thus, the term “alkyl” includes straight, branched and cyclic alkyl groups. An analogous convention applies to other generic terms such as “alkenyl”, “alkynyl”, and the like. Furthermore, the terms “alkyl”, “alkenyl”, “alkynyl”, and the like encompass both substituted and unsubstituted groups. In certain embodiments, “lower alkyl” is used to indicate those alkyl groups (cyclic, acyclic, substituted, unsubstituted, branched or unbranched) having 1-6 carbon atoms.

**[0027]** In certain embodiments, the alkyl, alkenyl, and alkynyl groups employed in the disclosure contain 1-20 aliphatic carbon atoms. In certain other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the disclosure contain 1-10 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the disclosure contain 1-8 aliphatic carbon atoms. In still other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the disclosure contain 1-6 aliphatic carbon atoms. In yet other embodiments, the alkyl, alkenyl, and alkynyl groups employed in the disclosure contain 1-4 carbon atoms. Illustrative aliphatic groups thus include, but are not limited to, for example, methyl, ethyl, n-propyl, isopropyl, cyclopropyl, -CH<sub>2</sub>-cyclopropyl, vinyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH<sub>2</sub>-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH<sub>2</sub>-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH<sub>2</sub>-cyclohexyl moieties and the like, which again, may bear one or more substituents. Alkenyl groups include, but are not limited to, for example, ethenyl, propenyl, butenyl, 1-methyl-2-buten-1-yl, and the like. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (propargyl), 1-propynyl, and the like.

**[0028]** The term “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 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>), propyl (C<sub>3</sub>) (*e.g.*, *n*-propyl, isopropyl), butyl (C<sub>4</sub>) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, *iso*-butyl), pentyl (C<sub>5</sub>) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C<sub>6</sub>) (*e.g.*, *n*-hexyl). 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 unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents (*e.g.*, halogen, such as F). In certain embodiments, the alkyl group is an unsubstituted C<sub>1-10</sub> alkyl (such as unsubstituted C<sub>1-6</sub> alkyl, *e.g.*, -CH<sub>3</sub> (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted *n*-propyl (*n*-Pr), unsubstituted isopropyl (*i*-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted *n*-butyl (*n*-Bu), unsubstituted *tert*-butyl (*tert*-Bu or *t*-Bu), unsubstituted *sec*-butyl (*sec*-Bu or *s*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C<sub>1-10</sub> alkyl (such as substituted C<sub>1-6</sub> alkyl, *e.g.*, benzyl (Bn) or -CF<sub>3</sub>).

**[0029]** “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. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, -CH=CHCH<sub>3</sub> or ) may be an (*E*)- or (*Z*)-double bond.

**[0030]** “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-butyne) or terminal (such as in 1-butyne). 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-butyne (C<sub>4</sub>), 2-butyne (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.

**[0031]** “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 zero 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 substituted C<sub>3-10</sub> carbocyclyl.

**[0032]** 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>5</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.

**[0033]** “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.

**[0034]** 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.

**[0035]** Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, aziridinyl, oxiranyl, thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, 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, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridiny, 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, oxecanyl 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.

**[0036]** “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.

**[0037]** “Aralkyl” refers to a substituted or unsubstituted alkyl group substituted by a substituted or unsubstituted aryl group. In certain embodiments, the aralkyl is substituted or unsubstituted benzyl. In certain embodiments, the aralkyl is benzyl. In certain embodiments, the aralkyl is substituted or unsubstituted phenethyl. *In* certain embodiments, the aralkyl is phenethyl.

**[0038]** “Heteroaryl” refers to a radical of a 5-10 membered, monocyclic or bicyclic 4n+2 aromatic ring system (*e.g.*, having 6 or 10 pi 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).

**[0039]** 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.

**[0040]** Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

**[0041]** “Heteroaralkyl” is a subset of alkyl and heteroaryl and refers to a substituted or unsubstituted alkyl group substituted by a substituted or unsubstituted heteroaryl group.

**[0042]** “Unsaturated” or “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). Likewise, “saturated” refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

**[0043]** Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, which are divalent linking groups, are further referred to using the suffix -ene, *e.g.*, alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene.

**[0044]** An atom, moiety, or group described herein may be unsubstituted or substituted, as valency permits, unless otherwise provided expressly. The term “optionally substituted” refers to substituted or unsubstituted.

**[0045]** A group is substituted or unsubstituted unless expressly provided otherwise. The term “optionally substituted” refers to being substituted or unsubstituted. In certain embodiments, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups are substituted or unsubstituted (*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 disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, 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. In certain embodiments, the substituent is a carbon atom substituent. In certain embodiments, the substituent is a nitrogen atom substituent. In certain embodiments,

the substituent is an oxygen atom substituent. In certain embodiments, the substituent is a sulfur atom substituent.

**[0046]** Exemplary carbon atom substituents include, but are not limited to, halogen,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{N}_3$ ,  $-\text{SO}_2\text{H}$ ,  $-\text{SO}_3\text{H}$ ,  $-\text{OH}$ ,  $-\text{OR}^{\text{aa}}$ ,  $-\text{ON}(\text{R}^{\text{bb}})_2$ ,  $-\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$ ,  $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$ ,  $-\text{SH}$ ,  $-\text{SR}^{\text{aa}}$ ,  $-\text{SSR}^{\text{cc}}$ ,  $-\text{C}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{CO}_2\text{H}$ ,  $-\text{CHO}$ ,  $-\text{C}(\text{OR}^{\text{cc}})_2$ ,  $-\text{CO}_2\text{R}^{\text{aa}}$ ,  $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{OCO}_2\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$ ,  $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$ ,  $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$ ,  $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{SO}_2\text{OR}^{\text{aa}}$ ,  $-\text{OSO}_2\text{R}^{\text{aa}}$ ,  $-\text{S}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{Si}(\text{R}^{\text{aa}})_3$ ,  $-\text{OSi}(\text{R}^{\text{aa}})_3$ ,  $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$ ,  $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$ ,  $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$ ,  $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$ ,  $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$ ,  $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$ ,  $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$ ,  $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$ ,  $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$ ,  $-\text{P}(\text{R}^{\text{cc}})_2$ ,  $-\text{P}(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(\text{R}^{\text{cc}})_4$ ,  $-\text{P}(\text{OR}^{\text{cc}})_4$ ,  $-\text{OP}(\text{R}^{\text{cc}})_2$ ,  $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{OP}(\text{OR}^{\text{cc}})_2$ ,  $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{OP}(\text{R}^{\text{cc}})_4$ ,  $-\text{OP}(\text{OR}^{\text{cc}})_4$ ,  $-\text{B}(\text{R}^{\text{aa}})_2$ ,  $-\text{B}(\text{OR}^{\text{cc}})_2$ ,  $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$ ,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  perhaloalkyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl, hetero $\text{C}_{1-10}$  alkyl, hetero $\text{C}_{2-10}$  alkenyl, hetero $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-10}$  carbocyclyl, 3-14 membered heterocyclyl,  $\text{C}_{6-14}$  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  $\text{R}^{\text{dd}}$  groups; wherein  $\text{X}^-$  is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group  $=\text{O}$ ,  $=\text{S}$ ,  $=\text{NN}(\text{R}^{\text{bb}})_2$ ,  $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$ ,  $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$ ,  $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$ ,  $=\text{NR}^{\text{bb}}$ , or  $=\text{NOR}^{\text{cc}}$ ;

each instance of  $\text{R}^{\text{aa}}$  is, independently, selected from  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  perhaloalkyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl, hetero $\text{C}_{1-10}$  alkyl, hetero $\text{C}_{2-10}$  alkenyl, hetero $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-10}$  carbocyclyl, 3-14 membered heterocyclyl,  $\text{C}_{6-14}$  aryl, and 5-14 membered heteroaryl, or two  $\text{R}^{\text{aa}}$  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  $\text{R}^{\text{dd}}$  groups;

each instance of  $\text{R}^{\text{bb}}$  is, independently, selected from hydrogen,  $-\text{OH}$ ,  $-\text{OR}^{\text{aa}}$ ,  $-\text{N}(\text{R}^{\text{cc}})_2$ ,  $-\text{CN}$ ,  $-\text{C}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$ ,  $-\text{CO}_2\text{R}^{\text{aa}}$ ,  $-\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$ ,  $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$ ,  $-\text{SO}_2\text{R}^{\text{cc}}$ ,  $-\text{SO}_2\text{OR}^{\text{cc}}$ ,  $-\text{SOR}^{\text{aa}}$ ,  $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$ ,  $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$ ,  $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$ ,  $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{cc}})_2)_2$ ,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  perhaloalkyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl, hetero $\text{C}_{1-10}$  alkyl, hetero $\text{C}_{2-10}$  alkenyl, hetero $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-10}$

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>gg</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>, -NH<sub>2</sub>SO<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.

**[0047]** In certain embodiments, the carbon atom substituents are independently halogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, or -OR<sup>aa</sup>.

**[0048]** The term “hydroxyl” or “hydroxy” refers to the group -OH. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from -OR<sup>aa</sup>, -ON(R<sup>bb</sup>)<sub>2</sub>, -OC(=O)SR<sup>aa</sup>, -OC(=O)R<sup>aa</sup>, -OCO<sub>2</sub>R<sup>aa</sup>, -OC(=O)N(R<sup>bb</sup>)<sub>2</sub>, -OC(=NR<sup>bb</sup>)R<sup>aa</sup>, -OC(=NR<sup>bb</sup>)OR<sup>aa</sup>, -OC(=NR<sup>bb</sup>)N(R<sup>bb</sup>)<sub>2</sub>, -OS(=O)R<sup>aa</sup>, -OSO<sub>2</sub>R<sup>aa</sup>, -OSi(R<sup>aa</sup>)<sub>3</sub>, -OP(R<sup>cc</sup>)<sub>2</sub>, -OP(R<sup>cc</sup>)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -OP(OR<sup>cc</sup>)<sub>2</sub>, -OP(OR<sup>cc</sup>)<sub>3</sub><sup>+</sup>X<sup>-</sup>, -OP(=O)(R<sup>aa</sup>)<sub>2</sub>, -OP(=O)(OR<sup>cc</sup>)<sub>2</sub>, and -OP(=O)(N(R<sup>bb</sup>))<sub>2</sub>, wherein R<sup>aa</sup>, R<sup>bb</sup>, and R<sup>cc</sup> are as defined herein.

**[0049]** A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*,  $F^-$ ,  $Cl^-$ ,  $Br^-$ ,  $I^-$ ),  $NO_3^-$ ,  $ClO_4^-$ ,  $OH^-$ ,  $H_2PO_4^-$ ,  $HSO_4^-$ , sulfonate ions (*e.g.*, methanesulfonate, 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), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like). Further exemplary counterions include, but are not limited to,  $BF_4^-$ ,  $PF_4^-$ ,  $PF_6^-$ ,  $AsF_6^-$ ,  $SbF_6^-$ ,  $B[3,5-(CF_3)_2C_6H_3]_4^-$ ,  $B(C_6F_5)_4^-$ ,  $BPh_4^-$ ,  $Al(OC(CF_3)_3)_4^-$ , and carborane anions (*e.g.*,  $CB_{11}H_{12}^-$  or  $(HCB_{11}Me_5Br_6)^-$ ). Exemplary counterions which may be multivalent include  $CO_3^{2-}$ ,  $HPO_4^{2-}$ ,  $PO_4^{3-}$ ,  $B_4O_7^{2-}$ ,  $SO_4^{2-}$ ,  $S_2O_3^{2-}$ , 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

**[0050]** “Halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

**[0051]** “Acyl” refers to a moiety selected from the group consisting of  $-C(=O)R^{aa}$ ,  $-CHO$ ,  $-CO_2R^{aa}$ ,  $-C(=O)N(R^{bb})_2$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{bb})OR^{aa}$ ,  $-C(=NR^{bb})N(R^{bb})_2$ ,  $-C(=O)NR^{bb}SO_2R^{aa}$ ,  $-C(=S)N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ , or  $-C(=S)SR^{aa}$ , wherein  $R^{aa}$  and  $R^{bb}$  are as defined herein.

**[0052]** 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,  $-OH$ ,  $-OR^{aa}$ ,  $-N(R^{cc})_2$ ,  $-CN$ ,  $-C(=O)R^{aa}$ ,  $-C(=O)N(R^{cc})_2$ ,  $-CO_2R^{aa}$ ,  $-SO_2R^{aa}$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{cc})OR^{aa}$ ,  $-C(=NR^{cc})N(R^{cc})_2$ ,  $-SO_2N(R^{cc})_2$ ,  $-SO_2R^{cc}$ ,  $-SO_2OR^{cc}$ ,  $-SOR^{aa}$ ,  $-C(=S)N(R^{cc})_2$ ,  $-C(=O)SR^{cc}$ ,  $-C(=S)SR^{cc}$ ,  $-P(=O)(OR^{cc})_2$ ,  $-P(=O)(R^{aa})_2$ ,  $-P(=O)(N(R^{cc})_2)_2$ ,  $C_{1-10}$  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, or two  $R^{cc}$  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  $R^{dd}$  groups, and wherein  $R^{aa}$ ,  $R^{bb}$ ,  $R^{cc}$  and  $R^{dd}$  are as defined above.

**[0053]** 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, incorporated herein by reference.

**[0054]** For example, nitrogen protecting groups such as amide groups (*e.g.*, -C(=O)R<sup>aa</sup>) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxycetamide, acetoacetamide, (*N*'-dithiobenzoyloxyacylamino)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.

**[0055]** Nitrogen protecting groups such as carbamate groups (*e.g.*, -C(=O)OR<sup>aa</sup>) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl 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 or 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, alkylthio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl 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 (TcroC), *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.

**[0056]** Nitrogen protecting groups such as sulfonamide groups (*e.g.*, -S(=O)<sub>2</sub>R<sup>aa</sup>) 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), β-trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-

dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenaclysulfonamide.

**[0057]** 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-tetramethyldisilylazacyclopentane 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-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-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 phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys). In certain embodiments, a nitrogen protecting group is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

**[0058]** 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,  $-R^{aa}$ ,  $-N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ ,  $-C(=O)R^{aa}$ ,  $-CO_2R^{aa}$ ,  $-C(=O)N(R^{bb})_2$ ,  $-C(=NR^{bb})R^{aa}$ ,  $-C(=NR^{bb})OR^{aa}$ ,  $-C(=NR^{bb})N(R^{bb})_2$ ,  $-S(=O)R^{aa}$ ,

$-\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{Si}(\text{R}^{\text{aa}})_3$ ,  $-\text{P}(\text{R}^{\text{cc}})_2$ ,  $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ , and  $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$ , wherein  $\text{R}^{\text{aa}}$ ,  $\text{R}^{\text{bb}}$ , and  $\text{R}^{\text{cc}}$  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, incorporated herein by reference.

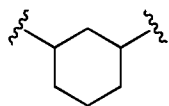
**[0059]** Exemplary oxygen atom substituents include, but are not limited to,  $-\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$ ,  $-\text{C}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{CO}_2\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{S}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{Si}(\text{R}^{\text{aa}})_3$ ,  $-\text{P}(\text{R}^{\text{cc}})_2$ ,  $-\text{P}(\text{R}^{\text{cc}})_3$ ,  $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$ ,  $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$ , and  $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$ , wherein  $\text{R}^{\text{aa}}$ ,  $\text{R}^{\text{bb}}$ , and  $\text{R}^{\text{cc}}$  are as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). 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, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, methyl, *t*-butyloxycarbonyl (BOC or Boc), 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 (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 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,  $\alpha$ -naphthylmethyl, *p*-methoxyphenyldiphenylmethyl, 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(benzoyloxyphenyl)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-dioxido, 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, monosuccinoate, (*E*)-2-methyl-2-butenolate, *o*-(methoxyacyl)benzoate,  $\alpha$ -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts). In certain embodiments, an oxygen protecting group is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

**[0060]** 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,  $-R^{aa}$ ,  $-N(R^{bb})_2$ ,  $-C(=O)SR^{aa}$ ,  $-C(=O)R^{aa}$ ,  $-CO_2R^{aa}$ ,

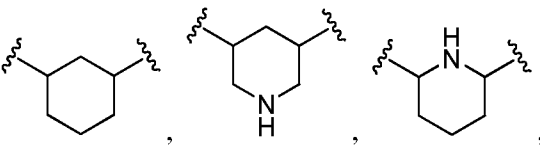
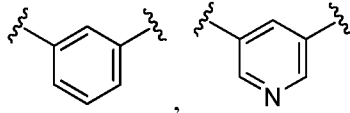
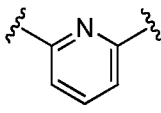
$-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$ ,  $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$ ,  $-\text{S}(=\text{O})\text{R}^{\text{aa}}$ ,  $-\text{SO}_2\text{R}^{\text{aa}}$ ,  $-\text{Si}(\text{R}^{\text{aa}})_3$ ,  $-\text{P}(\text{R}^{\text{cc}})_2$ ,  $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(\text{OR}^{\text{cc}})_2$ ,  $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$ ,  $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$ ,  $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$ , and  $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$ , wherein  $\text{R}^{\text{aa}}$ ,  $\text{R}^{\text{bb}}$ , and  $\text{R}^{\text{cc}}$  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, incorporated herein by reference. In certain embodiments, a sulfur protecting group is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl.

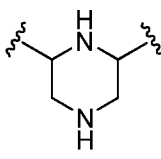
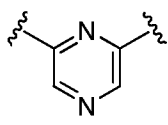
**[0061]** A “hydrocarbon chain” refers to a substituted or unsubstituted divalent alkyl, alkenyl, or alkynyl group. A hydrocarbon chain includes (1) one or more chains of carbon atoms immediately between the two radicals of the hydrocarbon chain; (2) optionally one or more hydrogen atoms on the chain(s) of carbon atoms; and (3) optionally one or more substituents (“non-chain substituents,” which are not hydrogen) on the chain(s) of carbon atoms. A chain of carbon atoms consists of consecutively connected carbon atoms (“chain atoms” or “carbon units”) and does not include hydrogen atoms or heteroatoms. However, a non-chain substituent of a hydrocarbon chain may include any atoms, including hydrogen atoms, carbon atoms, and heteroatoms. For example, hydrocarbon chain  $-\text{C}^{\text{A}}\text{H}(\text{C}^{\text{B}}\text{H}_2\text{C}^{\text{C}}\text{H}_3)-$  includes one chain atom  $\text{C}^{\text{A}}$ , one hydrogen atom on  $\text{C}^{\text{A}}$ , and non-chain substituent  $-(\text{C}^{\text{B}}\text{H}_2\text{C}^{\text{C}}\text{H}_3)$ . The term “ $\text{C}_x$  hydrocarbon chain,” wherein  $x$  is a positive integer, refers to a hydrocarbon chain that includes  $x$  number of chain atom(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,  $-\text{CH}(\text{C}_2\text{H}_5)-$  is a  $\text{C}_1$

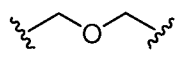


hydrocarbon chain, and is a  $\text{C}_3$  hydrocarbon chain. When a range of values is used, the meaning of the range is as described herein. For example, a  $\text{C}_{3-10}$  hydrocarbon chain refers to a hydrocarbon chain where the number of chain atoms of the shortest chain of carbon atoms immediately between the two radicals of the hydrocarbon chain is 3, 4, 5, 6, 7, 8, 9, or 10. A hydrocarbon chain may be saturated (*e.g.*,  $-(\text{CH}_2)_4-$ ). A hydrocarbon chain may also be unsaturated and include one or more  $\text{C}=\text{C}$  and/or  $\text{C}\equiv\text{C}$  bonds anywhere in the hydrocarbon chain. For instance,  $-\text{CH}=\text{CH}-(\text{CH}_2)_2-$ ,  $-\text{CH}_2-\text{C}\equiv\text{C}-\text{CH}_2-$ , and  $-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-$  are all examples of a unsubstituted and unsaturated hydrocarbon chain. In certain embodiments, the hydrocarbon chain is unsubstituted (*e.g.*,  $-\text{C}\equiv\text{C}-$  or  $-(\text{CH}_2)_4-$ ). In certain embodiments, the hydrocarbon chain is substituted (*e.g.*,  $-\text{CH}(\text{C}_2\text{H}_5)-$  and  $-\text{CF}_2-$ ). Any two substituents on the hydrocarbon chain may be joined to form a substituted or unsubstituted carbocyclyl,

substituted or unsubstituted heterocyclcyl, substituted or unsubstituted aryl, or substituted or

unsubstituted heteroaryl ring. For instance, , , 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. When a chain atom of a C<sub>x</sub> hydrocarbon chain is replaced with a heteroatom, the resulting group is referred to as a C<sub>x</sub> hydrocarbon chain wherein a chain atom is replaced with a heteroatom, as opposed to a C<sub>x-1</sub> hydrocarbon chain.

For example,  is a C<sub>3</sub> hydrocarbon chain wherein one chain atom is replaced with an oxygen atom.

**[0062]** The term “leaving group” is given its ordinary meaning in the art of synthetic organic chemistry and refers to an atom or a group capable of being displaced by a nucleophile. Examples of suitable leaving groups include, but are not limited to, halogen (such as F, Cl, Br, or I (iodine)), alkoxycarbonyloxy, 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), -OS(=O)<sub>2</sub>(CF<sub>2</sub>)<sub>3</sub>CF<sub>3</sub> (nonaflate, -ONf), 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. 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. Further 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<sup>aa</sup>, -OC(=O)R<sup>aa</sup>, -OCO<sub>2</sub>R<sup>aa</sup>, -OC(=O)N(R<sup>bb</sup>)<sub>2</sub>, -OC(=NR<sup>bb</sup>)R<sup>aa</sup>, -OC(=NR<sup>bb</sup>)OR<sup>aa</sup>, -OC(=NR<sup>bb</sup>)N(R<sup>bb</sup>)<sub>2</sub>, -OS(=O)R<sup>aa</sup>, -OSO<sub>2</sub>R<sup>aa</sup>, -OP(R<sup>cc</sup>)<sub>2</sub>, -OP(R<sup>cc</sup>)<sub>3</sub>, -OP(=O)<sub>2</sub>R<sup>aa</sup>, -OP(=O)(R<sup>aa</sup>)<sub>2</sub>, -

$\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$ ,  $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$ , and  $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$ , wherein  $\text{R}^{\text{aa}}$ ,  $\text{R}^{\text{bb}}$ , and  $\text{R}^{\text{cc}}$  are as defined herein).

#### *Other definitions*

**[0063]** 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, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein 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  $\text{N}^+(\text{C}_{1-4} \text{ alkyl})_4^-$  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.

**[0064]** 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 described herein 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 isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

**[0065]** 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  $R \cdot x H_2O$ , wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrate, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ( $R \cdot 0.5 H_2O$ )), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ( $R \cdot 2 H_2O$ ) and hexahydrates ( $R \cdot 6 H_2O$ )).

**[0066]** The term "tautomers" or "tautomeric" refers to two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a single bond, or *vice versa*). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may be catalyzed by acid or base. Exemplary tautomerizations include keto-to-enol, amide-to-imide, lactam-to-lactim, enamine-to-imine, and enamine-to-(a different enamine) tautomerizations.

**[0067]** 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".

**[0068]** 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”.

**[0069]** 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.

**[0070]** The term “co-crystal” refers to a crystalline structure composed of at least two components. In certain embodiments, a co-crystal may contain a compound of the present invention and one or more other component, including but not limited to, atoms, ions, molecules, or solvent molecules. In certain embodiments, a co-crystal may contain a compound of the present invention and one or more components related to said compound, including not limited to, an isomer, tautomer, salt, solvate, hydrate, synthetic precursor, synthetic derivative, fragment or impurity of said compound.

**[0071]** The term “isotopically labeled derivative” or “isotopically labeled” refers to a compound wherein one or more atoms in the compound (or in an associated ion or molecule of a salt, hydrate, or solvate) has been replaced with an isotope of the same element. For the given element or position in the molecule the isotope will be enriched, or present in a higher percentage of all atoms of the element or of all atoms at the position in the molecule in a sample, relative to an unlabeled variant. In certain embodiments, the enriched isotope will be a stable isotope. In certain embodiments, the enriched isotope will be an unstable or radioactive isotope (*e.g.*, a radionuclide). In certain embodiments, the enriched isotope may be detected by a measurement technique, including but not limited to nuclear magnetic resonance, mass spectrometry, infrared spectroscopy, or a technique that measures radioactive decay.

**[0072]** The term “prodrugs” refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds described herein have activity in both their acid and acid derivative forms, but in the acid sensitive form often offer 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 described herein 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>-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 described herein may be preferred.

**[0073]** The term “inhibition”, “inhibiting”, “inhibit,” or “inhibitor” refer to the ability of a compound to reduce, slow, halt or prevent activity of a particular biological process (*e.g.*, activity of a bromodomain and/or a bromodomain-containing protein) in a cell relative to vehicle.

**[0074]** When a compound, pharmaceutical composition, method, use, or kit is referred to as “selectively,” “specifically,” or “competitively” binding a first protein or a first chromatin, the compound, pharmaceutical composition, method, use, or kit binds the first protein or the first chromatin with a higher binding affinity (*e.g.*, not less than about 2-fold, not less than about 5-fold, not less than about 10-fold, not less than about 30-fold, not less than about 100-fold, not less than about 1,000-fold, or not less than about 10,000-fold) than binding a second protein or second chromatin that is different from the first protein and the first chromatin.

When a compound, pharmaceutical composition, method, use, or kit is referred to as “selectively,” “specifically,” or “competitively” modulating (*e.g.*, increasing or inhibiting) the activity of a bromodomain-containing protein, the compound, pharmaceutical composition, method, use, or kit modulates the activity of the bromodomain-containing protein to a greater extent (*e.g.*, not less than about 2-fold, not less than about 5-fold, not less than about 10-fold, not less than about 30-fold, not less than about 100-fold, not less than about 1,000-fold, or not less than about 10,000-fold) than the activity of at least one protein that is different from the bromodomain-containing protein.

**[0075]** The term “aberrant activity” refers to activity deviating from normal activity, that is, abnormal activity. The term “increased activity” refers to activity higher than normal activity.

**[0076]** The terms “composition” and “formulation” are used interchangeably.

**[0077]** A “subject” to which administration is contemplated refers to a human (*i.e.*, male or female of any age group, *e.g.*, pediatric subject (*e.g.*, infant, child, or adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) or non-human animal. In certain embodiments, the non-human animal is a mammal (*e.g.*, primate (*e.g.*, cynomolgus monkey or rhesus monkey), commercially relevant mammal (*e.g.*, cattle, pig, horse, sheep, goat, cat, or dog), or bird (*e.g.*, commercially relevant bird, such as chicken, duck, goose, or turkey)). In certain embodiments, the non-human animal is a fish, reptile, or amphibian. The non-human animal may be a male or female at any stage of development. The non-human animal may be a transgenic animal or genetically engineered animal. A “patient” refers to a human subject in need of treatment of a disease.

**[0078]** 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, mucous, 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 another biological sample.

**[0079]** The terms “administer,” “administering,” or “administration” refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, into, in, or on a subject.

**[0080]** The terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease described herein. In some embodiments, treatment may be administered after one or more signs or symptoms of the disease have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease. For example, treatment may be administered to a susceptible subject prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a pathogen). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

**[0081]** The terms “condition,” “disease,” and “disorder” are used interchangeably.

**[0082]** An “effective amount” of a compound described herein 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 described herein 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. In certain embodiments, an effective amount is a therapeutically effective amount. In certain embodiments, an effective amount is a prophylactic treatment. In certain embodiments, an effective amount is the amount of a compound described herein in a single dose. In certain embodiments, an effective amount is the combined amounts of a compound described herein in multiple doses.

**[0083]** A “therapeutically effective amount” of a compound described herein 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, signs, or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent.

**[0084]** A “prophylactically effective amount” of a compound described herein 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.

**[0085]** 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, diseases associated with angiogenesis, inflammatory diseases, and autoimmune diseases.

**[0086]** The term “angiogenesis” refers to the physiological process through which new blood vessels form from pre-existing vessels. Angiogenesis is distinct from vasculogenesis, which is the *de novo* formation of endothelial cells from mesoderm cell precursors. The first vessels in a developing embryo form through vasculogenesis, after which angiogenesis is responsible for most blood vessel growth during normal or abnormal development. Angiogenesis is a vital process in growth and development, as well as in wound healing and in the formation of granulation tissue. However, angiogenesis is also a fundamental step in the transition of tumors from a benign state to a malignant one, leading to the use of angiogenesis inhibitors in the treatment of cancer. Angiogenesis may be chemically stimulated by angiogenic proteins, such as growth factors (*e.g.*, VEGF). “Pathological angiogenesis” refers to abnormal (*e.g.*, excessive or insufficient) angiogenesis that amounts to and/or is associated with a disease.

**[0087]** The terms “neoplasm” and “tumor” are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated as in the growth of 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. 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.

**[0088]** The term “cancer” refers to a class of diseases characterized by the development of abnormal cells that proliferate uncontrollably and have the ability to infiltrate and destroy normal body tissues. See, *e.g.*, *Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990. Exemplary cancers include, but are not limited to, hematological malignancies. Additional exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast, triple negative breast cancer (TNBC)); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi’s sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett’s adenocarcinoma); Ewing’s sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familial 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)); heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms’ tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic

leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovioma; testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma); thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer); urethral cancer; vaginal cancer; and vulvar cancer (*e.g.*, Paget's disease of the vulva).

**[0089]** The term "hematological malignancy" refers to tumors that affect blood, bone marrow, and/or lymph nodes. Exemplary hematological malignancies include, but are not limited to, leukemia, such as acute lymphoblastic 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 (DLBCL, *e.g.*, activated B-cell (ABC) DLBCL (ABC-DLBCL))), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphoma (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphoma, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt's lymphoma, Waldenström's macroglobulinemia (WM, lymphoplasmacytic lymphoma), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, central nervous system (CNS) lymphoma (*e.g.*, primary CNS lymphoma and secondary 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); lymphoma of an immune privileged site (*e.g.*, cerebral lymphoma, ocular lymphoma, lymphoma of the placenta, lymphoma of the fetus, testicular lymphoma); a mixture of one or more leukemia/lymphoma as described above; myelodysplasia; and multiple myeloma (MM).

**[0090]** The term “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, hay fever, 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.

**[0091]** 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 disease, Guillain-Barré syndrome, Hashimoto’s thyroiditis, and cardiomyopathy.

**[0092]** The term “kinase” is a type of enzyme that transfers phosphate groups from high energy donor molecules, such as ATP, to specific substrates, referred to as phosphorylation. Kinases are part of the larger family of phosphotransferases. Kinases are used extensively to transmit signals and control complex processes in cells. Various other kinases act on small molecules such as lipids, carbohydrates, amino acids, and nucleotides, either for signaling or to prime them for metabolic pathways. Kinases are often named after their substrates. More than 500 different protein kinases have been identified in humans. In some embodiments, the kinase is a protein kinase. A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them (phosphorylation). In some embodiments, the protein kinase is Cyclin dependent kinases (CDKs). CDKs are a group of several different kinases involved in regulation of the cell cycle. They phosphorylate other proteins on their serine or threonine residues, but CDKs must first bind to a cyclin protein in order to be

active. In some embodiments, the protein kinase is mitogen-activated protein kinases (MAPKs). MAP kinases (MAPKs) are a family of serine/threonine kinases that respond to a variety of extracellular growth signals. In some embodiments, the kinase is a lipid kinases that phosphorylate lipids in the cell, both on the plasma membrane as well as on the membranes of the organelles. The addition of phosphate groups can change the reactivity and localization of the lipid and can be used in signal transmission. In some embodiments, the lipid kinase is a phosphatidylinositol kinase that phosphorylates phosphatidylinositol species, to create species such as phosphatidylinositol 3,4-bisphosphate (PI(3,4)P<sub>2</sub>), phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>), and phosphatidylinositol 3-phosphate (PI3P). In some embodiments, the lipid kinase is sphingosine kinase (SK), a lipid kinase that catalyzes the conversion of sphingosine to sphingosine-1-phosphate (S1P). In certain embodiments, the SK is SK1 or SK2. Exemplary human protein kinases include, but are not limited to, AAK1, ABL, ACK, ACTR2, ACTR2B, AKT1, AKT2, AKT3, ALK, ALK1, ALK2, ALK4, ALK7, AMPKa1, AMPKa2, ANKRD3, ANPa, ANPb, ARAF, ARAFps, ARG, AurA, AurAps1, AurAps2, AurB, AurBps1, AurC, AXL, BARK1, BARK2, BIKE, BLK, BMPR1A, BMPR1Aps1, BMPR1Aps2, BMPR1B, BMPR2, BMX, BRAF, BRAFps, BRK, BRSK1, BRSK2, BTK, BUB1, BUBR1, CaMK1a, CaMK1b, CaMK1d, CaMK1g, CaMK2a, CaMK2b, CaMK2d, CaMK2g, CaMK4, CaMKK1, CaMKK2, caMLCK, CASK, CCK4, CCRK, CDC2, CDC7, CDK10, CDK11, CDK2, CDK3, CDK4, CDK4ps, CDK5, CDK5ps, CDK6, CDK7, CDK7ps, CDK8, CDK8ps, CDK9, CDKL1, CDKL2, CDKL3, CDKL4, CDKL5, CGDps, CHED, CHK1, CHK2, CHK2ps1, CHK2ps2, CK1a, CK1a2, CK1aps1, CK1aps2, CK1aps3, CK1d, CK1e, CK1g1, CK1g2, CK1g2ps, CK1g3, CK2a1, CK2a1-rs, CK2a2, CLIK1, CLIK1L, CLK1, CLK2, CLK2ps, CLK3, CLK3ps, CLK4, COT, CRIK, CRK7, CSK, CTK, CYGD, CYGF, DAPK1, DAPK2, DAPK3, DCAMKL1, DCAMKL2, DCAMKL3, DDR1, DDR2, DLK, DMPK1, DMPK2, DRAK1, DRAK2, DYRK1A, DYRK1B, DYRK2, DYRK3, DYRK4, EGFR, EphA1, EphA10, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB6, Erk1, Erk2, Erk3, Erk3ps1, Erk3ps2, Erk3ps3, Erk3ps4, Erk4, Erk5, Erk7, FAK, FER, FERps, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT1ps, FLT3, FLT4, FMS, FRK, Fused, FYN, GAK, GCK, GCN2, GCN22, GPRK4, GPRK5, GPRK6, GPRK6ps, GPRK7, GSK3A, GSK3B, Haspin, HCK, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4, HH498, HIPK1, HIPK2, HIPK3, HIPK4, HPK1, HRI, HRIps, HSER, HUNK, ICK, IGF1R, IKKa, IKKb, IKKe, ILK, INSR, IRAK1, IRAK2, IRAK3, IRAK4, IRE1, IRE2, IRR, ITK, JAK1, JAK2, JAK3, JNK1, JNK2, JNK3, KDR, KHS1, KHS2, KIS, KIT, KSGCps, KSR1, KSR2, LATS1, LATS2,

LCK, LIMK1, LIMK2, LIMK2ps, LKB1, LMR1, LMR2, LMR3, LOK, LRRK1, LRRK2,  
 LTK, LYN, LZK, MAK, MAP2K1, MAP2K1ps, MAP2K2, MAP2K2ps, MAP2K3,  
 MAP2K4, MAP2K5, MAP2K6, MAP2K7, MAP3K1, MAP3K2, MAP3K3, MAP3K4,  
 MAP3K5, MAP3K6, MAP3K7, MAP3K8, MAPKAPK2, MAPKAPK3, MAPKAPK5,  
 MAPKAPKps1, MARK1, MARK2, MARK3, MARK4, MARKps01, MARKps02,  
 MARKps03, MARKps04, MARKps05, MARKps07, MARKps08, MARKps09, MARKps10,  
 MARKps11, MARKps12, MARKps13, MARKps15, MARKps16, MARKps17, MARKps18,  
 MARKps19, MARKps20, MARKps21, MARKps22, MARKps23, MARKps24, MARKps25,  
 MARKps26, MARKps27, MARKps28, MARKps29, MARKps30, MAST1, MAST2,  
 MAST3, MAST4, MASTL, MELK, MER, MET, MISR2, MLK1, MLK2, MLK3, MLK4,  
 MLKL, MNK1, MNK1ps, MNK2, MOK, MOS, MPSK1, MPSK1ps, MRCKa, MRCKb,  
 MRCKps, MSK1, MSK12, MSK2, MSK22, MSSK1, MST1, MST2, MST3, MST3ps,  
 MST4, MUSK, MYO3A, MYO3B, MYT1, NDR1, NDR2, NEK1, NEK10, NEK11, NEK2,  
 NEK2ps1, NEK2ps2, NEK2ps3, NEK3, NEK4, NEK4ps, NEK5, NEK6, NEK7, NEK8,  
 NEK9, NIK, NIM1, NLK, NRBP1, NRBP2, NuaK1, NuaK2, Obscn, Obscn2, OSR1, p38a,  
 p38b, p38d, p38g, p70S6K, p70S6Kb, p70S6Kps1, p70S6Kps2, PAK1, PAK2, PAK2ps,  
 PAK3, PAK4, PAK5, PAK6, PASK, PBK, PCTAIRE1, PCTAIRE2, PCTAIRE3, PDGFRa,  
 PDGFRb, PDK1, PEK, PFTAIRE1, PFTAIRE2, PHKg1, PHKg1ps1, PHKg1ps2,  
 PHKg1ps3, PHKg2, PIK3R4, PIM1, PIM2, PIM3, PINK1, PIP4K2A, PIP4K2B, PIPK□,  
 PITSLRE, PKACa, PKACb, PKACg, PKCa, PKCb, PKCd, PKCe, PKCg, PKCh, PKCi,  
 PKCips, PKCt, PKCz, PKD1, PKD2, PKD3, PKG1, PKG2, PKN1, PKN2, PKN3, PKR,  
 PLK1, PLK1ps1, PLK1ps2, PLK2, PLK3, PLK4, PRKX, PRKXps, PRKY, PRP4, PRP4ps,  
 PRPK, PSKH1, PSKH1ps, PSKH2, PYK2, QIK, QSK, RAF1, RAF1ps, RET, RHOK,  
 RIPK1, RIPK2, RIPK3, RNaseL, ROCK1, ROCK2, RON, ROR1, ROR2, ROS, RSK1,  
 RSK12, RSK2, RSK22, RSK3, RSK32, RSK4, RSK42, RSKL1, RSKL2, RYK, RYKps,  
 SAKps, SBK, SCYL1, SCYL2, SCYL2ps, SCYL3, SGK, SgK050ps, SgK069, SgK071,  
 SgK085, SgK110, SgK196, SGK2, SgK223, SgK269, SgK288, SGK3, SgK307, SgK384ps,  
 SgK396, SgK424, SgK493, SgK494, SgK495, SgK496, SIK(*e.g.*, SIK1, SIK2), skMLCK,  
 SLK, Slob, smMLCK, SNRK, SPEG, SPEG2, SRC, SRM, SRPK1, SRPK2, SRPK2ps,  
 SSTK, STK33, STK33ps, STLK3, STLK5, STLK6, STLK6ps1, STLK6-rs, SuRTK106,  
 SYK, TAK1, TAO1, TAO2, TAO3, TBCK, TBK1, TEC, TESK1, TESK2, TGFbR1,  
 TGFbR2, TIE1, TIE2, TLK1, TLK1ps, TLK2, TLK2ps1, TLK2ps2, TNK1, Trad, Trb1,  
 Trb2, Trb3, Trio, TRKA, TRKB, TRKC, TSSK1, TSSK2, TSSK3, TSSK4, TSSKps1,  
 TSSKps2, TTBK1, TTBK2, TTK, TTN, TXK, TYK2, TYK22, TYRO3, TYRO3ps, ULK1,

ULK2, ULK3, ULK4, VACAMKL, VRK1, VRK2, VRK3, VRK3ps, Wee1, Wee1B, Wee1Bps, Wee1ps1, Wee1ps2, Wnk1, Wnk2, Wnk3, Wnk4, YANK1, YANK2, YANK3, YES, YESps, YSK1, ZAK, ZAP70, ZC1/HGK, ZC2/TNIK, ZC3/MINK, and ZC4/NRK.

**[0093]** 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, CDK3, CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, CDK11, CDK12, CDK13, CDK14, CDK15, CDK16, CDK17, CDK18, CDK19 and CDK20.

**[0094]** 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, incorporated herein by reference. The amino acid sequence of this CDK7 is as follows:

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MALDVKSRAKRYEKLDFLGEGQFATVYKARDKNTNQIVAIKKIKLGHRSKADGINRTAL
REIKLLQELSHPNIIIGLLDAFGHKSNI SLVFD FMETDLEVI IKDNSLVLT PSHIKAYMLM
TLQGLEYLHQHWILHRDLKPNNLLLDENGVLKLADFG LAKSFGSPN RAYTHQVVTRWYRA
PELLFGARMYGVGVDMWAVGCILAELLLRV PFLPGDSDLDQLTRIFETLGTPT EEQWPDM
CSLPDYVTFKSFPFIPLHHIFSAAGD DLDLIQGLFLFNPCARITATQAL KMKYFSNRPG
PTPGCQLPRPNCPVETLKEQSNPALAIKRKRTEALEQGG LPKKLIF
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**[0095]** 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, which is incorporated herein by reference. The amino acid sequence of this CDK12 is as follows:

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MPNSERHGGKKDGGSGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSDMGLVTPEA
ASLGTVIKPLVEYDDISSDSTFSDDMAFKLDRRENDERRGSDRSDDLHKHRRHHQHRRSR
DLLKAKQTEKEKSQEVSSKSGSMKDRISSGSKRSNEETDDYGKAQVAKSSSKESRSSKLH
KEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSRSPHRKWSDDSKQDDSPSGA
SYGQDYDLSPSRSHSTSSNYDSYKKSPGSTSRRQSVSPPYKEPSAYQSSTRSPSPYSRRQR
SVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSPFLSKRSLRSPLPSRKSMKSRSRSP
AYSRHSSSHSKKKRSSSRHSSI SPVRLPLNSSLGAELSRKKKRAAAAAAAKMDGKES
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KGSPVFLPRKENS SVEAKDSGLSESKKLPRSVKLEKSAPDTELNVNTHLNTTEVKNSSDTGK  
 VKLDENSEKHLVKDLKAQGTRDSKPIALKEEIVTPKETETSEKETPPPLPTIASPPPLP  
 TTTPPPQTPLPLPLPIPALPQQPPLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQAN  
 SQPPVQVSVKTQVSVTAAIPLHKTSTLPLPLPLPLPGDDMDSPKETLPSKPVKKEKEQ  
 RTRHLLTDLPLPELPGGDLSPDPSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWG  
 KRCVDKFDIIGIIGEGTYGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIKILRQ  
 LIHRSVNMKEIVTDKQDALDFKKDKGAFYLVFEYMDHDLMLGLESGLVHFSEDHIKSFM  
 KQLMEGLEYCHKKNF LHRDIKCSNILLNNSGQIKLADFG LARLYNSEESRPYTNKVITLW  
 YRPPELLLGEERYTPAIDVWSCGCILGELFTTKPIFQANLELAQLELISRLCGSPCPAVW  
 PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLDHMLTLDP SKRCTAEQTLQSDFL  
 KDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETTSGTSTEPVK  
 NSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQTDL SIPQMAQLLNI  
 HSNPEMQQLEALNQSISALTEATSQQQDSE TMAPEESLKEAPSAPVILPSAEQTTLEAS  
 STPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQGPRRTPTMPQEEAACPPHIL  
 PPEKRPPEPPGPPPPPPPPPLVEGDLSSAPQELNPAVTAALLQLLSQPEAEPPGHLPEH  
 QALRPMEYSTRPRPNRTYNTDGPETGFS AIDTDERN SGPALTESLVQTLVKNRTFSGSL  
 SHLGESSYQGTGSVQFPGDQDLRFARVPLALHPVVGQPFLKAEGSSNSVVAETKLQNY  
 GELGPGTTGASSSGAGLHWGGPTQSSAYGKLYRGPTRVPPRGGRGGRGPVY

**[0096]** 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, which is incorporated herein by reference. The amino acid sequence of this CDK13 is as follows:

MPSSSDTALGGGGGLSWAEKKLEERRKRRRFLSPQQPPLLLPLLPQLLPQPPPPPPPLLF  
 LAAPGTAAAAAASSSCFSPGPPLEVKRLARGKRRAGGRQKRRRGPRAGQEA EKRRV  
 FSLPQPQQDGGGGASSGGGVTPLEVEDVSSQSEQGLLLGGASAATAATAAGGTGGSGGS  
 PASSSGTQRRGEGSERRPRRRSSSGRSKERHREHRRRDGQRGGSEASKSRSRHSHSGE  
 ERAEVAKSGSSSSSGRRKSASATSSSSSRKDRDSKAHRSRTKSSKEPPSAYKEPPKAY  
 REDKTEPKAYRRRRSLSP LGGRDDSPVSHRASQSLRSRKSPSPAGGGSSPYSRRLPRSPS  
 PYSRRRSPSYSRHSSYERGGDVSPSPYSSSSWRRSRSPYSPVLRSGKSRSRSPYSSRHS  
 RSRSRHRLSRSRHSSI PSTLT LKSSLAAELNKNKKARAAEAARAAEA AKA AEATKAA  
 EAAAKAAKASNTSTPTKGN TETSASASQTNHV KDVKKIKIEHAPSPSSGGTLKNDKAKTK  
 PPLQVT KVENNLIVDKATK KAVIVGKESKAATKEESVSLKEKTKPLTPSIGAKEKEQH V  
 ALVTSTLPLPLPLPMLPEDKEADSLRGNISVKAVKKEVEKKLRCLLADLPLPELPGGDD  
 LSKSPEEKKTATQLHSKRRPKICGPRYGETKEKDIDWGKRCVDKFDIIGIIGEGTYGQVY  
 KARDKDTGEMVALKKVRLDNEKEGFPITAIKILRQLTHQSIINMKEIVTDKEDALDF  
 KKDKGAFYLVFEYMDHDLMLGLESGLVHFNENHIKSFM RQLMEGLDYCHKKNF LHRDIK

SNILLNNRGQIKLADFGFLARLYSSEESRPYTNKVITLWYRPELLLGEERYTPAIDVWSC  
 GCILGELFTKKPIFQANQELAQLELISRICGSPCAVWPDVIKLPYFNTMKPKKQYRRKL  
 REEFVFIPAAALDLFDYMLALDPSKRCTAEQALQCEFLRDVEPSKMPPDLPLWQDCHEL  
 WSKRRRRQKQMGMTDDVSTIKAPRKDLGLGLDDSRNTNPQGVLPSSQLKSQGSNNVAPVK  
 TGPGQHLNHSELAILLNLLQSKTSVNMAADFVQVLNIKVNSETQQQLNKINLPAGILATGE  
 KQTDPTPQQESSKPLGGIQPSSQTIQPKVETDAAQAAVQSAFAVLLTQLIKAQQSKQKD  
 VLLEERENGSGHEASLQLRPPPEPSTPVSGQDDLIQHQDMRILELTPEPDRPRILPPDQR  
 PPEPPEPPPVTEEDLDYRTENQHVPPTSSSLTDPHAGVKAALLQLLAQHQPQDDPKREGG  
 IDYQAGDTYVSTSDYKDNFGSSSFSSAPYVSNLGLGSSAPPLERRSFIGNSDIQSLDNY  
 STASSHSGGPPQPSAFSESFSSVAGYGDYILNAGPMLFSGDKDHRFEYSHGPIAVLANS  
 SDPSTGPSTHPLPAKMHNNYGGNLQENPSGPSLMHGQTWTSPAQGPQGYRGHIST  
 STGRGRGRGLPY

**[0097]** The term “PIP kinases”, also known as “PIPKs,” refers to phosphatidylinositol phosphate kinases or phosphatidylinositol-5-phosphate 4-kinases, a class of enzymes that catalyzes the chemical reaction:  $\text{ATP} + 1\text{-phosphatidyl-1D-myo-inositol 4-phosphate} \rightleftharpoons \text{ADP} + 1\text{-phosphatidyl-1D-myo-inositol 4,5-bisphosphate}$ . PIP kinases are divided into two classes, type I and type II. The type I and type II PIP kinases are 35% identical at the kinase domain. Their sequences are significantly divergent for a stretch of about 25 amino acids in the region of the kinase domain that corresponds to the activation loop of protein kinases. There are three isoforms of type II PIP4-kinase in mammalian cells, namely  $\alpha$  (PIP4K2A),  $\beta$  (PIP4K2B), and  $\gamma$  (PIP4K2C) isoforms (Liu *et al.*, Nat. Rev. Drug. Discov., 2009, 8(8): 627-644). At the protein level, the  $\alpha$  and  $\beta$  isoforms are 83% identical and the  $\gamma$  isoform is about 60% identical to either one of them. All isoforms are ubiquitously expressed, but the  $\alpha$  isoform is found predominantly in brain and platelets, the  $\beta$  isoform in brain and muscle, and the  $\gamma$  isoform in brain and kidney. Although the type II PIP4-kinase isoforms are ubiquitously expressed, changes in protein levels may play a role in the regulation of their cellular function. The type II PIP4-kinase  $\beta$  isoform gene, which localizes to the chromosome 17q11-12, was found to be amplified in primary breast cancer samples with Heregulin 2 gene amplifications and in a subset of breast cancer cell lines. These gene amplifications resulted in increased protein expression, which correlated with increased breast cancer cell proliferation and anchorage-independent growth (Emerling *et al.*, Cell, 2013, 155(4): 844-857). In certain embodiments, the PIPK is PI5P4K $\alpha$  (*i.e.* PIP4K2A enzyme) encoded by PIP4K2A gene. In certain embodiments, the PIPK is PI5P4K $\beta$  (*i.e.* PIP4K2B enzyme) encoded by PIP4K2B gene. In certain embodiments, the PIPK is PI5P4K $\gamma$  (*i.e.* PIP4K2C enzyme) encoded by PIP4K2C gene. As used herein, type II PIP4Ks enzymes are referred as

follows: PI5P4K is interchangeable with PIP4K; PI5P4K $\alpha$  is interchangeable with PIP4K $\alpha$ , PIP4K2A, PIP4K2A enzyme, and PIP4K2A protein; PI5P4K $\beta$  is interchangeable with PIP4K $\beta$ , PIP4K2B, PIP4K2B enzyme, and PIP4K2B protein; PI5P4K $\gamma$  is interchangeable with PIP4K $\gamma$ , PIP4K2C, PIP4K2C enzyme, and PIP4K2C protein.

**[0098]** In certain embodiments, the PIP4K2A enzyme is splP48426|PI42A\_HUMAN Phosphatidylinositol 5-phosphate 4-kinase type-2 alpha (OS=Homo sapiens, GN=PIP4K2A, PE=1, and SV=2) and of the following sequence:

MATPGNLGSSVLASKTKTKKKHFVAQKVKLFRASDPLL SVLMWGVNHSINELSHVQIPVML  
MPDDFKAYSKI KVDNHLFNKENMPSHFKFKEYCPMVFRNLRRERFGIDDQDFQNSLTRSAPL  
PNDSQARSGARFHTSYDKRYIIKTITSEDVAEMHNILKKYHQYIVECHGITLLPQFLGMYRLN  
VDGVEIYVIVTRNVFSHRLSVYRKYDLKGSTVAREASDKEKAKELPTLKDNDFINEGQKIYID  
DNNKKVFLEKLKLDVEFLAQLKLM DYSLLVGIHDVERAEQEVECEENDGEEEGESDGTHP  
VGTPPDSPGNTLNSSPPLAPGEFDPNIDVYGIKCHENS PRKEVYFMAIIDILTHYDAKKKAAH  
AAKTVKHGAGAEISTVNPEQYSKRFLDFIGHILT

**[0099]** In certain embodiments, the PIP4K2B enzyme is splP78356|PI42B\_HUMAN Phosphatidylinositol 5-phosphate 4-kinase type-2 beta (OS=Homo sapiens, GN=PIP4K2B, PE=1, and SV=1) and of the following sequence:

MSSNCTSTTAVAVAPLSASKTKTKKKHFVCQKVKLFRASEPILSVLMWGVNHTINELSNVPV  
PVMLMPDDFKAYSKI KVDNHLFNKENLPSRFKFKEYCPMVFRNLRRERFGIDDQDYQNSVTR  
SAPINSDSQGRGTRFLT TYDRRFVIKT VSSDVAEMHNILKKYHQFIVECHGNTLLPQFLG  
MYRLTVDGVETYMVVTRNVFSHRLTVHRKYDLKGSTVAREASDKEKAKDLPTFKDNDFLN  
EGQKLHVGEESKKNFLEKLKRDVEFLAQLKIMDYSLLVGIHDVDRAEQEEMEVEERADEE  
CENDGVGGNLLCSYGTTPD SPGNLLSFPRFFGPGFDP SVDVYAMKSHESPKEVYFMA  
IIDILTPYDTKKKAAHAAKTVKHGAGAEISTVNPEQYSKRFNEFMSNILT

**[00100]** In certain embodiments, the PIP4K2C enzyme is splQ8TBX8|PI42C\_HUMAN Phosphatidylinositol 5-phosphate 4-kinase type-2 gamma (OS=Homo sapiens, GN=PIP4K2C, PE=1, and SV=3) and of the following sequence:

MASSSVPPATVSAATAGPGPGFGFASKTKKKHFVQQKVVFRAADPLVGVFLWGVAHSIN  
ELSQVPPPVM LLPDDFKASSKIKVNNHLFHRENLP SHFKFKEYCPQVFRNL RDRFGIDDQD  
YLVSLTRNPPSESEGSDGRFLISYDRTLVIKEVSSEDIADMHSNLSNYHQYIVKCHGNTLLPQ  
FLGMYRVSDNEDSYMLVMRNMFSHRLPVHRKYDLKGSLSVSREADSDEKVKELPTLKDMD  
FLNKNQKVYIGEEEEKIFLEKLKRDVEFLVQLKIMDYSLLLGIHDIIRGSEPEEEAPVREDESE  
VDGDCSLTGPPALVGSYGTSP EGIGGYIHSRPLGPGEFESFIDVYAIRSAEGAPQKEVYFM  
GLIDILTQYDAKKKAAHAAKTVKHGAGAEISTVHPEQYAKRFLDFITNIFA

**[00101]** In certain embodiments, the PIP4K2A gene of Gene ID: 5305 and HGNC:8997 and has the cDNA sequence as follows:

ATGGCGACCCCCGGAACCTAGGGTCCTCTGTCCTGGCGAGCAAGACCAAGACCAAG  
AAGAAGCACTTCGTAGCGCAGAAAGTGAAGCTGTTTCGGGCCAGCGACCCGCTGCTCA  
GCGTCCTCATGTGGGGGGTAAACCACTCGATCAATGAACTGAGCCATGTTCAAATCCCT  
GTTATGTTGATGCCAGATGACTTCAAAGCCTATTCAAAAATAAAGGTGGACAATCACCTT  
TTTAACAAAGAAAACATGCCGAGCCATTTCAAGTTTAAGGAATACTGCCCGATGGTCTT  
CCGTAACTGCGGGAGAGGTTTGAATTGATGATCAAGATTTCCAGAATTCCCTGACCA  
GGAGCGCACCCCTCCCCAACGACTCCCAGGCCCGCAGTGGAGCTCGTTTTCACACTTC  
CTACGACAAAAGATACATCATCAAGACTATTACCAGTGAAGACGTGGCCGAAATGCACA  
ACATCCTGAAGAAATACCACCAGTACATAGTGGAATGTCATGGGATCACCTTCTTCCC  
CAGTTCTTGGGCATGTACCGGCTTAATGTTGATGGAGTTGAAATATATGTGATAGTTACA  
AGAAATGTATTCAGCCACCGTTTGTCTGTGTATAGGAAATACGACTTAAAGGGCTCTAC  
AGTGGCTAGAGAAGCTAGTGACAAAGAAAAGGCCAAAGAACTGCCAACTCTGAAAGAT  
AATGATTTCAATTAATGAGGGCCAAAAGATTTATATTGATGACAACAACAAGAAGGTCTTC  
CTGGAAAACTAAAAAAGGATGTTGAGTTTCTGGCCCAGCTGAAGCTCATGGACTACAG  
TCTGCTGGTGGGAATTCATGATGTGGAGAGAGCCGAACAGGAGGAAGTGGAGTGTGA  
GGAGAACGATGGGGAGGAGGAGGGCGAGAGCGATGGCACCCACCCGGTGGGAACCC  
CCCCAGATAGCCCCGGGAATACACTGAACAGCTCACCACCCCTGGCTCCCGGGGAGT  
TCGATCCGAACATCGACGTCTATGGAATTAAGTGCCATGAAAACCTCGCCTAGGAAGGA  
GGTGTACTTCATGGCAATTATTGACATCCTTACTCATTATGATGCAAAAAAGAAAGCTGC  
CCATGCTGCAAAAACCTGTTAAACATGGCGCTGGCGCGGAGATCTCCACCGTGAACCCA  
GAACAGTATTCAAAGCGCTTTTTGGACTTTATTGGCCACATCTTGACGTAA

**[00102]** In certain embodiments, the PIP4K2B gene of Gene ID: 8396 and HGNC:8998, and has the cDNA sequence as follows:

ATGTCGTCCAACCTGCACCAGCACCCACGGCGGTGGCGGTGGCGCCGCTCAGCGCCAGC  
AAGACCAAGACCAAGAAGAAGCATTTCGTGTGCCAGAAAGTGAAGCTATTCCGGGCCA  
GCGAGCCGATCCTCAGCGTCCTGATGTGGGGGGTGAACCACACGATCAATGAGCTGA  
GCAATGTTCTGTTCCTGTCATGCTAATGCCAGATGACTTCAAAGCCTACAGCAAGATC  
AAGGTGGACAATCATCTCTTCAATAAGGAGAACCTGCCAGCCGCTTTAAGTTTAAGGA  
GTATTGCCCCATGGTGTTCGAAACCTTCGGGAGAGGTTTGAATTGATGATCAGGATT  
ACCAGAATTCAGTGACGCGCAGCGCCCCCATCAACAGTGACAGCCAGGGTCCGGTGTG  
GCACGCGTTTCCTCACCACTACGACCGGCGCTTTGTCATCAAGACTGTGTCCAGCGA  
GGACGTGGCGGAGATGCACAACATCTTAAAGAAATACCACCAGTTTATAGTGGAGTGTG  
ATGGCAACACGCTTTTGCCACAGTTCCTGGGCATGTACCGCCTGACCGTGGATGGTGT

GGAAACCTACATGGTGGTTACCAGGAACGTGTTTACGCCATCGGCTCACTGTGCATCGC  
AAGTATGACCTCAAGGGTTCTACGGTTGCCAGAGAAGCGAGCGACAAGGAGAAGGCCA  
AGGACTTGCCAACATTCAAAGACAATGACTTCCTCAATGAAGGGCAGAAGCTGCATGTG  
GGAGAGGAGAGTAAAAAGAACTTCCTGGAGAACTGAAGCGGGACGTTGAGTTCTTGG  
CACAGCTGAAGATCATGGACTACAGCCTGCTGGTGGGCATCCACGACGTGGACCGGG  
CAGAGCAGGAGGAGATGGAGGTGGAGGAGCGGGCAGAGGACGAGGAGTGTGAGAAT  
GATGGGGTGGGTGGCAACCTACTCTGCTCCTATGGCACACCTCCGGACAGCCCTGGC  
AACCTCCTCAGCTTTCCTCGGTTCTTTGGTCCTGGGGAATTCGACCCCTCTGTTGACGT  
CTATGCCATGAAAAGCCATGAAAGTTCCCCAAGAAGGAGGTGTATTTTCATGGCCATCA  
TTGATATCCTCACGCCATACGATACAAAGAAGAAAGCTGCACATGCTGCCAAAACGGTG  
AAACACGGGGCAGGGGCCGAGATCTCGACTGTGAACCCTGAGCAGTACTCCAAACGC  
TTCAACGAGTTTATGTCCAACATCCTGACGTAG

**[00103]** In certain embodiments, the PIP4K2C gene of Gene ID: 79837 and HGNC:23786, and has the cDNA sequence as follows:

ATGGCGTCCTCCTCGGTCCCACCAGCCACGGTATCGGCGGCGACAGCAGGCCCCCGGC  
CCAGGTTTCGGCTTCGCCTCCAAGACCAAGAAGAAGCATTTCGTGCAGCAGAAGGTGA  
AGGTGTTCCGGGCGGCCGACCCGCTGGTGGGTGTGTTCTGTGGGGCGTAGCCCACT  
CGATCAATGAGCTCAGCCAGGTGCCTCCCCCGGTGATGCTGCTGCCAGATGACTTTAA  
GGCCAGCTCCAAGATCAAGGTCAACAATCACCTTTTCCACAGGGAAAATCTGCCCAGTC  
ATTTCAAGTTCAAGGAGTATTGTCCCCAGGTCTTCAGGAACCTCCGTGATCGATTTGGC  
ATTGATGACCAAGATTACTTGGTGTCCCTTACCCGAAACCCCCCAGCGAAAGTGAAG  
GCAGTGATGGTCGCTTCCTTATCTCCTACGATCGGACTCTGGTCATCAAAGAAGTATCC  
AGTGAGGACATTGCTGACATGCATAGCAACCTCTCCAATATCACCAGTACATTGTGAA  
GTGCCATGGCAACACGCTTCTGCCCCAGTTCTGGGGATGTACCGAGTCAGTGTGGAC  
AACGAAGACAGCTACATGCTTGTGATGCGCAATATGTTTAGCCACCGTCTTCCTGTGCA  
CAGGAAGTATGACCTCAAGGGTTCCCTAGTGTCCCGGGAAGCCAGCGATAAGGAAAAG  
GTTAAAGAATTGCCACCCCTTAAGGATATGGACTTTCTCAACAAGAACCAGAAAGTATAT  
ATTGGTGAAGAGGAGAAGAAAATATTTCTGGAGAAGCTGAAGAGAGATGTGGAGTTTCT  
AGTGCAGCTGAAGATCATGGACTACAGCCTTCTGCTAGGCATCCACGACATCATTCCG  
GGCTCTGAACCAGAGGAGGAAGCGCCCGTGCAGGAGGATGAGTCAGAGGTGGATGG  
GGACTGCAGCCTGACTGGACCTCCTGCTCTGGTGGGCTCCTATGGCACCTCCCCAGA  
GGGTATCGGAGGCTACATCCATTCCCATCGGCCCTGGGCCAGGAGAGTTTGAGTCC  
TTCATTGATGTCTATGCCATCCGGAGTGCTGAAGGAGCCCCCAGAAGGAGGTCTACT  
TCATGGGCCTCATTGATATCCTTACACAGTATGATGCTAAGAAGAAAGCAGCTCATGCA  
GCCAAAACGTCAAGCATGGGGCTGGGGCAGAGATCTCTACTGTCCATCCGGAGCAGT  
ATGCTAAGCGATTCTGGATTTTATTACCAACATCTTTGCCTAA

## BRIEF DESCRIPTION OF THE DRAWINGS

**[00104]** *Figure 1* shows that loss of PIP4K2 $\alpha/\beta$  restricts tumor death after p53 deletion. Kaplan-Meier plot analysis was conducted for tumor free survival after p53 deletion. 15 TP53<sup>-/-</sup> PIP4K2A<sup>+/+</sup> PIP4K2B<sup>+/+</sup> and 20 TP53<sup>-/-</sup> PIP4K2A<sup>-/-</sup> PIP4K2B<sup>+/-</sup> mice were tested. \*p < 0.05 with two-tailed Student's t test. TP53<sup>-/-</sup> PIP4K2A<sup>-/-</sup> PIP4K2B<sup>+/-</sup> mice had a great increase of tumor free survival compared to TP53<sup>-/-</sup> PIP4K2A<sup>+/+</sup> PIP4K2B<sup>+/+</sup> mice. (Emerling *et al.*, Cell, 2013, 155(4):844-57).

**[00105]** *Figure 2* shows an exemplary synthesis of Compound 7.

**[00106]** *Figures 3A and 3B* show the inhibition of PI5P4K $\alpha/\beta$  by compound THZ-CE-A7. *Figure 3A*: THZ-CE-A7 inhibited the kinase activity of both PI5P4K $\alpha$  and PI5P4K $\beta$ . Radiometric kinase assay was performed using C<sup>32</sup>P-ATP and PI5P. The radiolabeled product, PI(4,5)P<sub>2</sub>, was measured after the separation by thin layer chromatography. *Figure 3B*: THZ-CE-A7 inhibited the proliferation of TP53 mutant BT474 cells at 1  $\mu$ M (left panel). The inhibition stayed effective after 6 hours of treatment and washout (middle panel). THZ-CE-A7 did not inhibit TP53 wild type MCF7 cells at 1  $\mu$ M (right panel).

## DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

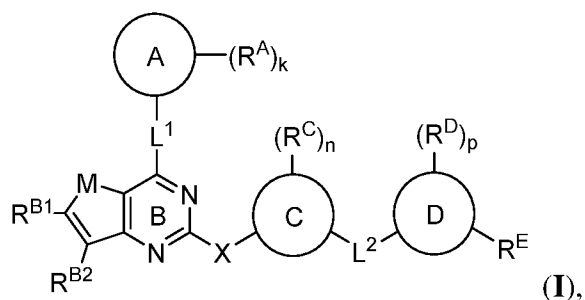
**[00107]** Recent studies have shown that lipid kinases play an essential role in inhibiting cancer cell growth when the TP53 function is absent. Depletion of two lipid kinases, PIP4K2A and PIP4K2B, selectively inhibited the proliferation of TP53 mutant breast cancer cell line (BT474 cells) while cells that were wild-type for TP53 were unaffected (Emerling *et al.*, Cell, 2013, 155: 844-857). Further research has shown that mice expressing one allele of PIP4K2B and homozygous deletion of PIP4K2A and TP53 are viable and exhibit a dramatic reduction in cancers and extended lifespan compared to their littermates that were TP53 deleted with wild type PIP4K2A. Therefore, small molecule inhibitors of lipid kinases may hold promise as a therapeutic agent for treating proliferative diseases.

**[00108]** 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 a lipid kinase, such as PIP4K. The present invention further provides methods of using the compounds described herein, *e.g.*, as biological probes to study the modulation of the activity of a kinase (*e.g.*, a lipid kinase such as PIP4K), 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.*, a lipid kinase such as PIP4K). In certain embodiments, the disease being treated and/or prevented is

a proliferative disease. Exemplary proliferative diseases include, but are not limited to, cancers (*e.g.*, lung cancer, breast cancer, leukemia, melanoma, multiple myeloma), benign neoplasms, 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.*, a lipid kinase such as PIP4K).

### Compounds

**[00109]** In one aspect of the present invention, provided are compounds of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a substituted or unsubstituted, monocyclic or bicyclic heteroaryl ring or a substituted or unsubstituted, monocyclic heterocyclic ring;

each instance of  $R^A$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

each instance of  $R^a$  is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of  $R^a$  are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring;

k is 0, 1, 2, 3, 4, 5, or 6;

M is  $\text{NR}^{\text{M}}$ , O, or S;

$\text{R}^{\text{M}}$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

$\text{L}^1$  is a bond,  $-\text{C}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ , or  $-\text{NR}^{\text{c}}-$ ;

each instance of  $\text{R}^{\text{b}}$  is independently hydrogen, halogen, or substituted or unsubstituted  $\text{C}_{1-6}$  alkyl;

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

$\text{R}^{\text{B1}}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^{\text{a}}$ ,  $-\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{SR}^{\text{a}}$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{C}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{C}(=\text{O})\text{OR}^{\text{a}}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{OC}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ;

$\text{R}^{\text{B2}}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^{\text{a}}$ ,  $-\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{SR}^{\text{a}}$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{R}^{\text{a}}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{OR}^{\text{a}}$ ,  $-\text{C}(=\text{NR}^{\text{a}})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{C}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{C}(=\text{O})\text{OR}^{\text{a}}$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{OR}^{\text{a}}$ ,  $-\text{NR}^{\text{a}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ,  $-\text{OC}(=\text{O})\text{R}^{\text{a}}$ ,  $-\text{OC}(=\text{O})\text{OR}^{\text{a}}$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{a}})_2$ ;

X is  $-\text{C}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ ,  $-\text{NR}^{\text{c}}-$ ,  $-\text{C}(\text{R}^{\text{b}})_2\text{C}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(\text{R}^{\text{b}})_2\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{C}(\text{R}^{\text{b}})_2-$ ,  $(E)-\text{CR}^{\text{b}}=\text{CR}^{\text{b}}-$ ,  $(Z)-\text{CR}^{\text{b}}=\text{CR}^{\text{b}}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{SC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{S}-$ ,  $-\text{NR}^{\text{c}}\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^{\text{c}}-$ ,  $-\text{OC}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(\text{R}^{\text{b}})_2\text{O}-$ ,  $-\text{SC}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(\text{R}^{\text{b}})_2\text{S}-$ ,  $-\text{NR}^{\text{c}}\text{C}(\text{R}^{\text{b}})_2-$ ,  $-\text{C}(\text{R}^{\text{b}})_2\text{NR}^{\text{c}}-$ ,  $-\text{S}(=\text{O})\text{O}-$ ,  $-\text{OS}(=\text{O})-$ ,  $-\text{S}(=\text{O})\text{NR}^{\text{c}}-$ ,  $-\text{NR}^{\text{c}}\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2\text{O}-$ ,  $-\text{OS}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{NR}^{\text{c}}-$ , or  $-\text{NR}^{\text{c}}\text{S}(=\text{O})_2-$ ;

Ring C is a substituted or unsubstituted phenyl ring;

Ring D is a substituted or unsubstituted phenyl ring;

each instance of  $\text{R}^{\text{C}}$  is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^a$ ,  $-\text{N}(\text{R}^a)_2$ ,  $-\text{SR}^a$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^a)\text{R}^a$ ,  $-\text{C}(=\text{NR}^a)\text{OR}^a$ ,  $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$ ,  $-\text{C}(=\text{O})\text{R}^a$ ,  $-\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{OC}(=\text{O})\text{R}^a$ ,  $-\text{OC}(=\text{O})\text{OR}^a$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$ ;

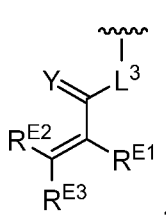
$n$  is 0, 1, 2, 3, or 4;

$\text{L}^2$  is  $-\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ ,  $-\text{NR}^c-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $(E)-\text{CR}^b=\text{CR}^b-$ ,  $(Z)-\text{CR}^b=\text{CR}^b-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{SC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{S}-$ ,  $-\text{NR}^c\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^c-$ ,  $-\text{OC}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{O}-$ ,  $-\text{SC}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{S}-$ ,  $-\text{NR}^c\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{NR}^c-$ ,  $-\text{S}(=\text{O})\text{O}-$ ,  $-\text{OS}(=\text{O})-$ ,  $-\text{S}(=\text{O})\text{NR}^c-$ ,  $-\text{NR}^c\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2\text{O}-$ ,  $-\text{OS}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{NR}^c-$ ,  $-\text{NR}^c\text{S}(=\text{O})_2-$ ,  $-\text{OC}(=\text{O})\text{O}-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{O}-$ ,  $-\text{OC}(=\text{O})\text{NR}^c-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{NR}^c-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{OC}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{O}-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{NR}^c-$ , or a substituted or unsubstituted  $\text{C}_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ , or  $-\text{NR}^c-$ ;

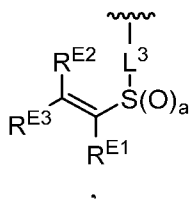
each instance of  $\text{R}^D$  is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^a$ ,  $-\text{N}(\text{R}^a)_2$ ,  $-\text{SR}^a$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^a)\text{R}^a$ ,  $-\text{C}(=\text{NR}^a)\text{OR}^a$ ,  $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$ ,  $-\text{C}(=\text{O})\text{R}^a$ ,  $-\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{OC}(=\text{O})\text{R}^a$ ,  $-\text{OC}(=\text{O})\text{OR}^a$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$ ;

$p$  is 0, 1, 2, 3, or 4;

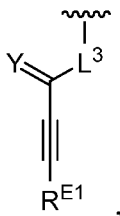
$\text{R}^E$  is of the formula:



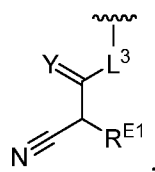
(i-1)



(i-2)



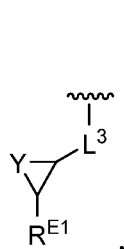
(i-3)



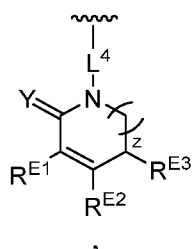
(i-4)



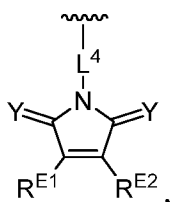
(i-5)



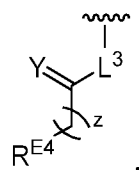
(i-6)



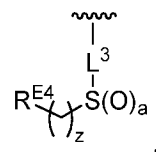
(i-7)



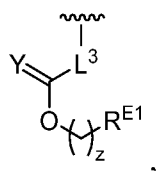
(i-8)



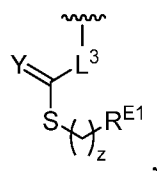
(i-9)



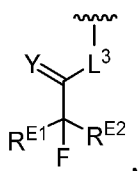
(i-10)



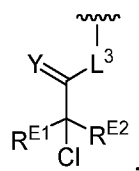
(i-11)



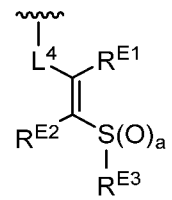
(i-12)



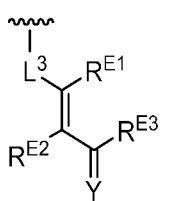
(i-13)



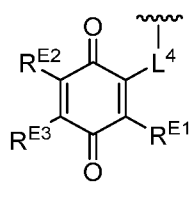
(i-14)



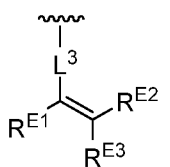
(i-15)



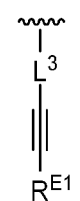
(i-16)



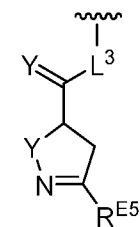
(i-17)



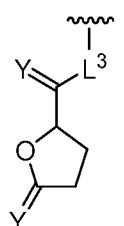
(i-18)



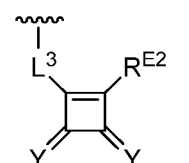
(i-19)



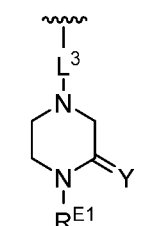
(i-20)



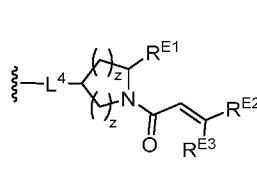
(i-21)



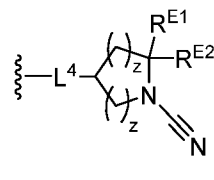
(i-22)



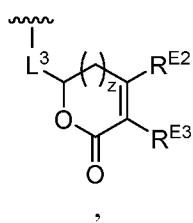
(i-23)



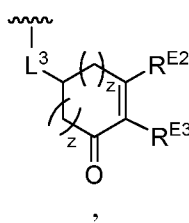
(i-24)



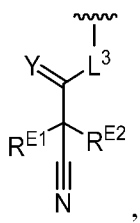
(i-25)



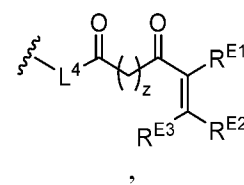
(i-26)



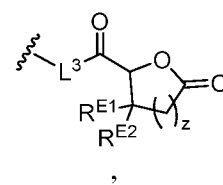
(i-27)



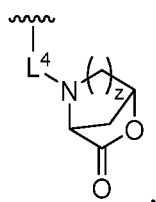
(i-28)



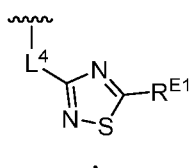
(i-29)



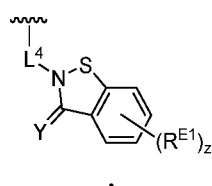
(i-30)



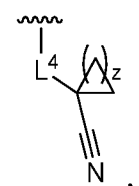
(i-31)



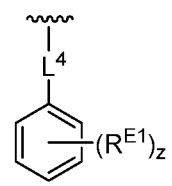
(i-32)



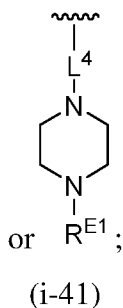
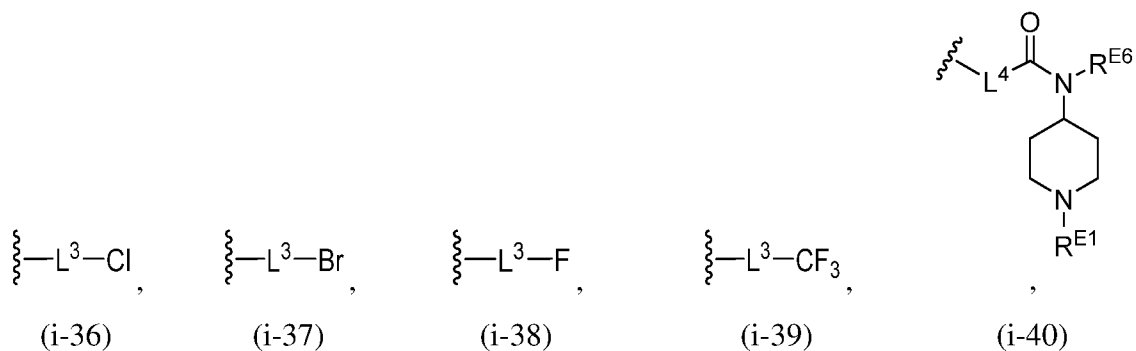
(i-33)



(i-34)



(i-35)



$L^3$  is  $-\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ ,  $-\text{NR}^c-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $(E)-\text{CR}^b=\text{CR}^b-$ ,  $(Z)-\text{CR}^b=\text{CR}^b-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{SC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{S}-$ ,  $-\text{NR}^c\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^c-$ ,  $-\text{OC}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{O}-$ ,  $-\text{SC}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{S}-$ ,  $-\text{NR}^c\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{NR}^c-$ ,  $-\text{S}(=\text{O})\text{O}-$ ,  $-\text{OS}(=\text{O})-$ ,  $-\text{S}(=\text{O})\text{NR}^c-$ ,  $-\text{NR}^c\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2\text{O}-$ ,  $-\text{OS}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{NR}^c-$ ,  $-\text{NR}^c\text{S}(=\text{O})_2-$ ,  $-\text{OC}(=\text{O})\text{O}-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{O}-$ ,  $-\text{OC}(=\text{O})\text{NR}^c-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{NR}^c-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{OC}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{O}-$ ,  $-\text{NR}^c\text{C}(=\text{O})\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(\text{R}^b)_2\text{C}(=\text{O})\text{NR}^c-$ , or a substituted or unsubstituted  $\text{C}_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ , or  $-\text{NR}^c-$ ;

$L^4$  is a bond or substituted or unsubstituted  $\text{C}_{1-6}$  hydrocarbon chain;

each of  $\text{R}^{\text{E}1}$ ,  $\text{R}^{\text{E}2}$ , and  $\text{R}^{\text{E}3}$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{CN}$ ,  $-\text{CH}_2\text{OR}^a$ ,  $-\text{CH}_2\text{N}(\text{R}^a)_2$ ,  $-\text{CH}_2\text{SR}^a$ ,  $-\text{OR}^a$ ,  $-\text{N}(\text{R}^a)_2$ ,  $-\text{SR}^a$ , or  $-\text{Si}(\text{R}^a)_3$ ; 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 a substituted or unsubstituted, carbocyclic ring, or substituted or unsubstituted, 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 Y is independently O, S, or NR<sup>c</sup>;

a is 1 or 2; and

each instance of z is independently 0, 1, 2, 3, 4, 5, or 6.

**[00110]** In certain embodiments, the compound described herein is of Formula (I), or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a substituted or unsubstituted, bicyclic heteroaryl ring or a substituted or unsubstituted, monocyclic heterocyclic ring;

each instance of R<sup>A</sup> is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR<sup>a</sup>, -N(R<sup>a</sup>)<sub>2</sub>, -SR<sup>a</sup>, -CN, -SCN, -C(=NR<sup>a</sup>)R<sup>a</sup>, -C(=NR<sup>a</sup>)OR<sup>a</sup>, -C(=NR<sup>a</sup>)N(R<sup>a</sup>)<sub>2</sub>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>a</sup>, -C(=O)N(R<sup>a</sup>)<sub>2</sub>, -NO<sub>2</sub>, -NR<sup>a</sup>C(=O)R<sup>a</sup>, -NR<sup>a</sup>C(=O)OR<sup>a</sup>, -NR<sup>a</sup>C(=O)N(R<sup>a</sup>)<sub>2</sub>, -OC(=O)R<sup>a</sup>, -OC(=O)OR<sup>a</sup>, or -OC(=O)N(R<sup>a</sup>)<sub>2</sub>;

each instance of R<sup>a</sup> is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R<sup>a</sup> are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring;

k is 0, 1, 2, 3, 4, 5, or 6;

M is NR<sup>M</sup>, O, or S;

R<sup>M</sup> is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or a nitrogen protecting group;

L<sup>1</sup> is a bond, -C(R<sup>b</sup>)<sub>2</sub>-, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)<sub>2</sub>-, or -NR<sup>c</sup>-;

each instance of R<sup>b</sup> is independently hydrogen, halogen, or substituted or unsubstituted C<sub>1-6</sub> alkyl;

each instance of R<sup>c</sup> is independently hydrogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, or a nitrogen protecting group;

$R^{B1}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

$R^{B2}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

X is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ , or  $-NR^cS(=O)_2-$ ;

Ring C is a substituted or unsubstituted phenyl ring;

Ring D is a substituted or unsubstituted phenyl ring;

each instance of  $R^C$  is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

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

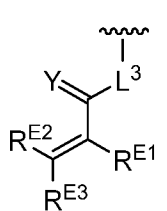
$L^2$  is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ , or  $-NR^cS(=O)_2-$ ;

$\text{NR}^c\text{S(=O)}-$ ,  $-\text{S(=O)}_2\text{O}-$ ,  $-\text{OS(=O)}_2-$ ,  $-\text{S(=O)}_2\text{NR}^c-$ ,  $-\text{NR}^c\text{S(=O)}_2-$ ,  $-\text{OC(=O)O}-$ ,  $-\text{NR}^c\text{C(=O)O}-$ ,  $-\text{OC(=O)NR}^c-$ ,  $-\text{NR}^c\text{C(=O)NR}^c-$ ,  $-\text{C(R}^b)_2\text{C(=O)C(R}^b)_2-$ ,  $-\text{OC(=O)C(R}^b)_2-$ ,  $-\text{C(R}^b)_2\text{C(=O)O}-$ ,  $-\text{NR}^c\text{C(=O)C(R}^b)_2-$ ,  $-\text{C(R}^b)_2\text{C(=O)NR}^c-$ , or a substituted or unsubstituted  $\text{C}_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-\text{C(=O)}-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S(=O)}-$ ,  $-\text{S(=O)}_2-$ , or  $-\text{NR}^c-$ ;

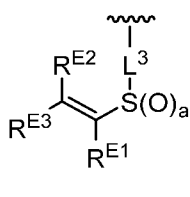
each instance of  $\text{R}^D$  is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^a$ ,  $-\text{N(R}^a)_2$ ,  $-\text{SR}^a$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C(=NR}^a)\text{R}^a$ ,  $-\text{C(=NR}^a)\text{OR}^a$ ,  $-\text{C(=NR}^a)\text{N(R}^a)_2$ ,  $-\text{C(=O)R}^a$ ,  $-\text{C(=O)OR}^a$ ,  $-\text{C(=O)N(R}^a)_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^a\text{C(=O)R}^a$ ,  $-\text{NR}^a\text{C(=O)OR}^a$ ,  $-\text{NR}^a\text{C(=O)N(R}^a)_2$ ,  $-\text{OC(=O)R}^a$ ,  $-\text{OC(=O)OR}^a$ , or  $-\text{OC(=O)N(R}^a)_2$ ;

$p$  is 0, 1, 2, 3, or 4;

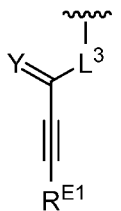
$\text{R}^E$  is of the formula:



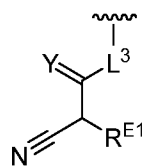
(i-1)



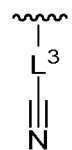
(i-2)



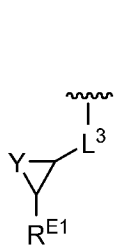
(i-3)



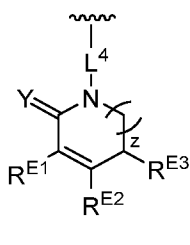
(i-4)



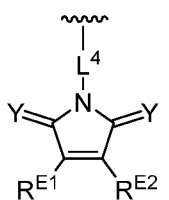
(i-5)



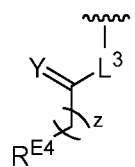
(i-6)



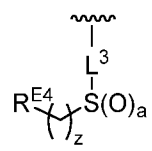
(i-7)



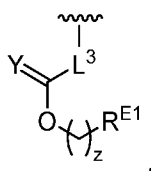
(i-8)



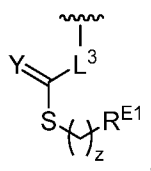
(i-9)



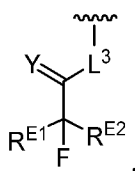
(i-10)



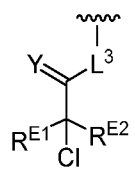
(i-11)



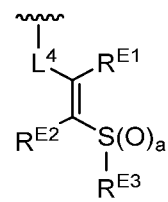
(i-12)



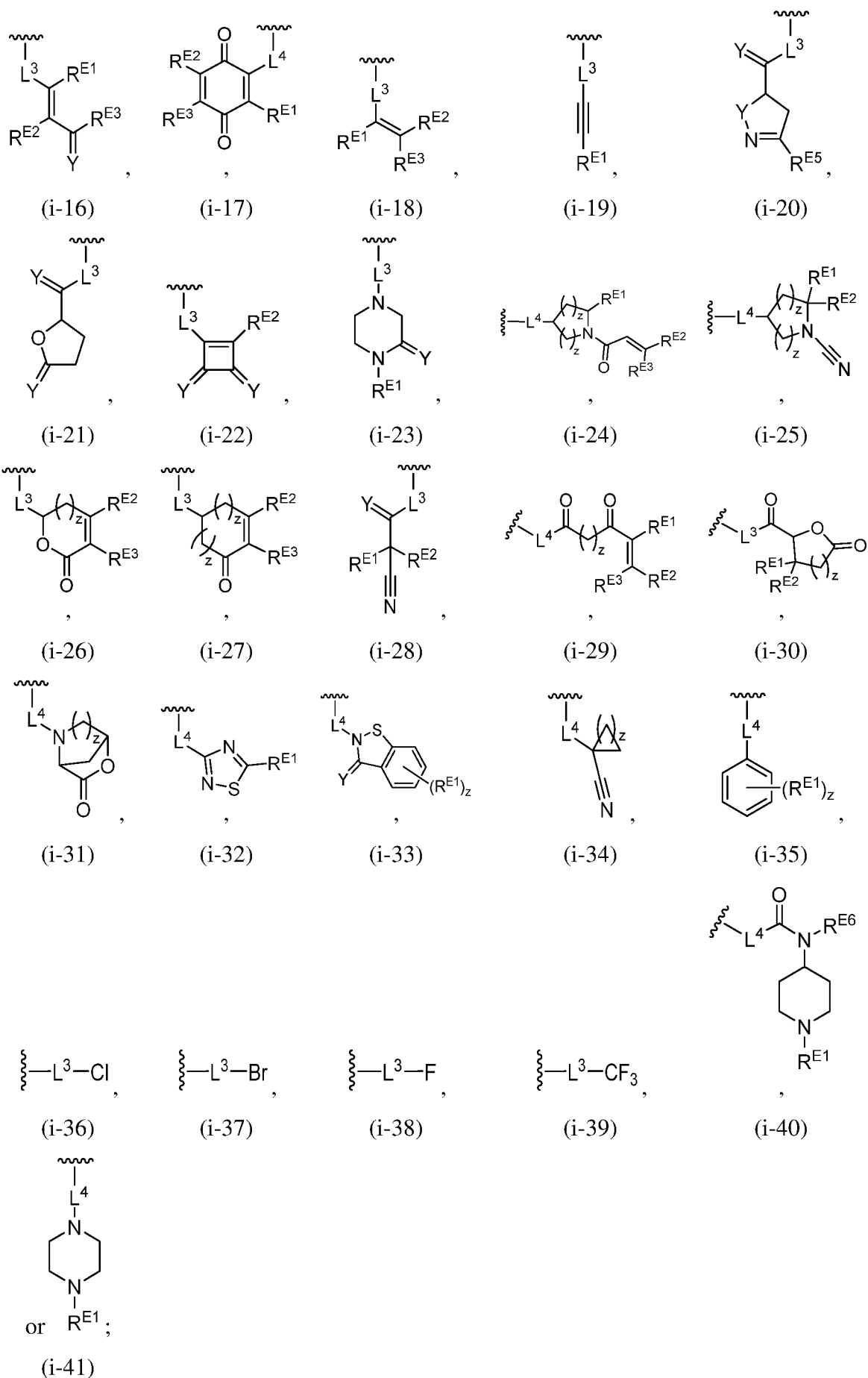
(i-13)



(i-14)



(i-15)



$L^3$  is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ ,  $-NR^cS(=O)_2-$ ,  $-OC(=O)O-$ ,  $-NR^cC(=O)O-$ ,  $-OC(=O)NR^c-$ ,  $-NR^cC(=O)NR^c-$ ,  $-C(R^b)_2C(=O)C(R^b)_2-$ ,  $-OC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)O-$ ,  $-NR^cC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)NR^c-$ , or a substituted or unsubstituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ ;

$L^4$  is a bond or substituted or unsubstituted  $C_{1-6}$  hydrocarbon chain;

each of  $R^{E1}$ ,  $R^{E2}$ , and  $R^{E3}$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-CH_2OR^a$ ,  $-CH_2N(R^a)_2$ ,  $-CH_2SR^a$ ,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ , or  $-Si(R^a)_3$ ; or  $R^{E1}$  and  $R^{E3}$ , or  $R^{E2}$  and  $R^{E3}$ , or  $R^{E1}$  and  $R^{E2}$  are joined to form a substituted or unsubstituted, carbocyclic ring, or substituted or unsubstituted, 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  $NR^c$ ;

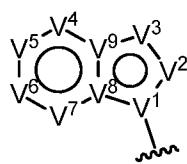
a is 1 or 2; and

each instance of z is independently 0, 1, 2, 3, 4, 5, or 6.

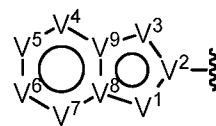
**[00111]** As generally defined herein, M is  $NR^M$ , O, or S. In certain embodiments, M is  $NR^M$ , wherein  $R^M$  is as defined herein. In certain embodiments, M is  $NR^M$ , wherein  $R^M$  is hydrogen, substituted or unsubstituted alkenyl, or a nitrogen protecting group. In certain embodiments, M is NH. In certain embodiments, M is O. In certain embodiments, M is S.

**[00112]** Compounds of Formula (I) include Ring A attached to Ring B through linker  $L^1$ . In certain embodiments, Ring A is a substituted or unsubstituted bicyclic heteroaryl ring. In certain embodiments, Ring A is a substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur, as valency permits. In certain embodiments, Ring

A is a substituted or unsubstituted bicyclic heteroaryl ring with one nitrogen. In certain embodiments, Ring A is a substituted or unsubstituted bicyclic heteroaryl ring with two nitrogen. In certain embodiments, Ring A is a substituted or unsubstituted monocyclic heteroaryl ring fused with a substituted or unsubstituted monocyclic aryl ring. In certain embodiments, Ring A is a substituted or unsubstituted monocyclic heteroaryl ring fused with another substituted or unsubstituted monocyclic heteroaryl ring. Ring A may be a substituted or unsubstituted 6,5-membered heteroaryl ring or a substituted or unsubstituted 5,6-membered heteroaryl ring. In certain embodiments, Ring A is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring fused with a substituted or unsubstituted monocyclic 6-membered aryl ring. In certain embodiments, Ring A is a substituted or unsubstituted monocyclic 5-membered heteroaryl ring fused with a substituted or unsubstituted 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 (i-1):

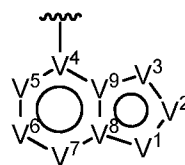


(i-1). In certain embodiments, Ring A is of Formula (i-2):



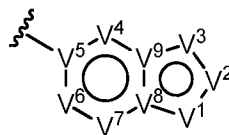
(i-2)

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



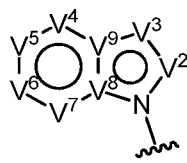
(i-3). In certain

embodiments, Ring A is of Formula (i-4):

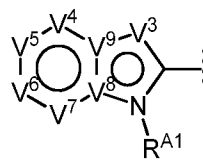


(i-4). In compounds of Formula

(I),  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , 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 the formula:

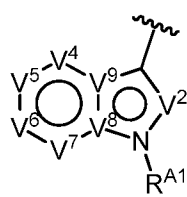


. In certain embodiments, Ring A is of the formula:

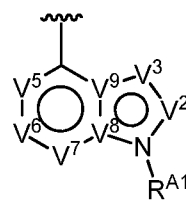


. In certain

embodiments, Ring A is of the formula:

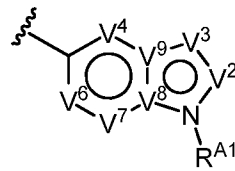


. In certain embodiments, Ring A is of the formula:



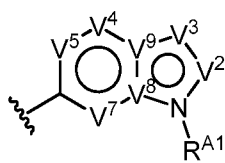
. In certain

embodiments, Ring A is of the formula:

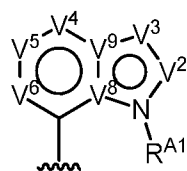


. In certain embodiments, Ring A

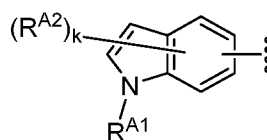
is of the formula:



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



**[00113]** In certain embodiments, only one of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  is selected from the group consisting of O, S, N, and  $NR^{A1}$ . In certain embodiments, only one of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  is selected from the group consisting of N and  $NR^{A1}$ . In certain embodiments,  $V^1$  is N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted indole ring.

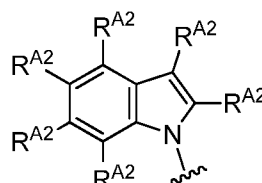


In certain embodiments, Ring A is of Formula (A-i):

(A-i), wherein  $R^{A1}$ ,

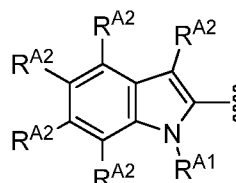
$R^{A2}$ , and k are as defined herein. In certain embodiments, k is 0, 1, 2, 3, 4, or 5. In certain

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

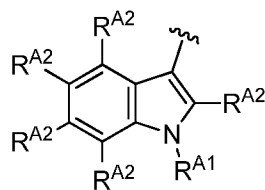


(iii-1). In certain

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

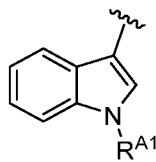


(iii-2). In certain embodiments,



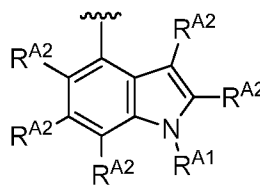
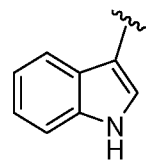
Ring A is of Formula (iii-3):

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



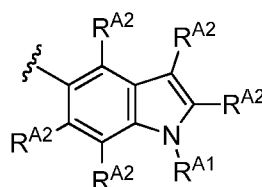
of the formula:

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



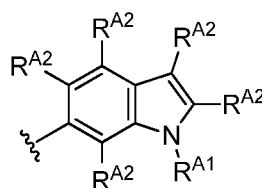
In certain embodiments, Ring A is of Formula (iii-4):

(iii-4). In certain



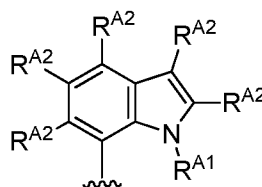
embodiments, Ring A is of Formula (iii-5):

(iii-5). In certain



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

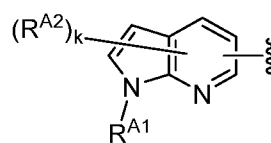
(iii-6). In certain



embodiments, Ring A is of Formula (iii-7):

(iii-7).

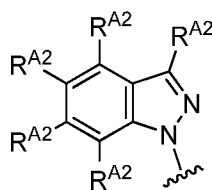
**[00114]** In certain embodiments, only two of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently selected from the group consisting of O, S, N, and  $NR^{A1}$ . In certain embodiments, only two of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently selected from the group consisting of N and  $NR^{A1}$ . In certain embodiments,  $V^1$  is N or  $NR^{A1}$ ; and only one of  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  is N or  $NR^{A1}$ . In certain embodiments,  $V^1$  and  $V^2$  are each independently N or  $NR^{A1}$ ;  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted indazole



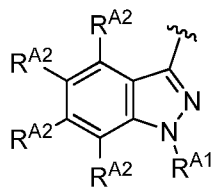
ring. In certain embodiments, Ring A is of Formula (A-ii):

(A-ii),

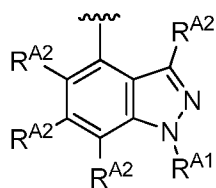
wherein  $R^{A1}$ ,  $R^{A2}$ , and  $k$  are as defined herein. In certain embodiments,  $k$  is 0, 1, 2, 3, or 4. In



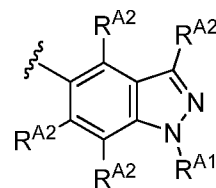
certain embodiments, Ring A is of the formula: . In certain embodiments,



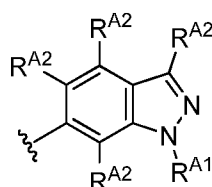
Ring A is of the formula: . In certain embodiments, Ring A is of the formula:



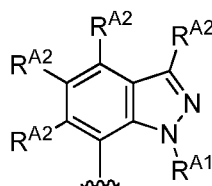
. In certain embodiments, Ring A is of the formula:



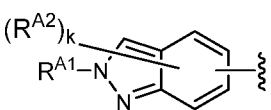
. In

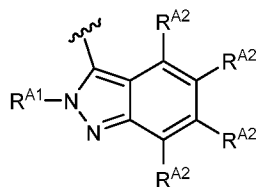


certain embodiments, Ring A is of the formula: . In certain embodiments,

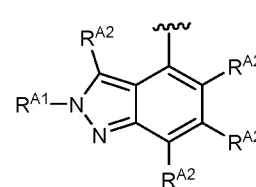


Ring A is of the formula: . In certain embodiments, Ring A is of Formula

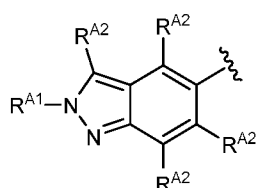
(A-iii):  (A-iii), wherein  $R^{A1}$ ,  $R^{A2}$ , and  $k$  are as defined herein. In certain embodiments,  $k$  is 0, 1, 2, 3, or 4. In certain embodiments, Ring A is of the formula:



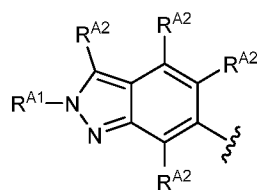
. In certain embodiments, Ring A is of the formula:



.

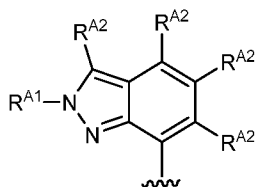


In certain embodiments, Ring A is of the formula: . In certain



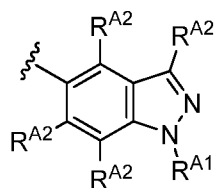
embodiments, Ring A is of the formula:

. In certain embodiments, Ring A

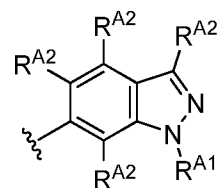


is of the formula:

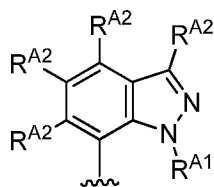
. In certain embodiments, Ring A is of the formula:



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

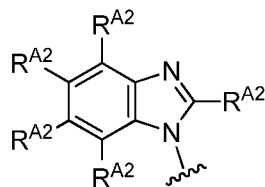


. In

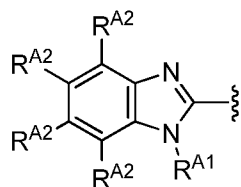


certain embodiments, Ring A is of the formula:

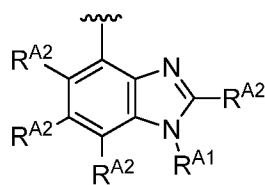
**[00115]** In certain embodiments,  $V^1$  and  $V^3$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted benzimidazole ring. In certain embodiments, Ring A is of Formula **(iv-1)**:



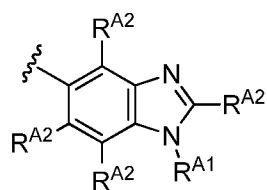
**(iv-1)**. In certain embodiments, Ring A is of Formula **(iv-2)**:



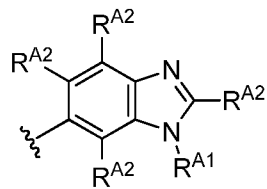
**(iv-2)**. In certain embodiments, Ring A is of Formula **(iv-3)**:



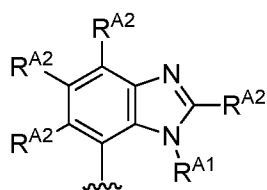
**(iv-3)**. In certain embodiments, Ring A is of Formula **(iv-4)**:



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

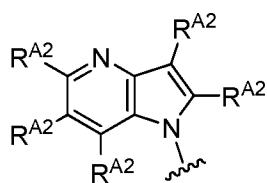


(iv-5). In certain embodiments, Ring A is of Formula (iv-6):

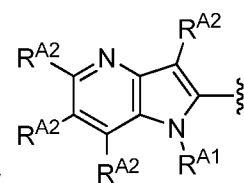


(iv-6).

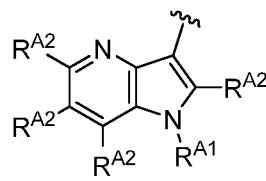
**[00116]** In certain embodiments,  $V^1$  and  $V^4$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 4-azaindazole ring. In certain embodiments, Ring A is of the formula:



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

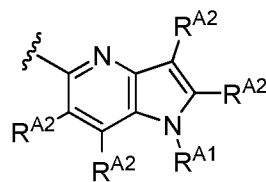


In certain embodiments, Ring A is of the formula:



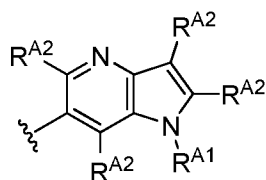
. In certain

embodiments, Ring A is of the formula:

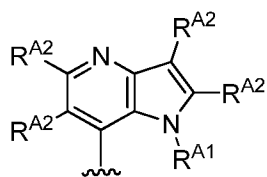


. In certain embodiments, Ring

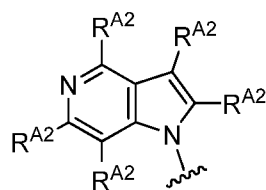
A is of the formula:



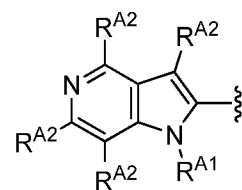
. In certain embodiments, Ring A is of the formula:



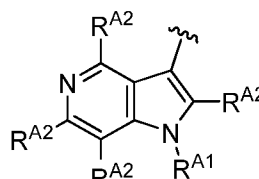
[00117] In certain embodiments,  $V^1$  and  $V^5$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 5-azaindazole ring. In certain embodiments, Ring A is of the formula:



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

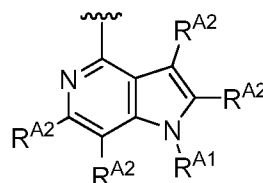


In certain embodiments, Ring A is of the formula:



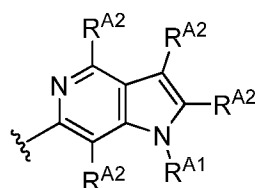
. In certain

embodiments, Ring A is of the formula:

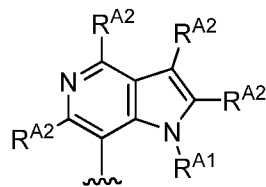


. In certain embodiments, Ring

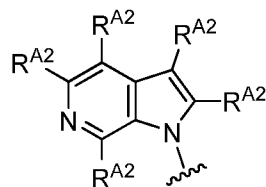
A is of the formula:



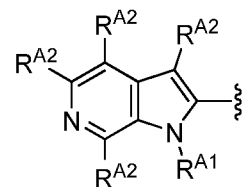
. In certain embodiments, Ring A is of the formula:



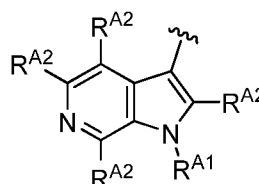
[00118] In certain embodiments,  $V^1$  and  $V^6$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 6-azaindole ring. In certain embodiments, Ring A is of the formula:



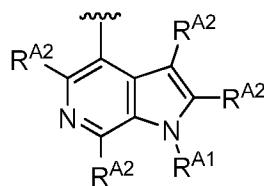
. In certain embodiments, Ring A is of the formula:



In certain embodiments, Ring A is of the formula:

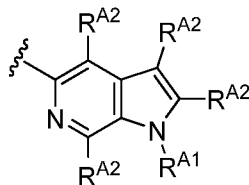


. In certain



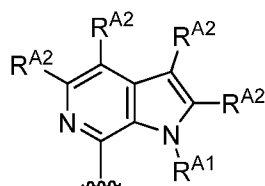
embodiments, Ring A is of the formula:

. In certain embodiments, Ring

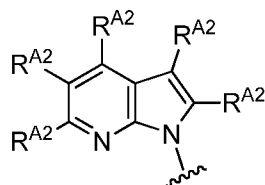


A is of the formula:

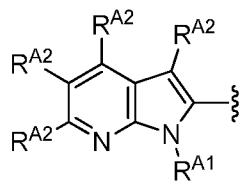
. In certain embodiments, Ring A is of the formula:



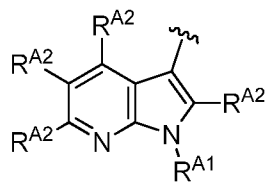
**[00119]** In certain embodiments,  $V^1$  and  $V^7$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^8$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 7-azaindole ring. In certain embodiments, Ring A is of Formula (**v-1**):



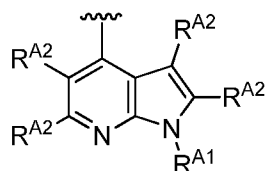
(**v-1**). In certain embodiments, Ring A is of Formula (**v-2**):



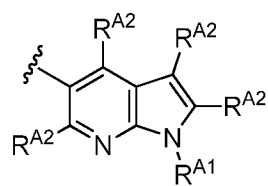
(**v-2**). In certain embodiments, Ring A is of Formula (**v-3**):



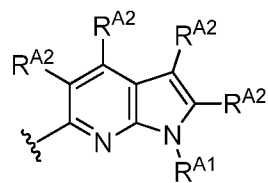
(**v-3**). In certain embodiments, Ring A is of Formula (**v-4**):



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

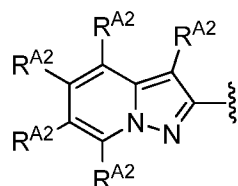


(v-5). In certain embodiments, Ring A is of Formula (v-6):

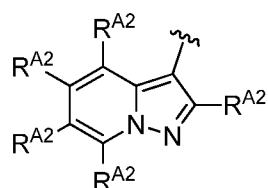


(v-6).

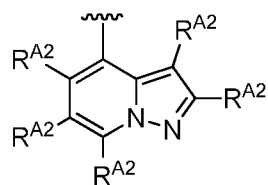
**[00120]** In certain embodiments,  $V^1$  and  $V^8$  are each independently N or  $NR^{A1}$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ , and  $V^9$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 8-azaindole ring. In certain embodiments, Ring A is of Formula (vi-1):



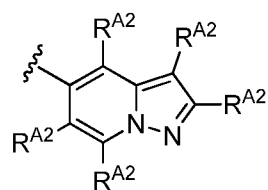
(vi-1). In certain embodiments, Ring A is of Formula (vi-2):



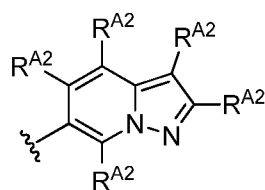
(vi-2). In certain embodiments, Ring A is of Formula (vi-3):



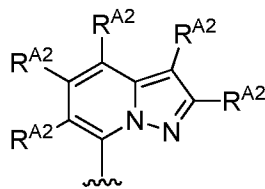
(vi-3). In certain embodiments, Ring A is of Formula (vi-4):



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

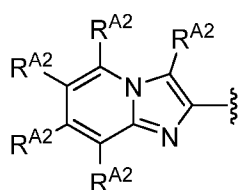


(vi-5). In certain embodiments, Ring A is of Formula (vi-6):

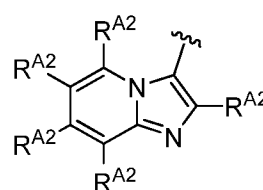


(vi-6).

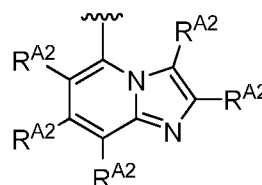
**[00121]** In certain embodiments,  $V^1$  and  $V^9$  are each independently N or  $NR^{A1}$ ;  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ , and  $V^8$  are each independently C or  $CR^{A2}$ ; and therefore, Ring A is a substituted or unsubstituted 9-azaindole ring. In certain embodiments, Ring A is of the formula:



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

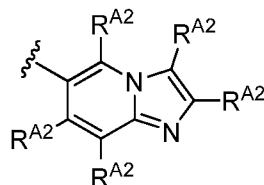


In certain embodiments, Ring A is of the formula:



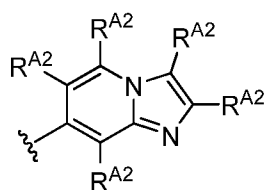
. In certain

embodiments, Ring A is of the formula:

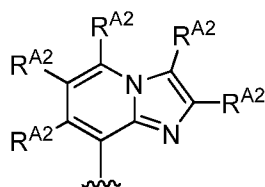


. In certain embodiments, Ring

A is of the formula:



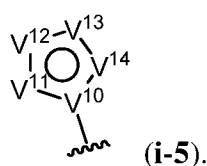
. In certain embodiments, Ring A is of the formula:



**[00122]** In certain embodiments, only three of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently selected from the group consisting of O, S, N, and  $NR^{A1}$ . In certain embodiments, only three of  $V^1$ ,  $V^2$ ,  $V^3$ ,  $V^4$ ,  $V^5$ ,  $V^6$ ,  $V^7$ ,  $V^8$ , and  $V^9$  are each independently

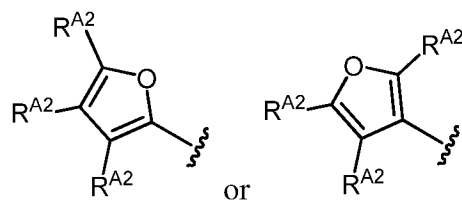
selected from the group consisting of N and  $\text{NR}^{\text{A1}}$ . In certain embodiments,  $\text{V}^1$  is N or  $\text{NR}^{\text{A1}}$ ; and only two of  $\text{V}^2$ ,  $\text{V}^3$ ,  $\text{V}^4$ ,  $\text{V}^5$ ,  $\text{V}^6$ ,  $\text{V}^7$ ,  $\text{V}^8$ , and  $\text{V}^9$  are each independently N or  $\text{NR}^{\text{A1}}$ .

**[00123]** In compounds of Formula (I), Ring A may also be a substituted or unsubstituted monocyclic heteroaryl ring. In certain embodiments, Ring A is a substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur, as valency permits. In compounds of Formula (I), Ring A may also be a substituted or unsubstituted 5-membered heteroaryl ring. In certain embodiments, Ring A is of Formula (i-5):

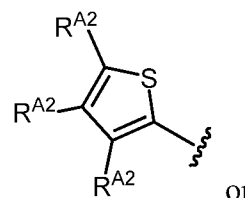
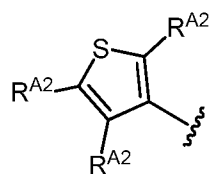


**[00124]** In compounds of Formula (I),  $\text{V}^{10}$ ,  $\text{V}^{11}$ ,  $\text{V}^{12}$ ,  $\text{V}^{13}$ , and  $\text{V}^{14}$  of Ring A may each independently be O, S, N,  $\text{NR}^{\text{A1}}$ , C, or  $\text{CR}^{\text{A2}}$ , as valency permits. In certain embodiments, only one of  $\text{V}^{10}$ ,  $\text{V}^{11}$ ,  $\text{V}^{12}$ ,  $\text{V}^{13}$ , and  $\text{V}^{14}$  is selected from the group consisting of O, S, N, and

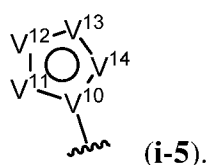
$\text{NR}^{\text{A1}}$ . In certain embodiments, Ring A is of the formula:



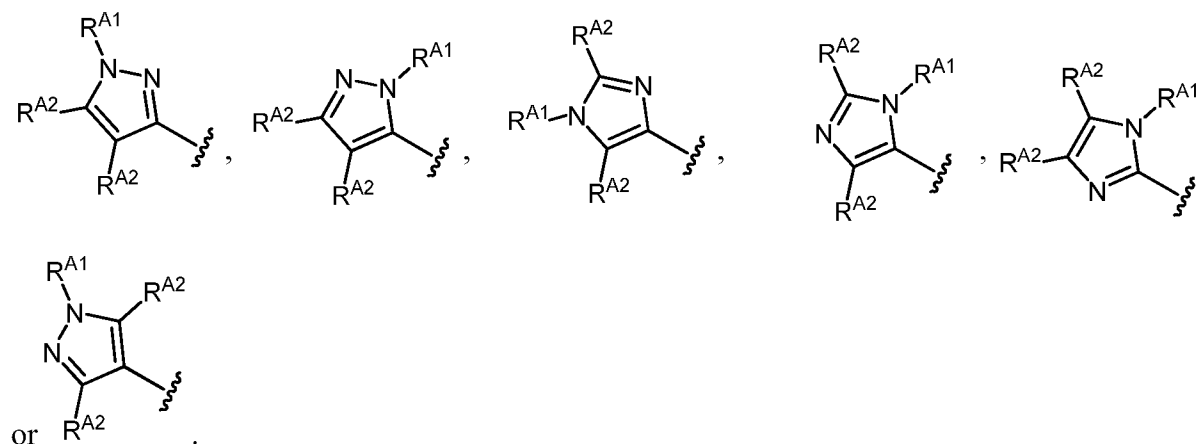
**[00125]** In certain embodiments, Ring A is of the formula:



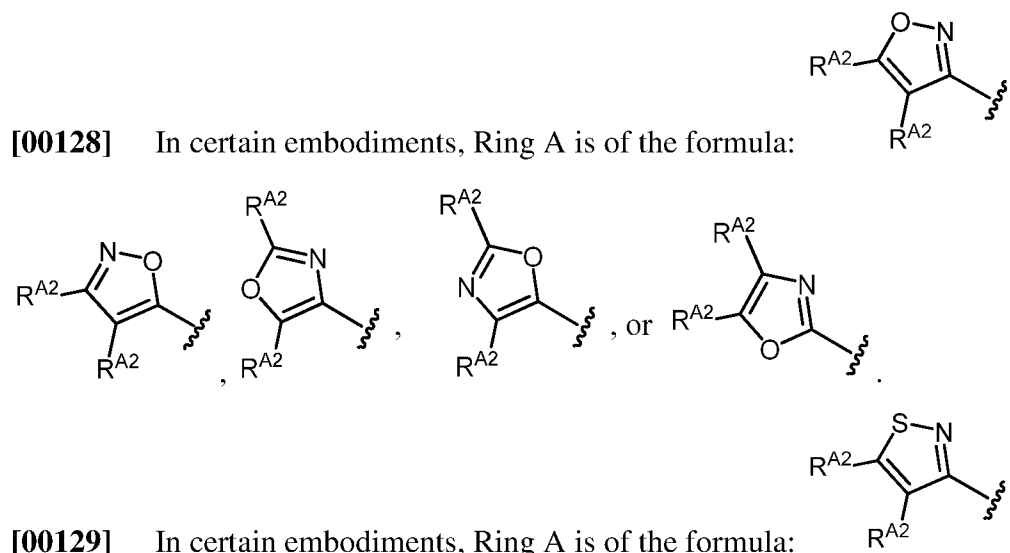
**[00126]** In compounds of Formula (I), Ring A may also be a substituted or unsubstituted monocyclic heteroaryl ring. In compounds of Formula (I), Ring A may also be a substituted or unsubstituted 5-membered heteroaryl ring. In certain embodiments, Ring A is of Formula (i-5):



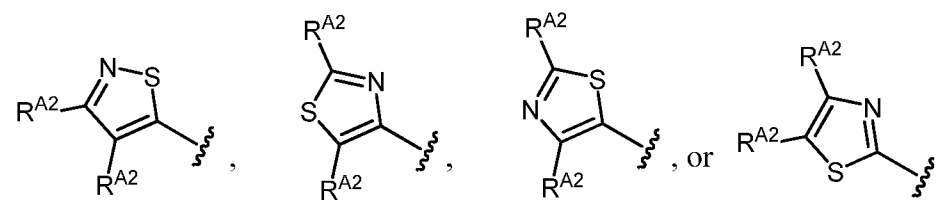
[00127] In certain embodiments, only two of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  are each independently selected from the group consisting of O, S, N, and  $NR^{A1}$ . In certain embodiments, Ring A is of the formula:

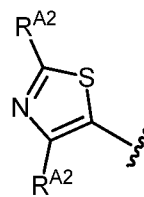


[00128] In certain embodiments, Ring A is of the formula:

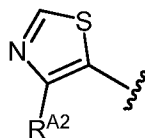


[00129] In certain embodiments, Ring A is of the formula:

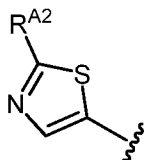




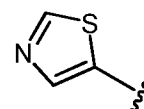
[00130] In certain embodiments, Ring A is of Formula (vii): (vii). In certain



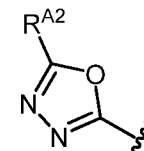
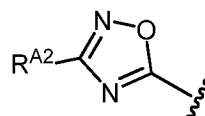
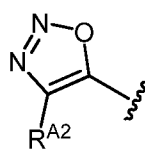
embodiments, Ring A is of the formula: . In certain embodiments, Ring A is of



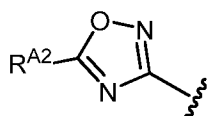
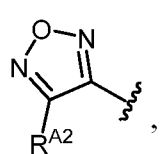
the formula: . In certain embodiments, Ring A is of the formula:



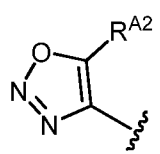
[00131] In certain embodiments, only three of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  are each independently selected from the group consisting of O, S, N, and  $NR^{A1}$ . In certain



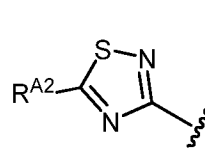
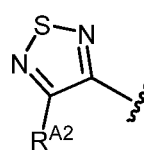
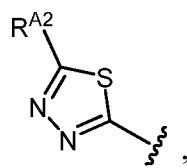
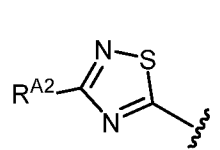
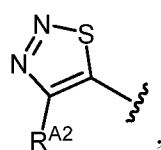
embodiments, Ring A is of the formula:



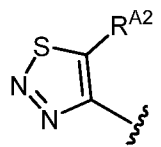
or



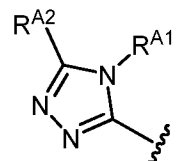
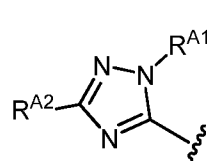
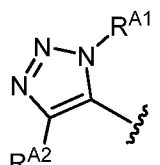
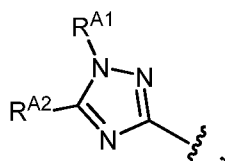
[00132] In certain embodiments, Ring A is of the formula:

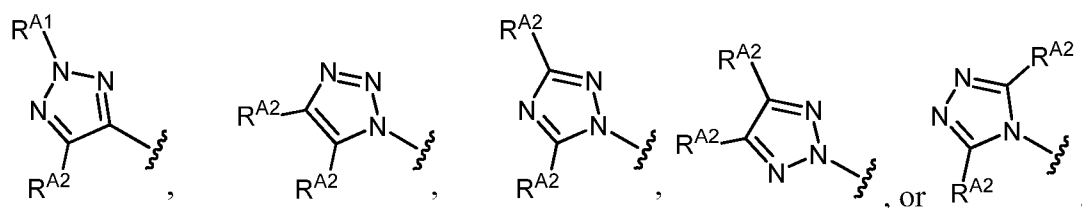


, or

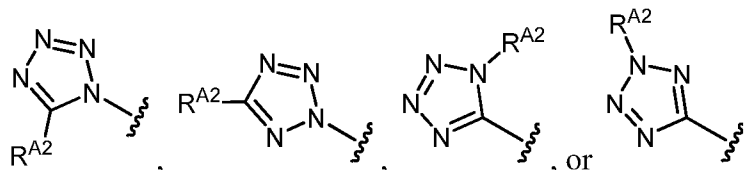


[00133] In certain embodiments, Ring A is of the formula:

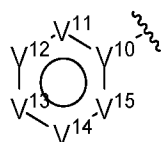




[00134] In certain embodiments, only four of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ , and  $V^{14}$  are each independently selected from the group consisting of N and  $NR^{A1}$ . In certain embodiments, Ring A is of the formula:

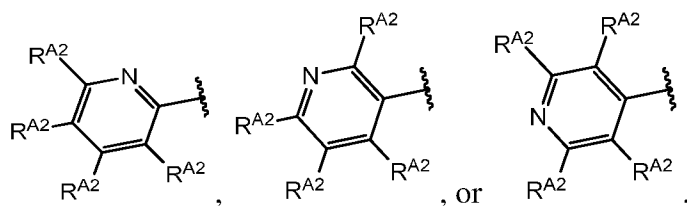


[00135] In compounds of Formula (I), Ring A may also be a substituted or unsubstituted 6-membered heteroaryl ring. In certain embodiments, Ring A is of Formula (i-6):

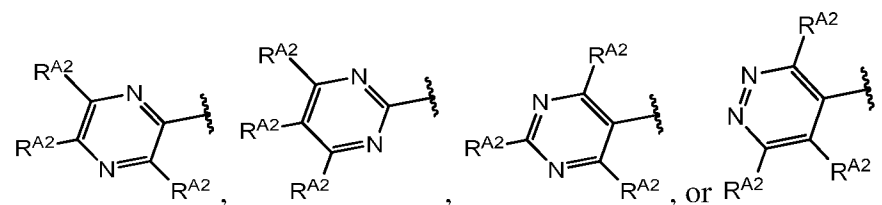
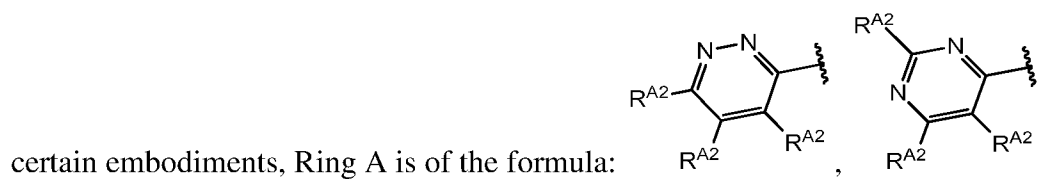


(i-6). In compounds of Formula (I),  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  of Ring A may each independently be N, C, or  $CR^{A2}$ , as valency permits. In certain embodiments, only one of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  is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

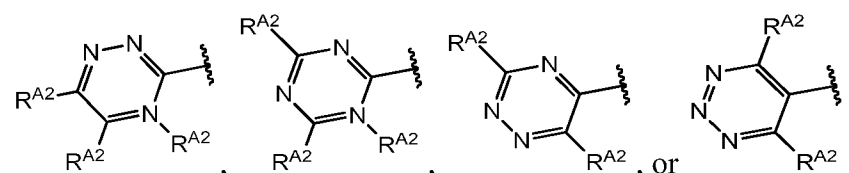
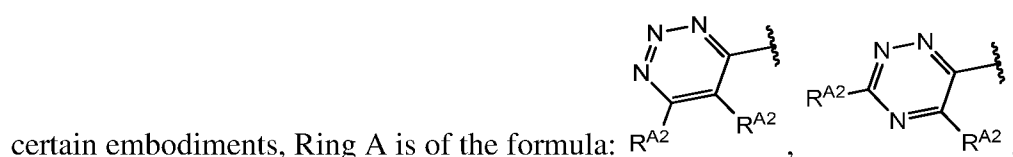
(A-v): (A-v), wherein  $R^{A2}$  and  $k$  are as defined herein. In certain embodiments,  $k$  is 0, 1, 2, 3, or 4. In certain embodiments, Ring A is of the formula:



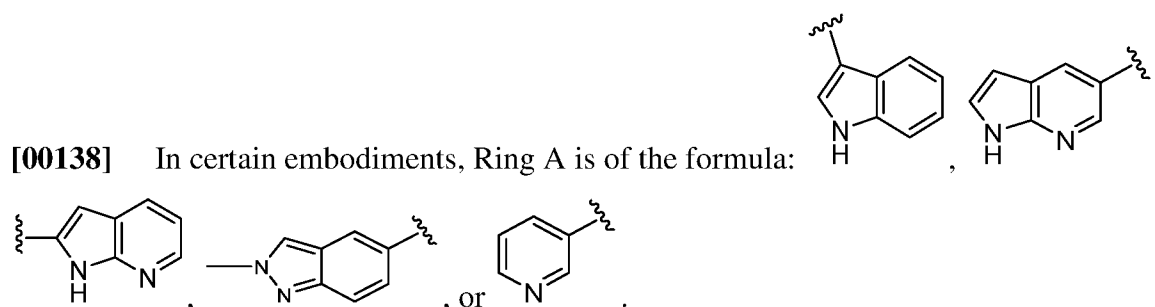
[00136] In certain embodiments, only two of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  are N. In



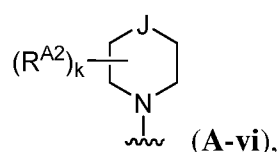
[00137] In certain embodiments, only three of  $V^{10}$ ,  $V^{11}$ ,  $V^{12}$ ,  $V^{13}$ ,  $V^{14}$ , and  $V^{15}$  are N. In



[00138] In certain embodiments, Ring A is of the formula:



[00139] In certain embodiments, Ring A is a substituted or unsubstituted, monocyclic heterocyclic ring. In certain embodiments, Ring A is a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits. In certain embodiments, Ring A is a substituted or unsubstituted 5-membered heterocyclic ring. In certain embodiments, Ring A is a substituted or unsubstituted 6-membered heterocyclic ring. In certain embodiments, Ring A is of Formula (A-vi):



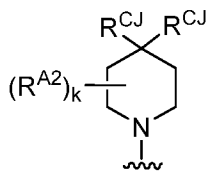
wherein  $R^{A2}$  is as defined herein;

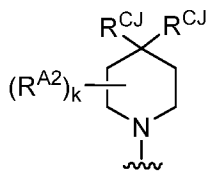
J is  $C(R^{CJ})_2$  or  $NR^{NJ}$ ;

each instance of  $R^{CJ}$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ; and

$R^{NJ}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group.

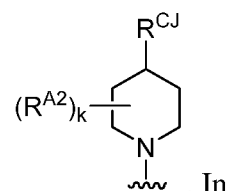
**[00140]** In certain embodiments, k is 0, 1, 2, 3, 4, 5, or 6. In certain embodiments, Ring A



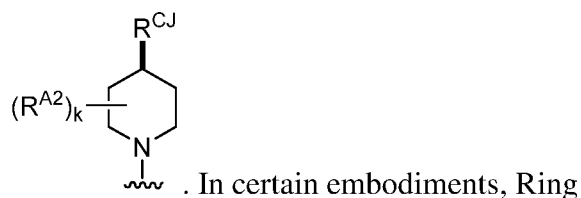
is of the formula: . In certain embodiments, at least one  $R^{CJ}$  is hydrogen. In certain embodiments, at least one  $R^{CJ}$  is halogen. In certain embodiments, at least one  $R^{CJ}$  is halogen. In certain embodiments, at least one  $R^{CJ}$  is F. In certain embodiments, at least one  $R^{CJ}$  is Cl. In certain embodiments, at least one  $R^{CJ}$  is Br. In certain embodiments, at least one  $R^{CJ}$  is I (iodine). In certain embodiments, at least one  $R^{CJ}$  is substituted alkyl. In certain embodiments, at least one  $R^{CJ}$  is unsubstituted alkyl. In certain embodiments, at least one  $R^{CJ}$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^{CJ}$  is methyl. In certain embodiments, at least one  $R^{CJ}$  is ethyl. In certain embodiments, at least one  $R^{CJ}$  is propyl. In certain embodiments, at least one  $R^{CJ}$  is  $-OR^a$ , wherein  $R^a$  is as defined herein. In certain embodiments, at least one  $R^{CJ}$  is  $-N(R^a)_2$ , wherein  $R^a$  is as defined herein. In certain embodiments, at least one  $R^{CJ}$  is  $-NHR^a$ , wherein  $R^a$  is as defined herein. In certain embodiments, at least one  $R^{CJ}$  is  $-N(R^a)_2$ , wherein two  $R^a$  are joined with the intervening nitrogen to form a substituted or unsubstituted heterocyclic ring. In certain embodiments, both instances of  $R^{CJ}$  are hydrogen. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is halogen. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is halogen. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is F. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is Cl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is Br.

In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is I (iodine). In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is substituted alkyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is unsubstituted alkyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is  $C_{1-6}$  alkyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is methyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is ethyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is propyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is  $-N(R^a)_2$ , wherein two  $R^a$  are joined with the intervening nitrogen to form a substituted or unsubstituted 5-membered heterocyclic ring. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is  $-N(R^a)_2$ , wherein two  $R^a$  are joined with the intervening nitrogen to form a substituted or unsubstituted 6-membered heterocyclic ring. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is substituted or unsubstituted morpholinyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is substituted or unsubstituted piperazinyl. In certain embodiments, one  $R^{CJ}$  is hydrogen and one  $R^{CJ}$  is substituted or

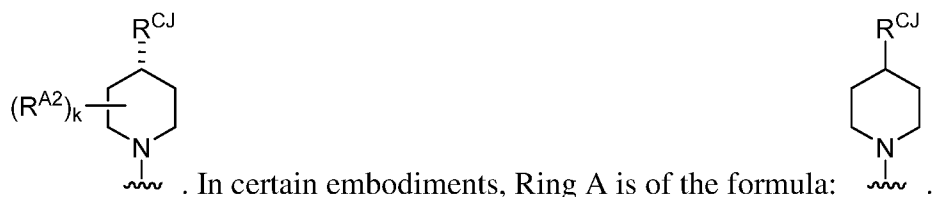
unsubstituted piperidinyl. In certain embodiments, Ring A is of the formula:



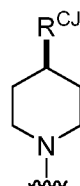
certain embodiments, Ring A is of the formula:



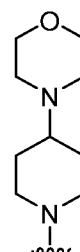
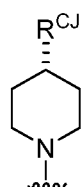
A is of the formula:

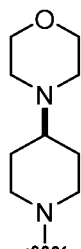


In certain embodiments, Ring A is of the formula:

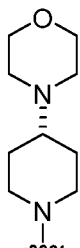


of the formula:

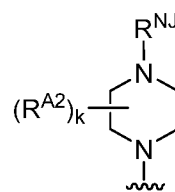




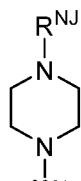
embodiments, Ring A is of the formula: . In certain embodiments, Ring A is of the




formula: .



**[00141]** In certain embodiments, Ring A is of the formula: . In certain



embodiments, Ring A is of the formula: . In certain embodiments,  $R^{NJ}$  is hydrogen. In certain embodiments,  $R^{NJ}$  is substituted alkyl. In certain embodiments,  $R^{NJ}$  is unsubstituted alkyl. In certain embodiments,  $R^{NJ}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{NJ}$  is methyl. In certain embodiments,  $R^{NJ}$  is ethyl. In certain embodiments,  $R^{NJ}$  is propyl. In certain embodiments,  $R^{NJ}$  is ethyl. In certain embodiments,  $R^{NJ}$  is a nitrogen protecting group. In certain embodiments,  $R^{NJ}$  is ethyl. In certain embodiments,  $R^{NJ}$  is Boc.

**[00142]** In compounds of Formula (I), Ring A may be substituted with one or more  $R^A$  groups when the  $R^A$  group is attached to a carbon atom. In certain embodiments, at least one  $R^A$  is halogen. In certain embodiments, at least one  $R^A$  is F. In certain embodiments, at least one  $R^A$  is Cl. In certain embodiments, at least one  $R^A$  is Br. In certain embodiments, at least one  $R^A$  is I (iodine). In certain embodiments, at least one  $R^A$  is substituted alkyl. In certain embodiments, at least one  $R^A$  is unsubstituted alkyl. In certain embodiments, at least one  $R^A$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^A$  is methyl. In certain embodiments, at least one  $R^A$  is ethyl. In certain embodiments, at least one  $R^A$  is propyl. In certain embodiments, at least one  $R^A$  is substituted alkenyl. In certain embodiments, at least one  $R^A$  is unsubstituted alkenyl. In certain embodiments, at least one  $R^A$  is vinyl. In certain

embodiments, at least one  $R^A$  is substituted alkynyl. In certain embodiments, at least one  $R^A$  is unsubstituted alkynyl. In certain embodiments, at least one  $R^A$  is ethynyl. In certain embodiments, at least one  $R^A$  is substituted carbocyclyl. In certain embodiments, at least one  $R^A$  is unsubstituted carbocyclyl. In certain embodiments, at least one  $R^A$  is substituted heterocyclyl. In certain embodiments, at least one  $R^A$  is unsubstituted heterocyclyl. In certain embodiments, at least one  $R^A$  is substituted aryl. In certain embodiments, at least one  $R^A$  is unsubstituted aryl. In certain embodiments, at least one  $R^A$  is substituted phenyl. In certain embodiments, at least one  $R^A$  is unsubstituted phenyl. In certain embodiments, at least one  $R^A$  is substituted heteroaryl. In certain embodiments, at least one  $R^A$  is  $-OR^a$ , wherein  $R^a$  is as defined herein. In certain embodiments, at least one  $R^A$  is  $-OR^{Aa}$ , wherein  $R^{Aa}$  is hydrogen. In certain embodiments, at least one  $R^A$  is  $-OR^a$ , wherein  $R^a$  is hydrogen or substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^A$  is  $-OR^a$ , wherein  $R^a$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^A$  is  $-OCH_3$ . In certain embodiments, at least one  $R^A$  is  $-N(R^a)_2$ , wherein  $R^a$  is hydrogen or substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^A$  is  $-NHR^a$ . In certain embodiments, at least one  $R^A$  is  $-SR^a$ .

**[00143]** In compounds of Formula (I), Ring A may be substituted with one or more  $R^A$  groups as valency permits. In certain embodiments,  $k$  is 0. In certain embodiments,  $k$  is 1. In certain embodiments,  $k$  is 2. In certain embodiments,  $k$  is 3. In certain embodiments,  $k$  is 5. In certain embodiments,  $k$  is 6.

**[00144]** 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. In certain embodiments, at least one instance of  $R^{A1}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

**[00145]** In certain embodiments, at least one  $R^{A1}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group. In certain embodiments, all instances of  $R^{A1}$  are each independently hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group. In certain embodiments, all instances of  $R^{A1}$  are hydrogen.

**[00146]** 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  $C_{1-6}$  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  $-OR^{A2a}$ , wherein  $R^{A2a}$  is as defined herein. In certain embodiments, at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is hydrogen. In certain embodiments, at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^{A2}$  is  $-OCH_3$ . In certain embodiments, at least one  $R^{A2}$  is  $-N(R^{A2a})_2$ . In certain embodiments, at least one  $R^{A2}$  is  $-SR^{A2a}$ . In certain embodiments, all instances of  $R^{A2}$  are hydrogen.

**[00147]** In certain embodiments, all  $R^{A1}$  and  $R^{A2}$  are hydrogen. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is substituted or unsubstituted alkyl. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is unsubstituted alkyl. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is methyl, ethyl, or n-propyl. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is as defined herein. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is  $-OR^{A2a}$ , wherein  $R^{A2a}$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^{A1}$  is hydrogen; and at least one  $R^{A2}$  is  $-OCH_3$ .

**[00148]** In certain embodiments,  $R^a$  is H. In certain embodiments,  $R^a$  is halogen. In certain embodiments,  $R^a$  is F. In certain embodiments,  $R^a$  is Cl. In certain embodiments,  $R^a$  is Br. In certain embodiments,  $R^a$  is I (iodine). In certain embodiments,  $R^a$  is substituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^a$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^a$  is methyl. In certain embodiments,  $R^a$  is ethyl. In certain embodiments, at least one  $R^a$  is H. In certain embodiments, each  $R^a$  is H. In certain embodiments, at least one  $R^a$  is halogen (*e.g.*, F, Cl, Br, or I (iodine)). In certain embodiments, at least one  $R^a$  is substituted or unsubstituted alkyl. In certain embodiments, at least one  $R^a$  is substituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^a$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^a$  is Me. In certain

embodiments, at least one  $R^a$  is substituted methyl (*e.g.*,  $-\text{CF}_3$  or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl). In certain embodiments, at least one  $R^a$  is substituted or unsubstituted alkenyl or substituted or unsubstituted alkynyl. In certain embodiments, at least one  $R^a$  is substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In certain embodiments, at least one  $R^a$  is a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom. In certain embodiments, two instances of  $R^a$  are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring.

**[00149]** As generally defined herein,  $R^{B1}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^a$ ,  $-\text{N}(\text{R}^a)_2$ ,  $-\text{SR}^a$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^a)\text{R}^a$ ,  $-\text{C}(=\text{NR}^a)\text{OR}^a$ ,  $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$ ,  $-\text{C}(=\text{O})\text{R}^a$ ,  $-\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{OC}(=\text{O})\text{R}^a$ ,  $-\text{OC}(=\text{O})\text{OR}^a$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$ , wherein  $R^a$  is as defined herein. In certain embodiments,  $R^{B1}$  is H. In certain embodiments,  $R^{B1}$  is halogen. In certain embodiments,  $R^{B1}$  is F. In certain embodiments,  $R^{B1}$  is Cl. In certain embodiments,  $R^{B1}$  is Br. In certain embodiments,  $R^{B1}$  is I (iodine). In certain embodiments,  $R^{B1}$  is substituted alkyl. In certain embodiments,  $R^{B1}$  is unsubstituted alkyl. In certain embodiments,  $R^{B1}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $R^{B1}$  is methyl. In certain embodiments,  $R^{B1}$  is ethyl. In certain embodiments,  $R^{B1}$  is propyl. In certain embodiments,  $R^{B1}$  is butyl. In certain embodiments,  $R^{B1}$  is  $-\text{OR}^{B1a}$ , wherein  $R^{B1a}$  is hydrogen or substituted or unsubstituted alkyl. In certain embodiments,  $R^{B1}$  is  $-\text{N}(\text{R}^{B1a})_2$ , wherein each instance of  $R^{B1a}$  is independently H or substituted or unsubstituted alkyl. In certain embodiments,  $R^{B1}$  is  $-\text{NHR}^{B1a}$ , wherein  $R^{B1a}$  is independently H or substituted or unsubstituted alkyl. In certain embodiments,  $R^{B1}$  is  $-\text{NH}_2$ ,

**[00150]** As generally defined herein,  $R^{B2}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-\text{OR}^a$ ,  $-\text{N}(\text{R}^a)_2$ ,  $-\text{SR}^a$ ,  $-\text{CN}$ ,  $-\text{SCN}$ ,  $-\text{C}(=\text{NR}^a)\text{R}^a$ ,  $-\text{C}(=\text{NR}^a)\text{OR}^a$ ,  $-\text{C}(=\text{NR}^a)\text{N}(\text{R}^a)_2$ ,  $-\text{C}(=\text{O})\text{R}^a$ ,  $-\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{NO}_2$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{R}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{OR}^a$ ,  $-\text{NR}^a\text{C}(=\text{O})\text{N}(\text{R}^a)_2$ ,  $-\text{OC}(=\text{O})\text{R}^a$ ,  $-\text{OC}(=\text{O})\text{OR}^a$ , or  $-\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$ ,

$\text{OC}(=\text{O})\text{N}(\text{R}^a)_2$ , wherein  $\text{R}^a$  is as defined herein. In certain embodiments,  $\text{R}^{\text{B}2}$  is H. In certain embodiments,  $\text{R}^{\text{B}2}$  is halogen. In certain embodiments,  $\text{R}^{\text{B}2}$  is F. In certain embodiments,  $\text{R}^{\text{B}2}$  is Cl. In certain embodiments,  $\text{R}^{\text{B}2}$  is Br. In certain embodiments,  $\text{R}^{\text{B}2}$  is I (iodine). In certain embodiments,  $\text{R}^{\text{B}2}$  is substituted alkyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is methyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is ethyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is propyl.

**[00151]** In certain embodiments,  $\text{R}^{\text{B}1}$  and  $\text{R}^{\text{B}2}$  are the same. In certain embodiments,  $\text{R}^{\text{B}1}$  and  $\text{R}^{\text{B}2}$  are different. In certain embodiments, both  $\text{R}^{\text{B}1}$  and  $\text{R}^{\text{B}2}$  are hydrogen. In certain embodiments,  $\text{R}^{\text{B}1}$  is hydrogen and  $\text{R}^{\text{B}2}$  is hydrogen, halogen, substituted or unsubstituted alkyl,  $-\text{OR}^a$ , or  $-\text{N}(\text{R}^a)_2$ , wherein each instance of  $\text{R}^a$  is independently hydrogen or substituted or unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}1}$  is hydrogen and  $\text{R}^{\text{B}2}$  is halogen. In certain embodiments,  $\text{R}^{\text{B}1}$  is hydrogen and  $\text{R}^{\text{B}2}$  is substituted or unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}1}$  is hydrogen and  $\text{R}^{\text{B}2}$  is unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}1}$  is hydrogen and  $\text{R}^{\text{B}2}$  is methyl or ethyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is hydrogen, halogen, substituted or unsubstituted alkyl,  $-\text{OR}^a$ , or  $-\text{N}(\text{R}^a)_2$ , wherein each instance of  $\text{R}^a$  is independently hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to oxygen, or a nitrogen protecting group when attached to nitrogen. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is halogen. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is substituted or unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is methyl or ethyl. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is  $-\text{OR}^a$ , wherein  $\text{R}^a$  is independently hydrogen, substituted or unsubstituted alkyl, or an oxygen protecting group. In certain embodiments,  $\text{R}^{\text{B}2}$  is hydrogen and  $\text{R}^{\text{B}1}$  is  $-\text{N}(\text{R}^a)$ , wherein each instance of  $\text{R}^a$  is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group.

**[00152]** In compounds of Formula (I),  $\text{L}^1$  is a divalent linker moiety connecting Ring A and Ring B.  $\text{L}^1$  may be a bond,  $-\text{C}(\text{R}^b)_2-$ ,  $-\text{C}(=\text{O})-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{S}(=\text{O})-$ ,  $-\text{S}(=\text{O})_2-$ , or  $-\text{NR}^c-$ ; wherein  $\text{R}^b$  and  $\text{R}^c$  are as defined herein. In certain embodiments,  $\text{L}^1$  is a bond. In certain embodiments,  $\text{L}^1$  is  $-\text{O}-$  or  $-\text{S}-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{O}-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{S}-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{NR}^c-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{NH}-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{C}(\text{R}^b)_2-$ . In certain embodiments,  $\text{L}^1$  is  $-\text{CH}_2-$ .

**[00153]** In certain embodiments,  $\text{R}^b$  is H. In certain embodiments,  $\text{R}^b$  is halogen. In certain embodiments,  $\text{R}^b$  is F. In certain embodiments,  $\text{R}^b$  is Cl. In certain embodiments,  $\text{R}^b$  is Br. In certain embodiments,  $\text{R}^b$  is I (iodine). In certain embodiments,  $\text{R}^b$  is substituted  $\text{C}_{1-6}$  alkyl. In

certain embodiments,  $R^b$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^b$  is methyl. In certain embodiments,  $R^b$  is ethyl. In certain embodiments, at least one  $R^b$  is H. In certain embodiments, each  $R^b$  is H. In certain embodiments, at least one  $R^b$  is halogen (*e.g.*, F, Cl, Br, or I (iodine)). In certain embodiments, at least one  $R^b$  is substituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^b$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^b$  is Me. In certain embodiments, at least one  $R^b$  is substituted methyl (*e.g.*,  $-CF_3$  or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl).

**[00154]** In certain embodiments,  $R^c$  is H. In certain embodiments,  $R^c$  is substituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^c$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments,  $R^c$  is methyl. In certain embodiments,  $R^c$  is ethyl. In certain embodiments,  $R^c$  is a nitrogen protecting group. In certain embodiments,  $R^c$  is BOC, acetyl, or Ts. In certain embodiments, at least one  $R^c$  is H. In certain embodiments, each  $R^c$  is H. In certain embodiments, at least one  $R^c$  is halogen (*e.g.*, F, Cl, Br, or I (iodine)). In certain embodiments, at least one  $R^c$  is substituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^c$  is unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^c$  is Me. In certain embodiments, at least one  $R^c$  is substituted methyl (*e.g.*,  $-CF_3$  or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl). In certain embodiments, at least one  $R^c$  is a nitrogen protecting group.

**[00155]** In compounds of Formula (I), X is a divalent linker moiety connecting Ring B and Ring C. As generally defined herein, X is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ , or  $-NR^cS(=O)_2-$ . In certain embodiments, X is  $-O-$ . In certain embodiments, X is  $-S-$ . In certain embodiments, X is  $-NR^c-$ , wherein  $R^c$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group. In certain embodiments, X is  $-NH-$ . In certain embodiments, X is  $-C(R^b)_2-$ . In certain embodiments, X is  $-CH_2-$ .

**[00156]** In certain embodiments,  $L^1$  is a bond,  $-O-$ ,  $-S-$ , or  $-NR^c-$ ; and X is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ , wherein  $R^b$  and  $R^c$  are as defined herein. In certain embodiments,  $L^1$  is a bond and X is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ , wherein  $R^b$  and  $R^c$  are as defined herein. In certain embodiments,  $L^1$  is a

bond and X is  $-O-$ . In certain embodiments,  $L^1$  is a bond and X is  $-S-$ . In certain embodiments,  $L^1$  is a bond and X is  $-NR^c-$ , wherein  $R^c$  is as defined herein. In certain embodiments,  $L^1$  is a bond and X is  $-NH-$ . In certain embodiments,  $L^1$  is  $-O-$  and X is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ , wherein  $R^b$  and  $R^c$  are as defined herein. In certain embodiments,  $L^1$  is  $-O-$  and X is  $-O-$ . In certain embodiments,  $L^1$  is  $-O-$  and X is  $-S-$ . In certain embodiments,  $L^1$  is  $-O-$  and X is  $-NR^c-$ , wherein  $R^c$  is as defined herein. In certain embodiments,  $L^1$  is  $-O-$  and X is  $-NH-$ . In certain embodiments,  $L^1$  is  $-NR^c-$  and X is  $-O-$ . In certain embodiments,  $L^1$  is  $-NR^c-$  and X is  $-S-$ . In certain embodiments,  $L^1$  is  $-NR^c-$  and X is independently  $-NR^c-$ , wherein  $R^c$  is as defined herein. In certain embodiments,  $L^1$  and X are  $-NH-$ .

**[00157]** In compounds of Formula (I),  $L^2$  is a divalent linker moiety connecting Ring C and Ring D.  $L^2$  may be  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ ,  $-NR^cS(=O)_2-$ ,  $-OC(=O)O-$ ,  $-NR^cC(=O)O-$ ,  $-OC(=O)NR^c-$ ,  $-NR^cC(=O)NR^c-$ ,  $-C(R^b)_2C(=O)C(R^b)_2-$ ,  $-OC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)O-$ ,  $-NR^cC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)NR^c-$ , or a substituted or unsubstituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ , wherein  $R^b$  and  $R^c$  are as defined herein. In certain embodiments,  $L^2$  is  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-C(=O)-$ ,  $-C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ , or  $-C(R^b)_2C(=O)NR^c-$ , wherein each instance of  $R^b$  is independently hydrogen, halogen, or substituted or unsubstituted  $C_{1-6}$  alkyl; and each instance of  $R^c$  is independently hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group. In certain embodiments,  $L^2$  is  $-C(=O)-$ . In certain embodiments,  $L^2$  is  $-C(R^b)_2-$ . In certain embodiments,  $L^2$  is  $-CH_2-$ . In certain embodiments,  $L^2$  is  $-NR^c-$ . In certain embodiments,  $L^2$  is  $-NH-$ . In certain embodiments,  $L^2$  is  $-NR^cC(=O)-$  or  $-C(=O)NR^c-$ . In certain embodiments,  $L^2$  is  $-NHC(=O)-$  or  $-C(=O)NH-$ . In certain embodiments,  $L^2$  is of the formula:  $-C(=O)NR^c-$ . In certain embodiments,  $L^2$  is of the formula:  $-C(=O)NH-$ . In certain embodiments,  $L^2$  is of the formula:  $-NR^cC(=O)-$ . In certain embodiments,  $L^2$  is of the formula:  $-NHC(=O)-$ . In certain embodiments,  $L^2$  is of the formula:  $-C(=O)NH-$  or  $-NH(=O)-$ . In certain embodiments,  $L^2$  is of the formula:  $-C(R^b)_2C(=O)-$ . In certain embodiments,  $L^2$  is of the formula:  $-CH_2C(=O)-$ .

In certain embodiments,  $L^2$  is of the formula:  $-C(R^b)_2C(=O)NR^c-$ . In certain embodiments,  $L^2$  is of the formula:  $-CH_2C(=O)NR^c-$ . In certain embodiments,  $L^2$  is of the formula:  $-CH_2C(=O)NH-$ .

**[00158]** As generally defined herein, Ring C is a substituted or unsubstituted phenyl ring. In certain embodiments, Ring C is a substituted phenyl ring. In certain embodiments, Ring C is an unsubstituted phenyl ring. In certain embodiments, Ring C is a substituted or unsubstituted 1,2-phenylene moiety. In certain embodiments, Ring C is a substituted or unsubstituted 1,3-phenylene moiety. In certain embodiments, Ring C is a substituted or unsubstituted 1,4-phenylene moiety. Ring C may be unsubstituted or may be substituted with one or more  $R^C$  groups. In certain embodiments, at least one  $R^C$  is halogen. In certain embodiments, at least one  $R^C$  is F. In certain embodiments, at least one  $R^C$  is Cl. In certain embodiments, at least one  $R^C$  is Br. In certain embodiments, at least one  $R^C$  is I (iodine). In certain embodiments, at least one  $R^C$  is substituted alkyl. In certain embodiments, at least one  $R^C$  is unsubstituted alkyl. In certain embodiments, at least one  $R^C$  is  $C_{1-6}$  alkyl. In certain embodiments, at least one  $R^C$  is methyl. In certain embodiments, at least one  $R^C$  is ethyl. In certain embodiments, at least one  $R^C$  is propyl. In certain embodiments, at least one  $R^C$  is substituted alkenyl. In certain embodiments, at least one  $R^C$  is unsubstituted alkenyl. In certain embodiments, at least one  $R^C$  is vinyl. In certain embodiments, at least one  $R^C$  is substituted alkynyl. In certain embodiments, at least one  $R^C$  is unsubstituted alkynyl. In certain embodiments, at least one  $R^C$  is ethynyl. In certain embodiments, at least one  $R^C$  is substituted carbocyclyl. In certain embodiments, at least one  $R^C$  is unsubstituted carbocyclyl. In certain embodiments, at least one  $R^C$  is substituted heterocyclyl. In certain embodiments, at least one  $R^C$  is unsubstituted heterocyclyl. In certain embodiments, at least one  $R^C$  is substituted aryl. In certain embodiments, at least one  $R^C$  is unsubstituted aryl. In certain embodiments, at least one  $R^C$  is substituted phenyl. In certain embodiments, at least one  $R^C$  is unsubstituted phenyl. In certain embodiments, at least one  $R^C$  is substituted heteroaryl. In certain embodiments, at least one  $R^C$  is unsubstituted heteroaryl. In certain embodiments, each instance of  $R^C$  is independently halogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or  $-OR^a$  (e.g.,  $-OH$  or  $-O$ (substituted or unsubstituted  $C_{1-6}$  alkyl)).

**[00159]** In certain embodiments, Ring C is a substituted phenyl ring and at least one  $R^C$  is independently halogen or substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, Ring C is a substituted phenyl ring and at least one  $R^C$  is independently halogen. In certain embodiments, Ring C is a substituted phenyl ring and at least one  $R^C$  is substituted or unsubstituted  $C_{1-6}$  alkyl. In certain embodiments, Ring C is a substituted phenyl ring and one

R<sup>C</sup> is substituted or unsubstituted C<sub>1-6</sub> alkyl. In certain embodiments, Ring C is a substituted phenyl ring and one R<sup>C</sup> is unsubstituted C<sub>1-6</sub> alkyl (*e.g.* methyl or ethyl).

**[00160]** Ring C may be unsubstituted or substituted with one or more R<sup>C</sup> groups as valency permits. In certain embodiments, Ring C is a substituted or unsubstituted phenyl ring and n is 0, 1, 2, 3, or 4. In certain embodiments, Ring C is unsubstituted, and thus 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.

**[00161]** As generally defined herein, Ring D is a substituted or unsubstituted phenyl ring. In certain embodiments, Ring D is a substituted phenyl ring. In certain embodiments, Ring D is an unsubstituted phenyl ring. In certain embodiments, Ring D is a substituted or unsubstituted 1,2-phenylene moiety. In certain embodiments, Ring D is a substituted or unsubstituted 1,3-phenylene moiety. In certain embodiments, Ring D is a substituted or unsubstituted 1,4-phenylene moiety.

**[00162]** In certain embodiments, Ring C is an unsubstituted phenyl ring and Ring D is a substituted or unsubstituted phenyl ring. In certain embodiments, Ring C is an unsubstituted phenyl ring and Ring D is an unsubstituted phenyl ring. In certain embodiments, Ring C is an unsubstituted phenyl ring and Ring D is a substituted phenyl ring. In certain embodiments, Ring C is a substituted phenyl ring and Ring D is a substituted phenyl ring. In certain embodiments, Ring C is a substituted phenyl ring and Ring D is an unsubstituted phenyl ring.

**[00163]** In compounds of Formula (I), Ring D is substituted with R<sup>E</sup> and may also be substituted with one or more R<sup>D</sup> groups. In certain embodiments, at least one R<sup>D</sup> is H. In certain embodiments, at least one R<sup>D</sup> is halogen. In certain embodiments, at least one R<sup>D</sup> is F. In certain embodiments, at least one R<sup>D</sup> is Cl. In certain embodiments, at least one R<sup>D</sup> is Br. In certain embodiments, at least one R<sup>D</sup> is I (iodine). In certain embodiments, at least one R<sup>D</sup> is substituted alkyl. In certain embodiments, at least one R<sup>D</sup> is unsubstituted alkyl. In certain embodiments, at least one R<sup>D</sup> is C<sub>1-6</sub> alkyl. In certain embodiments, at least one R<sup>D</sup> is methyl. In certain embodiments, at least one R<sup>D</sup> is ethyl. In certain embodiments, at least one R<sup>D</sup> is propyl. In certain embodiments, each instance of R<sup>C</sup> is independently halogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, or -OR<sup>a</sup> (*e.g.*, -OH or -O(substituted or unsubstituted C<sub>1-6</sub> alkyl)).

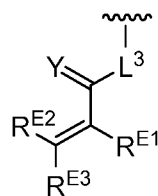
**[00164]** Ring D may be unsubstituted or substituted with one or more R<sup>D</sup> groups. In certain embodiments, Ring D is unsubstituted, and thus p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3. In certain embodiments, p is 4.

**[00165]** In certain embodiments, R<sup>D</sup> is halogen; and p is 1. In certain embodiments, R<sup>D</sup> is F; and p is 1. In certain embodiments, R<sup>D</sup> is Cl; and p is 1. In certain embodiments, R<sup>D</sup> is Br;

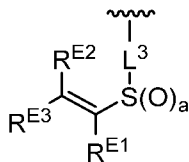
and p is 1. In certain embodiments,  $R^D$  is I (iodine); and p is 1. In certain embodiments,  $R^D$  is substituted alkyl; and p is 1. In certain embodiments,  $R^D$  is unsubstituted alkyl; and p is 1. In certain embodiments,  $R^D$  is  $C_{1-6}$  alkyl; and p is 1. In certain embodiments,  $R^D$  is methyl; and p is 1. In certain embodiments,  $R^D$  is ethyl, propyl, or butyl; and p is 1. In certain embodiments, each instance of  $R^D$  is independently halogen or substituted or unsubstituted alkyl; and p is 2. In certain embodiments, each instance of  $R^D$  is independently halogen or  $C_{1-6}$  alkyl; and p is 2.

**[00166]** In compounds of Formula (I), Ring D also includes a substituent  $R^E$ . In certain embodiments,  $R^E$  comprises a Michael acceptor moiety. This Michael acceptor moiety may react with a cysteine residue of a kinase (*e.g.*, PIP4K) to allow covalent attachment of the compound to the kinase. In certain embodiments, the covalent attachment is irreversible. In other embodiments, the covalent attachment is reversible.

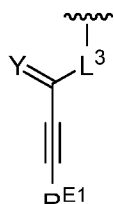
**[00167]** As generally defined herein in Formula (I),  $R^E$  may be any one of Formulae (i-1)-



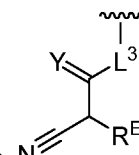
(i-41). In certain embodiments,  $R^E$  is of Formula (i-1): (i-1). In certain



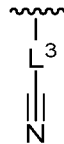
embodiments,  $R^E$  is of Formula (i-2): (i-2). In certain embodiments,  $R^E$  is of



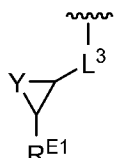
Formula (i-3): (i-3). In certain embodiments,  $R^E$  is of Formula (i-4): (i-4). In certain embodiments,  $R^E$  is of

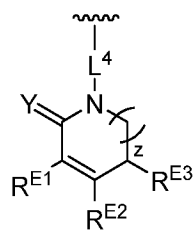


4). In certain embodiments,  $R^E$  is of Formula (i-5): (i-5). In certain embodiments,  $R^E$  is

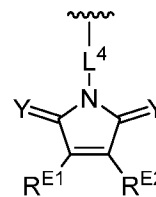


of Formula (i-6): (i-6). In certain embodiments,  $R^E$  is of Formula (i-7):

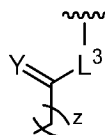




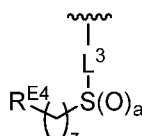
(i-7). In certain embodiments,  $R^E$  is of Formula (i-8):



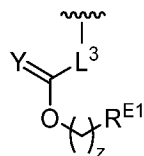
(i-8). In



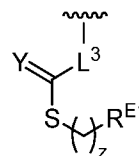
certain embodiments,  $R^E$  is of Formula (i-9):  $R^E4$  (i-9). In certain embodiments,  $R^E$  is



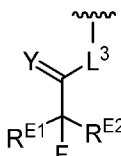
of Formula (i-10): (i-10). In certain embodiments,  $R^E$  is of Formula (i-11):



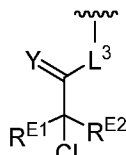
(i-11). In certain embodiments,  $R^E$  is of Formula (i-12):



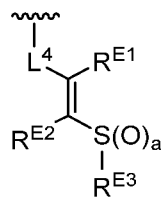
(i-12). In



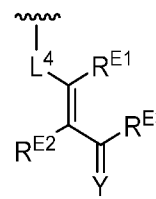
certain embodiments,  $R^E$  is of Formula (i-13): (i-13). In certain embodiments,  $R^E$  is



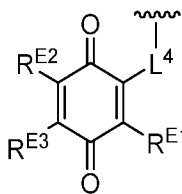
of Formula (i-14): (i-14). In certain embodiments,  $R^E$  is of Formula (i-15):



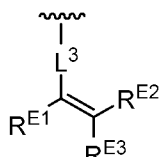
(i-15). In certain embodiments,  $R^E$  is of Formula (i-16):



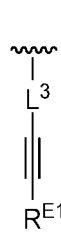
(i-16). In



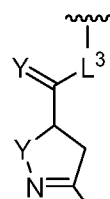
certain embodiments,  $R^E$  is of Formula (i-17): (i-17). In certain embodiments,



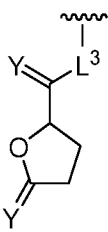
$R^E$  is of Formula (i-18): (i-18). In certain embodiments,  $R^E$  is of Formula (i-19):



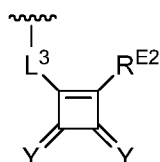
$R^{E1}$  (i-19). In certain embodiments,  $R^E$  is of Formula (i-20):



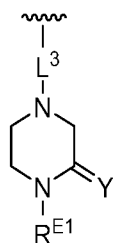
(i-20). In certain



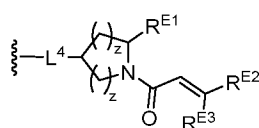
embodiments,  $R^E$  is of Formula (i-21): (i-21). In certain embodiments,  $R^E$  is of



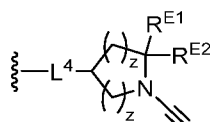
Formula (i-22): (i-22). In certain embodiments,  $R^E$  is of Formula (i-23):



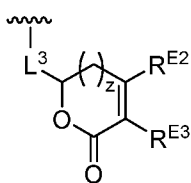
(i-23). In certain embodiments,  $R^E$  is of Formula (i-24):



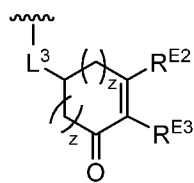
(i-24).



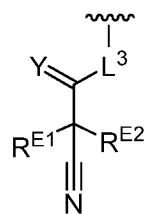
In certain embodiments,  $R^E$  is of Formula (i-25): (i-25). In certain



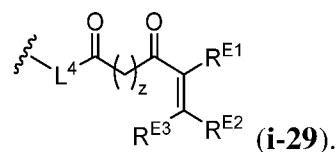
embodiments,  $R^E$  is of Formula (i-26): (i-26). In certain embodiments,  $R^E$  is



of Formula (i-27): (i-27). In certain embodiments,  $R^E$  is of Formula (i-28):

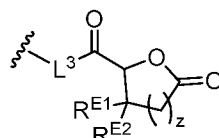


(i-28). In certain embodiments,  $R^E$  is of Formula (i-29):



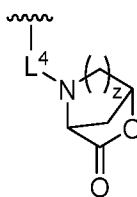
(i-29).

In certain embodiments,  $R^E$  is of Formula (i-30):



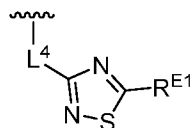
(i-30). In certain

embodiments,  $R^E$  is of Formula (i-31):

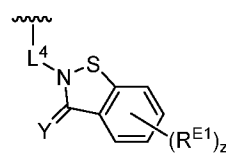


(i-31). In certain embodiments,  $R^E$  is of

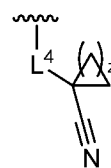
Formula (i-32):



(i-32). In certain embodiments,  $R^E$  is of Formula (i-33):

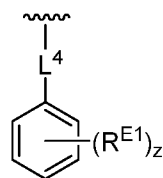


(i-33). In certain embodiments,  $R^E$  is of Formula (i-34):



(i-34). In

certain embodiments,  $R^E$  is of Formula (i-35):



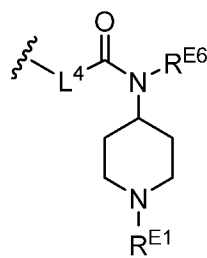
(i-35). In certain embodiments,

$R^E$  is of Formula (i-36):  $\text{---}L^3\text{---Cl}$  (i-36). In certain embodiments,  $R^E$  is of Formula (i-37):

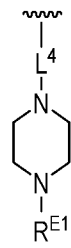
$\text{---}L^3\text{---Br}$  (i-37). In certain embodiments,  $R^E$  is of Formula (i-38):  $\text{---}L^3\text{---F}$  (i-38). In certain

embodiments,  $R^E$  is of Formula (i-39):  $\text{---}L^3\text{---CF}_3$  (i-39). In certain embodiments,  $R^E$  is of

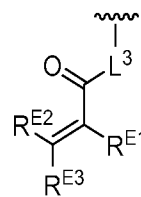
Formula (i-40):



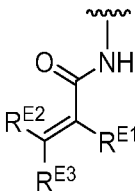
(i-40). In certain embodiments,  $R^E$  is of Formula (i-41):



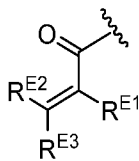
(i-41).



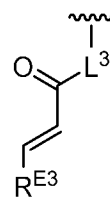
[00168] In certain embodiments,  $R^E$  is of Formula (i-1a): (i-1a). In certain



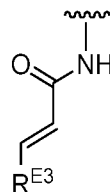
embodiments,  $R^E$  is of Formula (i-1b): (i-1b). In certain embodiments,  $R^E$  is of



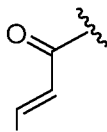
Formula (i-1c): (i-1c). In certain embodiments,  $R^E$  is of Formula (i-1d):



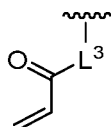
(i-1d). In certain embodiments,  $R^E$  is of Formula (i-1e):



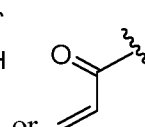
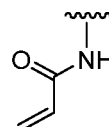
(i-1e). In certain



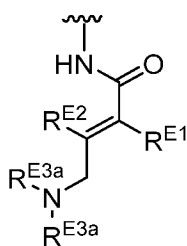
embodiments,  $R^E$  is of Formula (i-1f): (i-1f). In certain embodiments,  $R^E$  is of



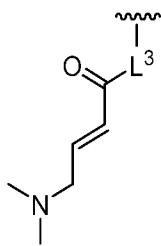
Formula (i-1g): (i-1g). In certain embodiments,  $R^E$  is



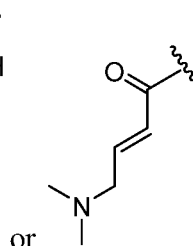
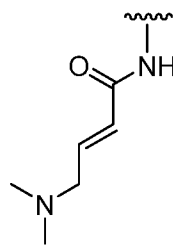
or . In certain



embodiments,  $R^E$  is of the formula: . In certain embodiments,  $R^E$  is of Formula

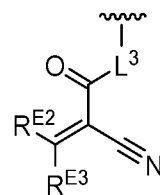


(i-1h): (i-1h). In certain embodiments,  $R^E$  is



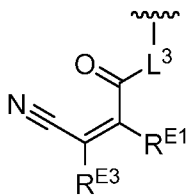
or .

[00169] In certain embodiments,  $R^E$  is of Formula (i-1a):



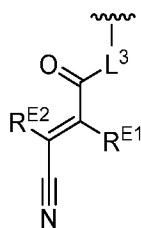
(i-1a). In certain

embodiments,  $R^E$  is of Formula (i-1b):



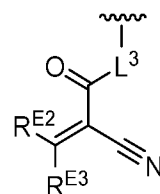
(i-1b). In certain embodiments,  $R^E$  is

of Formula (i-1c):



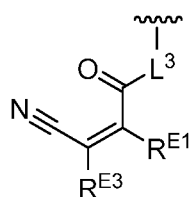
(i-1c).

[00170] In certain embodiments,  $R^E$  is of Formula (i-18a):



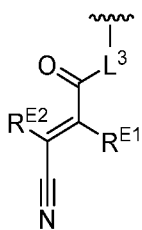
(i-18a). In certain

embodiments,  $R^E$  is of Formula (i-18b):

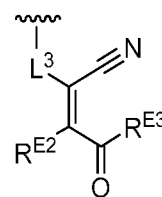


(i-18b). In certain embodiments,  $R^E$

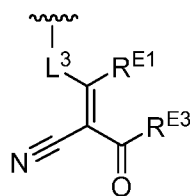
is of Formula (i-18c):



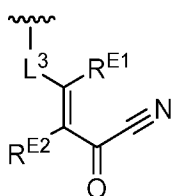
(i-18c).



[00171] In certain embodiments,  $R^E$  is of Formula (i-15a): (i-15a). In certain

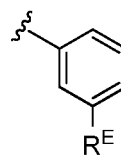


embodiments,  $R^E$  is of Formula (i-15b): (i-15b). In certain embodiments,  $R^E$

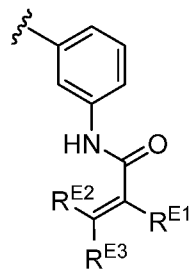


is of Formula (i-15c): (i-15c).

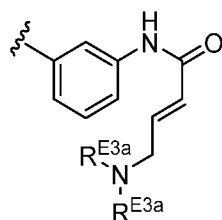
[00172] In certain embodiment, X and  $L^2$  are *para* or *meta* to each other. In certain embodiment, X and  $L^2$  are *para* to each other. In certain embodiments, X and  $L^2$  are *meta* to each other. In certain embodiment,  $R^E$  and  $L^2$  are *para* or *meta* to each other. In certain embodiments,  $R^E$  and  $L^2$  are *para* to each other. In certain embodiments,  $R^E$  and  $L^2$  are *meta*



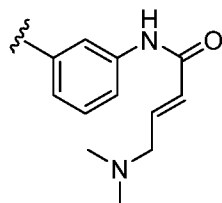
to each other. In certain embodiments, Ring D is of the formula:



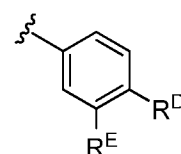
embodiments, Ring D is of the formula: . In certain embodiments, Ring D is of



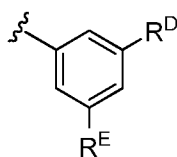
the formula: . In certain embodiments, Ring D is of the formula:



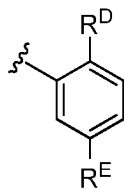
. In certain embodiments, Ring D is of the formula:



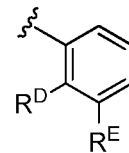
. In



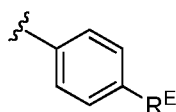
certain embodiments, Ring D is of the formula: . In certain embodiments, Ring



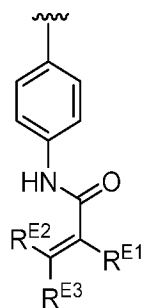
D is of the formula: . In certain embodiments, Ring D is of the formula:



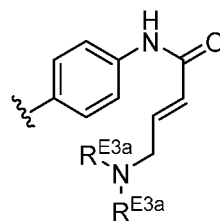
**[00173]** In certain embodiments,  $R^E$  and  $L^2$  are *para* to each other. In certain embodiments,



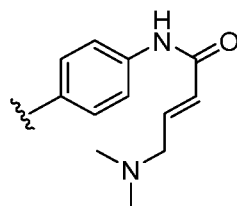
Ring D is of the formula: . In certain embodiments, Ring D is of the formula:



. In certain embodiments, Ring D is of the formula:

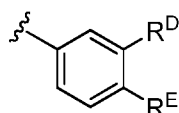


. In certain

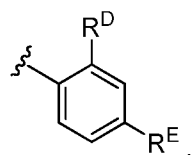


embodiments, Ring D is of the formula:

. In certain embodiments, Ring D



is of the formula: . In certain embodiments, Ring D is of the formula:



**[00174]** In compounds of Formula (I),  $L^3$  is a divalent linker moiety.  $L^3$  may contain 0-4 carbon or hetero atoms in the backbone of  $L^3$ .  $L^3$  may be saturated or unsaturated.  $L^3$  may be substituted or unsubstituted.  $L^3$  may be branched or unbranched. In certain embodiments,  $L^3$  is a bond. In certain embodiments,  $L^3$  is  $-O-$ . In certain embodiments,  $L^3$  is  $-S-$ . In certain embodiments,  $L^3$  is  $-NR^{L3a}-$ . In certain embodiments,  $L^3$  is  $-NH-$ . In certain embodiments,  $L^3$  is a substituted  $C_{1-4}$  hydrocarbon chain. In certain embodiments,  $L^3$  is an unsubstituted  $C_{1-4}$  hydrocarbon chain. In certain embodiments,  $L^3$  is  $-C(R^{L3b})_2-$ . In certain embodiments,  $L^3$  is

$-\text{CHR}^{\text{L3b}}-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{CH}_2-$ . In certain embodiments,  $\text{L}^3$  is a substituted  $\text{C}_2$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is an unsubstituted  $\text{C}_2$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is  $-\text{C}(\text{R}^{\text{L3b}})_2\text{C}(\text{R}^{\text{L3b}})_2-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{CH}_2\text{CH}_2-$ . In certain embodiments,  $\text{L}^3$  is *trans*- $\text{CR}^{\text{L3b}}=\text{CR}^{\text{L3b}}-$ . In certain embodiments,  $\text{L}^3$  is *trans*- $\text{CH}=\text{CH}-$ . In certain embodiments,  $\text{L}^3$  is *cis*- $\text{CR}^{\text{L3b}}=\text{CR}^{\text{L3b}}-$ . In certain embodiments,  $\text{L}^3$  is *cis*- $\text{CH}=\text{CH}-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{C}\equiv\text{C}-$ . In certain embodiments,  $\text{L}^3$  is a substituted  $\text{C}_3$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is an unsubstituted  $\text{C}_3$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is  $-(\text{CH}_2)_3-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{CH}=\text{CH}-\text{CH}_2-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $\text{L}^3$  is  $-\text{CH}_2-\text{CH}=\text{CH}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $\text{L}^3$  is  $-\text{C}\equiv\text{C}-\text{CH}_2-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{CH}_2-\text{C}\equiv\text{C}-$ . In certain embodiments,  $\text{L}^3$  is a substituted  $\text{C}_4$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is an unsubstituted  $\text{C}_4$  hydrocarbon chain. In certain embodiments,  $\text{L}^3$  is  $-(\text{CH}_2)_4-$ . In certain embodiments,  $\text{L}^3$  is  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ , wherein each instance of  $\text{CH}=\text{CH}$  is independently *trans* or *cis*. In certain embodiments,  $\text{L}^3$  is  $-\text{CH}=\text{CH}-\text{C}\equiv\text{C}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $\text{L}^3$  is  $-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $\text{L}^3$  is  $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-$ . In certain embodiments,  $\text{L}^3$  is a substituted or unsubstituted  $\text{C}_{1-4}$  hydrocarbon chain, wherein one or more carbon units of the hydrocarbon chain is replaced with  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{NR}^{\text{L3a}}-$ ,  $-\text{NR}^{\text{L3a}}\text{C}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{NR}^{\text{L3a}}-$ ,  $-\text{SC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{S}-$ ,  $-\text{OC}(=\text{O})-$ ,  $-\text{C}(=\text{O})\text{O}-$ ,  $-\text{NR}^{\text{L3a}}\text{C}(=\text{S})-$ ,  $-\text{C}(=\text{S})\text{NR}^{\text{L3a}}-$ , *trans*- $\text{CR}^{\text{L3b}}=\text{CR}^{\text{L3b}}-$ , *cis*- $\text{CR}^{\text{L3b}}=\text{CR}^{\text{L3b}}-$ ,  $-\text{C}\equiv\text{C}-$ ,  $-\text{S}(=\text{O})_2\text{O}-$ ,  $-\text{OS}(=\text{O})_2-$ ,  $-\text{S}(=\text{O})_2\text{NR}^{\text{L3a}}-$ , or  $-\text{NR}^{\text{L3a}}\text{S}(=\text{O})_2-$ .

**[00175]** In certain embodiments,  $\text{R}^{\text{L3a}}$  is H. In certain embodiments,  $\text{R}^{\text{L3a}}$  is substituted alkyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is unsubstituted alkyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is methyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is ethyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is propyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is butyl. In certain embodiments,  $\text{R}^{\text{L3a}}$  is a nitrogen protecting group. In certain embodiments,  $\text{R}^{\text{L3a}}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

**[00176]** In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is H. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is halogen. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is F. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is Cl. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is Br. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is I (iodine). In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is substituted alkyl. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is unsubstituted alkyl. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments, at least one  $\text{R}^{\text{L3b}}$  is methyl. In certain

embodiments, at least one  $R^{L3b}$  is ethyl. In certain embodiments, at least one  $R^{L3b}$  is propyl. In certain embodiments, at least one  $R^{L3b}$  is butyl. In certain embodiments, at least one  $R^{L3b}$  is substituted alkenyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted alkenyl. In certain embodiments, at least one  $R^{L3b}$  is vinyl. In certain embodiments, at least one  $R^{L3b}$  is substituted alkynyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted alkynyl. In certain embodiments, at least one  $R^{L3b}$  is ethynyl. In certain embodiments, at least one  $R^{L3b}$  is substituted carbocyclyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted carbocyclyl. In certain embodiments, at least one  $R^{L3b}$  is substituted heterocyclyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted heterocyclyl. In certain embodiments, at least one  $R^{L3b}$  is substituted aryl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted aryl. In certain embodiments, at least one  $R^{L3b}$  is substituted phenyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted phenyl. In certain embodiments, at least one  $R^{L3b}$  is substituted heteroaryl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted heteroaryl. In certain embodiments, at least one  $R^{L3b}$  is substituted pyridyl. In certain embodiments, at least one  $R^{L3b}$  is unsubstituted pyridyl. In certain embodiments, two  $R^{L3b}$  groups are joined to form a substituted carbocyclic ring. In certain embodiments, two  $R^{L3b}$  groups are joined to form an unsubstituted carbocyclic ring. In certain embodiments, two  $R^{L3b}$  groups are joined to form a substituted heterocyclic ring. In certain embodiments, two  $R^{L3b}$  groups are joined to form an unsubstituted heterocyclic ring.

**[00177]** In compounds of Formula (I),  $L^4$  is a divalent linker moiety.  $L^4$  may contain 0-4 carbon or hetero atoms in the backbone of  $L^4$ .  $L^4$  may be saturated or unsaturated.  $L^4$  may be substituted or unsubstituted.  $L^4$  may be branched or unbranched. In certain embodiments,  $L^4$  is a bond. In certain embodiments,  $L^4$  is a substituted  $C_{1-4}$  hydrocarbon chain. In certain embodiments,  $L^4$  is an unsubstituted  $C_{1-4}$  hydrocarbon chain. In certain embodiments,  $L^4$  is  $-C(R^{L4b})_2-$ . In certain embodiments,  $L^4$  is  $-CHR^{L4b}-$ . In certain embodiments,  $L^4$  is  $-CH_2-$ . In certain embodiments,  $L^4$  is a substituted  $C_2$  hydrocarbon chain. In certain embodiments,  $L^4$  is an unsubstituted  $C_2$  hydrocarbon chain. In certain embodiments,  $L^4$  is  $-C(R^{L4b})_2C(R^{L4b})_2-$ . In certain embodiments,  $L^4$  is  $-CH_2CH_2-$ . In certain embodiments,  $L^4$  is *trans*- $CR^{L4b}=CR^{L4b}-$ . In certain embodiments,  $L^4$  is *trans*- $CH=CH-$ . In certain embodiments,  $L^4$  is *cis*- $CR^{L4b}=CR^{L4b}-$ . In certain embodiments,  $L^4$  is *cis*- $CH=CH-$ . In certain embodiments,  $L^4$  is  $-C\equiv C-$ . In certain embodiments,  $L^4$  is a substituted  $C_3$  hydrocarbon chain. In certain embodiments,  $L^4$  is an unsubstituted  $C_3$  hydrocarbon chain. In certain embodiments,  $L^4$  is  $-(CH_2)_3-$ . In certain embodiments,  $L^4$  is  $-CH=CH-CH_2-$ , wherein  $CH=CH$  is *trans* or *cis*. In

certain embodiments,  $L^4$  is  $-\text{CH}_2-\text{CH}=\text{CH}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $L^4$  is  $-\text{C}\equiv\text{C}-\text{CH}_2-$ . In certain embodiments,  $L^4$  is  $-\text{CH}_2-\text{C}\equiv\text{C}-$ . In certain embodiments,  $L^4$  is a substituted  $\text{C}_4$  hydrocarbon chain. In certain embodiments,  $L^4$  is an unsubstituted  $\text{C}_4$  hydrocarbon chain. In certain embodiments,  $L^4$  is  $-(\text{CH}_2)_4-$ . In certain embodiments,  $L^4$  is  $-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ , wherein each instance of  $\text{CH}=\text{CH}$  is independently *trans* or *cis*. In certain embodiments,  $L^4$  is  $-\text{CH}=\text{CH}-\text{C}\equiv\text{C}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $L^4$  is  $-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-$ , wherein  $\text{CH}=\text{CH}$  is *trans* or *cis*. In certain embodiments,  $L^4$  is  $-\text{C}\equiv\text{C}-\text{C}\equiv\text{C}-$ .

**[00178]** In compounds of Formula (I),  $R^E$  may include a substituent  $R^{E1}$ . In certain embodiments,  $R^{E1}$  is H. In certain embodiments,  $R^{E1}$  is halogen. In certain embodiments,  $R^{E1}$  is F. In certain embodiments,  $R^{E1}$  is Cl. In certain embodiments,  $R^{E1}$  is Br. In certain embodiments,  $R^{E1}$  is I (iodine). In certain embodiments,  $R^{E1}$  is substituted acyl. In certain embodiments,  $R^{E1}$  is unsubstituted acyl. In certain embodiments,  $R^{E1}$  is acetyl. In certain embodiments,  $R^{E1}$  is substituted acetyl. In certain embodiments,  $R^{E1}$  is substituted alkyl. In certain embodiments,  $R^{E1}$  is unsubstituted alkyl. In certain embodiments,  $R^{E1}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $R^{E1}$  is methyl. In certain embodiments,  $R^{E1}$  is ethyl. In certain embodiments,  $R^{E1}$  is propyl. In certain embodiments,  $R^{E1}$  is butyl. In certain embodiments,  $R^{E1}$  is substituted alkenyl. In certain embodiments,  $R^{E1}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E1}$  is vinyl. In certain embodiments,  $R^{E1}$  is substituted alkynyl. In certain embodiments,  $R^{E1}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E1}$  is ethynyl. In certain embodiments,  $R^{E1}$  is substituted carbocyclyl. In certain embodiments,  $R^{E1}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E1}$  is substituted heterocyclyl. In certain embodiments,  $R^{E1}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E1}$  is substituted aryl. In certain embodiments,  $R^{E1}$  is unsubstituted aryl. In certain embodiments,  $R^{E1}$  is substituted phenyl. In certain embodiments,  $R^{E1}$  is unsubstituted phenyl. In certain embodiments,  $R^{E1}$  is substituted heteroaryl. In certain embodiments,  $R^{E1}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E1}$  is substituted pyridyl. In certain embodiments,  $R^{E1}$  is unsubstituted pyridyl. In certain embodiments,  $R^{E1}$  is  $-\text{CN}$ . In certain embodiments,  $R^{E1}$  is  $-\text{OR}^{E1a}$ . In certain embodiments,  $R^{E1}$  is  $-\text{N}(\text{R}^{E1a})_2$ . In certain embodiments,  $R^{E1}$  is  $-\text{SR}^{E1a}$ . In certain embodiments,  $R^{E1}$  is  $-\text{CH}_2\text{OR}^{E1a}$ . In certain embodiments,  $R^{E1}$  is  $-\text{CH}_2\text{N}(\text{R}^{E1a})_2$ . In certain embodiments,  $R^{E1}$  is  $-\text{CH}_2\text{SR}^{E1a}$ .

**[00179]** In certain embodiments, when  $R^{E1}$  is  $-\text{OR}^{E1a}$ ,  $-\text{N}(\text{R}^{E1a})_2$ ,  $-\text{SR}^{E1a}$ ,  $-\text{CH}_2\text{OR}^{E1a}$ ,  $-\text{CH}_2\text{N}(\text{R}^{E1a})_2$ , or  $-\text{CH}_2\text{SR}^{E1a}$ ,  $R^{E1a}$  is H. In certain embodiments,  $R^{E1}$  is  $-\text{Si}(\text{R}^{E1a})_3$ , optionally

wherein each instance of  $R^{E1a}$  is independently unsubstituted  $C_{1-6}$  alkyl or unsubstituted phenyl. In certain embodiments,  $R^{E1}$  is  $-\text{Si}(\text{Me})_3$ . In certain embodiments,  $R^{E1a}$  is substituted acyl. In certain embodiments,  $R^{E1a}$  is unsubstituted acyl. In certain embodiments,  $R^{E1a}$  is acetyl. In certain embodiments,  $R^{E1a}$  is substituted acetyl. In certain embodiments,  $R^{E1a}$  is substituted alkyl. In certain embodiments,  $R^{E1a}$  is unsubstituted alkyl. In certain embodiments,  $R^{E1a}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{E1a}$  is methyl. In certain embodiments,  $R^{E1a}$  is ethyl. In certain embodiments,  $R^{E1a}$  is propyl. In certain embodiments,  $R^{E1a}$  is butyl. In certain embodiments,  $R^{E1a}$  is substituted alkenyl. In certain embodiments,  $R^{E1a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E1a}$  is vinyl. In certain embodiments,  $R^{E1a}$  is substituted alkynyl. In certain embodiments,  $R^{E1a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E1a}$  is ethynyl. In certain embodiments,  $R^{E1a}$  is substituted carbocyclyl. In certain embodiments,  $R^{E1a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E1a}$  is substituted heterocyclyl. In certain embodiments,  $R^{E1a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E1a}$  is substituted aryl. In certain embodiments,  $R^{E1a}$  is unsubstituted aryl. In certain embodiments,  $R^{E1a}$  is substituted phenyl. In certain embodiments,  $R^{E1a}$  is unsubstituted phenyl. In certain embodiments,  $R^{E1a}$  is substituted heteroaryl. In certain embodiments,  $R^{E1a}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E1a}$  is substituted pyridyl. In certain embodiments,  $R^{E1a}$  is unsubstituted pyridyl. In certain embodiments,  $R^{E1a}$  is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments,  $R^{E1a}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments,  $R^{E1a}$  is an oxygen protecting group when attached to an oxygen atom. In certain embodiments,  $R^{E1a}$  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,  $R^{E1a}$  is a sulfur protecting group when attached to a sulfur atom. In certain embodiments,  $R^{E1a}$  is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfonyl, 2-pyridine-sulfonyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two  $R^{E1a}$  groups are joined to form a substituted heterocyclic ring. In certain embodiments, two  $R^{E1a}$  groups are joined to form an unsubstituted heterocyclic ring.

**[00180]** In compounds of Formula (I),  $R^E$  may include a substituent  $R^{E2}$ . In certain embodiments,  $R^{E2}$  is H. In certain embodiments,  $R^{E2}$  is halogen. In certain embodiments,  $R^{E2}$  is F. In certain embodiments,  $R^{E2}$  is Cl. In certain embodiments,  $R^{E2}$  is Br. In certain embodiments,  $R^{E2}$  is I (iodine). In certain embodiments,  $R^{E2}$  is substituted acyl. In certain embodiments,  $R^{E2}$  is unsubstituted acyl. In certain embodiments,  $R^{E2}$  is acetyl. In certain embodiments,  $R^{E2}$  is substituted acetyl. In certain embodiments,  $R^{E2}$  is substituted alkyl. In

certain embodiments,  $R^{E2}$  is unsubstituted alkyl. In certain embodiments,  $R^{E2}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{E2}$  is methyl. In certain embodiments,  $R^{E2}$  is ethyl. In certain embodiments,  $R^{E2}$  is propyl. In certain embodiments,  $R^{E2}$  is butyl. In certain embodiments,  $R^{E2}$  is substituted alkenyl. In certain embodiments,  $R^{E2}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E2}$  is vinyl. In certain embodiments,  $R^{E2}$  is substituted alkynyl. In certain embodiments,  $R^{E2}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E2}$  is ethynyl. In certain embodiments,  $R^{E2}$  is substituted carbocyclyl. In certain embodiments,  $R^{E2}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E2}$  is substituted heterocyclyl. In certain embodiments,  $R^{E2}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E2}$  is substituted aryl. In certain embodiments,  $R^{E2}$  is unsubstituted aryl. In certain embodiments,  $R^{E2}$  is substituted phenyl. In certain embodiments,  $R^{E2}$  is unsubstituted phenyl. In certain embodiments,  $R^{E2}$  is substituted heteroaryl. In certain embodiments,  $R^{E2}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E2}$  is substituted pyridyl. In certain embodiments,  $R^{E2}$  is unsubstituted pyridyl. In certain embodiments,  $R^{E2}$  is  $-CN$ . In certain embodiments,  $R^{E2}$  is  $-OR^{E2a}$ . In certain embodiments,  $R^{E2}$  is  $-N(R^{E2a})_2$ . In certain embodiments,  $R^{E2}$  is  $-SR^{E2a}$ . In certain embodiments,  $R^{E2}$  is  $-CH_2OR^{E2a}$ . In certain embodiments,  $R^{E2}$  is  $-CH_2N(R^{E2a})_2$ . In certain embodiments,  $R^{E2}$  is  $-CH_2SR^{E2a}$ .

**[00181]** In certain embodiments, when  $R^{E2}$  is  $-OR^{E2a}$ ,  $-N(R^{E2a})_2$ ,  $-SR^{E2a}$ ,  $-CH_2OR^{E2a}$ ,  $-CH_2N(R^{E2a})_2$ , or  $-CH_2SR^{E2a}$ ,  $R^{E2a}$  is H. In certain embodiments,  $R^{E2a}$  is substituted acyl. In certain embodiments,  $R^{E2a}$  is unsubstituted acyl. In certain embodiments,  $R^{E2a}$  is acetyl. In certain embodiments,  $R^{E2a}$  is substituted acetyl. In certain embodiments,  $R^{E2a}$  is substituted alkyl. In certain embodiments,  $R^{E2a}$  is unsubstituted alkyl. In certain embodiments,  $R^{E2a}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{E2a}$  is methyl. In certain embodiments,  $R^{E2a}$  is ethyl. In certain embodiments,  $R^{E2a}$  is propyl. In certain embodiments,  $R^{E2a}$  is butyl. In certain embodiments,  $R^{E2a}$  is substituted alkenyl. In certain embodiments,  $R^{E2a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E2a}$  is vinyl. In certain embodiments,  $R^{E2a}$  is substituted alkynyl. In certain embodiments,  $R^{E2a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E2a}$  is ethynyl. In certain embodiments,  $R^{E2a}$  is substituted carbocyclyl. In certain embodiments,  $R^{E2a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E2a}$  is substituted heterocyclyl. In certain embodiments,  $R^{E2a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E2a}$  is substituted aryl. In certain embodiments,  $R^{E2a}$  is unsubstituted aryl. In certain embodiments,  $R^{E2a}$  is substituted phenyl. In certain embodiments,  $R^{E2a}$  is unsubstituted phenyl. In certain embodiments,  $R^{E2a}$  is substituted heteroaryl. In certain embodiments,  $R^{E2a}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E2a}$  is substituted pyridyl. In certain embodiments,  $R^{E2a}$

is unsubstituted pyridyl. In certain embodiments,  $R^{E2a}$  is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments,  $R^{E2a}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments,  $R^{E2a}$  is an oxygen protecting group when attached to an oxygen atom. In certain embodiments,  $R^{E2a}$  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,  $R^{E2a}$  is a sulfur protecting group when attached to a sulfur atom. In certain embodiments,  $R^{E2a}$  is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two  $R^{E2a}$  groups are joined to form a substituted heterocyclic ring. In certain embodiments, two  $R^{E2a}$  groups are joined to form an unsubstituted heterocyclic ring.

**[00182]** In compounds of Formula (I),  $R^E$  may include a substituent  $R^{E3}$ . In certain embodiments,  $R^{E3}$  is H. In certain embodiments,  $R^{E3}$  is halogen. In certain embodiments,  $R^{E3}$  is F. In certain embodiments,  $R^{E3}$  is Cl. In certain embodiments,  $R^{E3}$  is Br. In certain embodiments,  $R^{E3}$  is I (iodine). In certain embodiments,  $R^{E3}$  is substituted acyl. In certain embodiments,  $R^{E3}$  is unsubstituted acyl. In certain embodiments,  $R^{E3}$  is acetyl. In certain embodiments,  $R^{E3}$  is substituted acetyl. In certain embodiments,  $R^{E3}$  is substituted alkyl. In certain embodiments,  $R^{E3}$  is unsubstituted alkyl. In certain embodiments,  $R^{E3}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{E3}$  is methyl. In certain embodiments,  $R^{E3}$  is ethyl. In certain embodiments,  $R^{E3}$  is propyl. In certain embodiments,  $R^{E3}$  is butyl. In certain embodiments,  $R^{E3}$  is substituted alkenyl. In certain embodiments,  $R^{E3}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E3}$  is vinyl. In certain embodiments,  $R^{E3}$  is substituted alkynyl. In certain embodiments,  $R^{E3}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E3}$  is ethynyl. In certain embodiments,  $R^{E3}$  is substituted carbocyclyl. In certain embodiments,  $R^{E3}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E3}$  is substituted heterocyclyl. In certain embodiments,  $R^{E3}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E3}$  is substituted aryl. In certain embodiments,  $R^{E3}$  is unsubstituted aryl. In certain embodiments,  $R^{E3}$  is substituted phenyl. In certain embodiments,  $R^{E3}$  is unsubstituted phenyl. In certain embodiments,  $R^{E3}$  is substituted heteroaryl. In certain embodiments,  $R^{E3}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E3}$  is substituted pyridyl. In certain embodiments,  $R^{E3}$  is unsubstituted pyridyl. In certain embodiments,  $R^{E3}$  is  $-CN$ . In certain embodiments,  $R^{E3}$  is  $-OR^{E3a}$ . In certain embodiments,  $R^{E3}$  is  $-N(R^{E3a})_2$ . In certain embodiments,  $R^{E3}$  is  $-SR^{E3a}$ . In certain embodiments,  $R^{E3}$  is  $-CH_2OR^{E3a}$ . In certain embodiments,  $R^{E3}$  is  $-CH_2N(R^{E3a})_2$ . In certain embodiments,  $R^{E3}$  is  $-CH_2SR^{E3a}$ .

**[00183]** In certain embodiments, when  $R^{E3}$  is  $-OR^{E3a}$ ,  $-N(R^{E3a})_2$ ,  $-SR^{E3a}$ ,  $-CH_2OR^{E3a}$ ,  $-CH_2N(R^{E3a})_2$ , or  $-CH_2SR^{E3a}$ ,  $R^{E3a}$  is H. In certain embodiments,  $R^{E3a}$  is substituted acyl. In certain embodiments,  $R^{E3a}$  is unsubstituted acyl. In certain embodiments,  $R^{E3a}$  is acetyl. In certain embodiments,  $R^{E3a}$  is substituted acetyl. In certain embodiments,  $R^{E3a}$  is substituted alkyl. In certain embodiments,  $R^{E3a}$  is unsubstituted alkyl. In certain embodiments,  $R^{E3a}$  is  $C_{1-6}$  alkyl. In certain embodiments,  $R^{E3a}$  is methyl. In certain embodiments,  $R^{E3a}$  is ethyl. In certain embodiments,  $R^{E3a}$  is propyl. In certain embodiments,  $R^{E3a}$  is butyl. In certain embodiments,  $R^{E3a}$  is substituted alkenyl. In certain embodiments,  $R^{E3a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E3a}$  is vinyl. In certain embodiments,  $R^{E3a}$  is substituted alkynyl. In certain embodiments,  $R^{E3a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E3a}$  is ethynyl. In certain embodiments,  $R^{E3a}$  is substituted carbocyclyl. In certain embodiments,  $R^{E3a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E3a}$  is substituted heterocyclyl. In certain embodiments,  $R^{E3a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E3a}$  is substituted aryl. In certain embodiments,  $R^{E3a}$  is unsubstituted aryl. In certain embodiments,  $R^{E3a}$  is substituted phenyl. In certain embodiments,  $R^{E3a}$  is unsubstituted phenyl. In certain embodiments,  $R^{E3a}$  is substituted heteroaryl. In certain embodiments,  $R^{E3a}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E3a}$  is substituted pyridyl. In certain embodiments,  $R^{E3a}$  is unsubstituted pyridyl. In certain embodiments,  $R^{E3a}$  is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments,  $R^{E3a}$  is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom. In certain embodiments,  $R^{E3a}$  is an oxygen protecting group when attached to an oxygen atom. In certain embodiments,  $R^{E3a}$  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,  $R^{E3a}$  is a sulfur protecting group when attached to a sulfur atom. In certain embodiments,  $R^{E3a}$  is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two  $R^{E3a}$  groups are joined to form a substituted heterocyclic ring. In certain embodiments, two  $R^{E3a}$  groups are joined to form an unsubstituted heterocyclic ring.

**[00184]** In compounds of Formula (I),  $R^{E1}$  and  $R^{E3}$ , or  $R^{E2}$  and  $R^{E3}$ , or  $R^{E1}$  and  $R^{E2}$  may be joined to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring. In certain embodiments,  $R^{E1}$  and  $R^{E3}$  are joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments,  $R^{E1}$  and  $R^{E3}$  are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments,  $R^{E2}$  and  $R^{E3}$  are joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments,  $R^{E2}$  and  $R^{E3}$

are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments,  $R^{E1}$  and  $R^{E2}$  are joined to form a substituted or unsubstituted carbocyclic ring. In certain embodiments,  $R^{E1}$  and  $R^{E2}$  are joined to form a substituted or unsubstituted heterocyclic ring.

**[00185]** In compounds of Formula (I),  $R^E$  may include a substituent  $R^{E4}$ . In certain embodiments,  $R^{E4}$  is a leaving group. In certain embodiments,  $R^{E4}$  is halogen. In certain embodiments,  $R^{E4}$  is F. In certain embodiments,  $R^{E4}$  is Cl. In certain embodiments,  $R^{E4}$  is Br. In certain embodiments,  $R^{E4}$  is I (iodine). In certain embodiments,  $R^{E4}$  is  $-\text{OS}(=\text{O})_w R^{E4a}$ . In certain embodiments,  $w$  is 1. In certain embodiments,  $w$  is 2. In certain embodiments,  $R^{E4}$  is  $-\text{OMs}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OTf}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OTs}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OBs}$ . In certain embodiments,  $R^{E4}$  is 2-nitrobenzenesulfonyloxy. In certain embodiments,  $R^{E4}$  is  $-\text{OR}^{E4a}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OMe}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OCF}_3$ . In certain embodiments,  $R^{E4}$  is  $-\text{OPh}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})R^{E4a}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{Me}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{CF}_3$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{Ph}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{Cl}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{OR}^{E4a}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{OMe}$ . In certain embodiments,  $R^{E4}$  is  $-\text{OC}(=\text{O})\text{O}(t\text{-Bu})$ .

**[00186]** In certain embodiments,  $R^{E4a}$  is substituted alkyl. In certain embodiments,  $R^{E4a}$  is unsubstituted alkyl. In certain embodiments,  $R^{E4a}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $R^{E4a}$  is methyl. In certain embodiments,  $R^{E4a}$  is ethyl. In certain embodiments,  $R^{E4a}$  is propyl. In certain embodiments,  $R^{E4a}$  is butyl. In certain embodiments,  $R^{E4a}$  is substituted alkenyl. In certain embodiments,  $R^{E4a}$  is unsubstituted alkenyl. In certain embodiments,  $R^{E4a}$  is vinyl. In certain embodiments,  $R^{E4a}$  is substituted alkynyl. In certain embodiments,  $R^{E4a}$  is unsubstituted alkynyl. In certain embodiments,  $R^{E4a}$  is ethynyl. In certain embodiments,  $R^{E4a}$  is substituted carbocyclyl. In certain embodiments,  $R^{E4a}$  is unsubstituted carbocyclyl. In certain embodiments,  $R^{E4a}$  is substituted heterocyclyl. In certain embodiments,  $R^{E4a}$  is unsubstituted heterocyclyl. In certain embodiments,  $R^{E4a}$  is substituted aryl. In certain embodiments,  $R^{E4a}$  is unsubstituted aryl. In certain embodiments,  $R^{E4a}$  is substituted phenyl. In certain embodiments,  $R^{E4a}$  is unsubstituted phenyl. In certain embodiments,  $R^{E4a}$  is substituted heteroaryl. In certain embodiments,  $R^{E4a}$  is unsubstituted heteroaryl. In certain embodiments,  $R^{E4a}$  is substituted pyridyl. In certain embodiments,  $R^{E4a}$  is unsubstituted pyridyl.

**[00187]** In compounds of Formula (I),  $R^E$  may include a Y group. In certain embodiments, Y is  $=\text{O}$ . In certain embodiments, Y is  $-\text{O}-$ . In certain embodiments, Y is  $=\text{S}$ . In certain embodiments, Y is  $-\text{S}-$ . In certain embodiments, Y is  $=\text{NR}^{E6}$ . In certain embodiments, Y is  $-\text{NR}^{E6}$ .

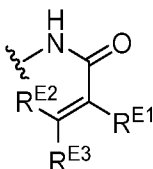
$\text{NR}^{\text{E6}}$ -. In certain embodiments, Y is =NH. In certain embodiments, Y is -NH-. In certain embodiments,  $\text{R}^{\text{E6}}$  is H. In certain embodiments,  $\text{R}^{\text{E6}}$  is substituted or unsubstituted  $\text{C}_{1-6}$  alkyl (e.g., -CH<sub>3</sub>). In certain embodiments,  $\text{R}^{\text{E6}}$  is a nitrogen protecting group (e.g., Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

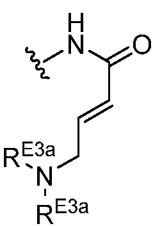
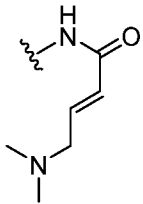
**[00188]** In compounds of Formula (I),  $\text{R}^{\text{E}}$  may include a substituent  $\text{R}^{\text{E5}}$ , which is halogen. In certain embodiments,  $\text{R}^{\text{E5}}$  is F, Cl, Br, or I (iodine).

**[00189]** In certain embodiments, a is 1. In certain embodiments, a is 2.

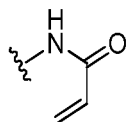
**[00190]** In certain embodiments, z is 0. In certain embodiments, z is 1. In certain embodiments, z is 2. In certain embodiments, z is 3. In certain embodiments, z is 4. In certain embodiments, z is 5. In certain embodiments, z is 6.

**[00191]** In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E1}}$  is hydrogen. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E2}}$  is hydrogen. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E3}}$  is hydrogen. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E2}}$  and  $\text{R}^{\text{E3}}$  are each hydrogen. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E1}}$ ,  $\text{R}^{\text{E2}}$  and  $\text{R}^{\text{E3}}$  are each hydrogen. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E1}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E1a}}$ ). In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E1}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E1a}}$ ); and  $\text{R}^{\text{E1a}}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E1}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E1a}}$ ); and  $\text{R}^{\text{E1a}}$  is methyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E2}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E2a}}$ ). In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E2}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E2a}}$ ); and  $\text{R}^{\text{E2a}}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E2}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E2a}}$ ); and  $\text{R}^{\text{E2a}}$  is methyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{R}^{\text{E3}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E3a}}$ ). In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E3}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E3a}}$ ); and  $\text{R}^{\text{E3a}}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1);  $\text{R}^{\text{E3}}$  is -CH<sub>2</sub>N( $\text{R}^{\text{E3a}}$ ); and  $\text{R}^{\text{E3a}}$  is methyl. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and Y is =O. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{L}^3$  is -NR<sup>L3a</sup>-. In certain embodiments,  $\text{R}^{\text{E}}$  is of Formula (i-1); and  $\text{L}^3$  is -NH-. In certain

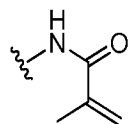
embodiments,  $\text{R}^{\text{E}}$  is of the formula: . In certain embodiments,  $\text{R}^{\text{E}}$  is of the

formula: . In certain embodiments,  $\text{R}^{\text{E}}$  is of the formula: . In certain

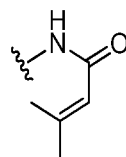
embodiments,  $R^E$  is of the formula:



. In certain embodiments,  $R^E$  is of the formula:

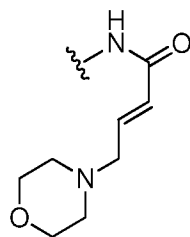


. In certain embodiments,  $R^E$  is of the formula:

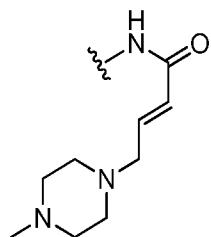


. In certain embodiments,

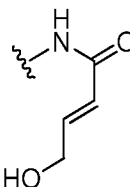
$R^E$  is of the formula:



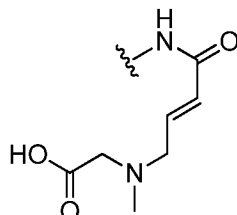
. In certain embodiments,  $R^E$  is of the formula:



. In certain embodiments,  $R^E$  is of the formula:  $HO-CH_2-CH=CH-C(=O)NH-$  . In certain

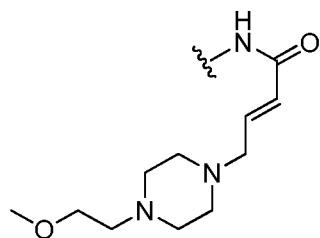


embodiments,  $R^E$  is of the formula:

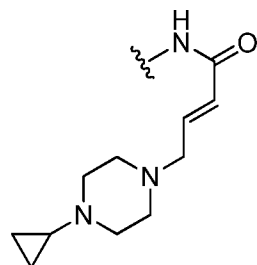


. In certain embodiments,  $R^E$  is of the

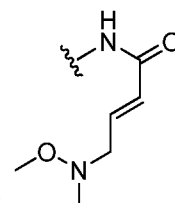
formula:



. In certain embodiments,  $R^E$  is of the formula:

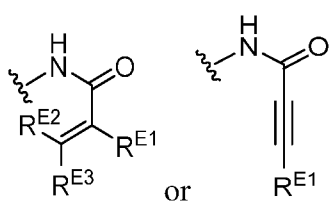


. In certain embodiments,  $R^E$  is of the formula:



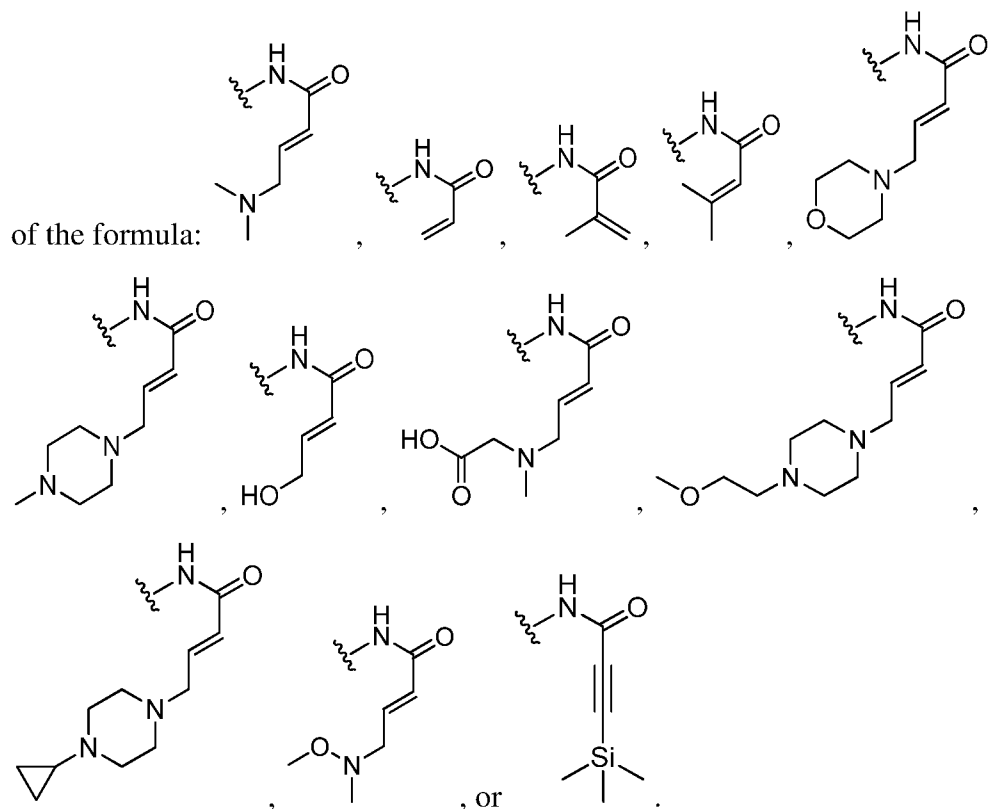
. In certain

embodiments,  $R^E$  is of the formula:

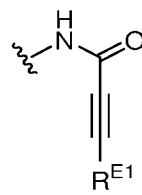


or  $R^{E1}$ . In certain embodiments,  $R^E$  is

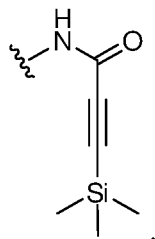
of the formula:



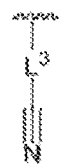
**[00192]** In certain embodiments,  $R^E$  is of Formula (i-3); and  $R^{E1}$  is hydrogen. In certain embodiments,  $R^E$  is of Formula (i-3); and  $R^{E1}$  is  $-\text{CH}_2\text{N}(R^{E1a})$ . In certain embodiments,  $R^E$  is of Formula (i-3); and  $R^{E1}$  is  $-\text{Si}(R^{E1a})_3$  (e.g.,  $-\text{Si}(\text{Me})_3$ ). In certain embodiments,  $R^E$  is of Formula (i-3);  $R^{E1}$  is  $-\text{CH}_2\text{N}(R^{E1a})$ ; and  $R^{E1a}$  is  $\text{C}_{1-6}$  alkyl. In certain embodiments,  $R^E$  is of Formula (i-3);  $R^{E1}$  is  $-\text{CH}_2\text{N}(R^{E1a})$ ; and  $R^{E1a}$  is methyl. In certain embodiments,  $R^E$  is of Formula (i-3); and  $Y$  is  $=\text{O}$ . In certain embodiments,  $R^E$  is of Formula (i-3); and  $L^3$  is  $-\text{NR}^{L3a}-$ . In certain embodiments,  $R^E$  is of Formula (i-3); and  $L^3$  is  $-\text{NH}-$ .



[00193] In certain embodiments,  $R^E$  is of the formula:  $R^{E1}$ . In certain



embodiments,  $R^E$  is of the formula:



[00194] In certain embodiments,  $R^E$  is not of the formula: (i-5).

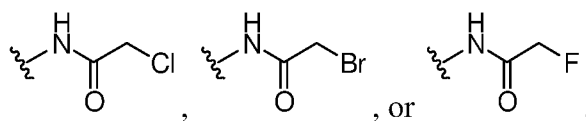
[00195] In certain embodiments,  $R^E$  is of the formula:

(i-36),

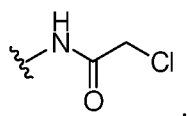
(i-37), or

(i-38).

[00196] In certain embodiments,  $R^E$  is of the formula:

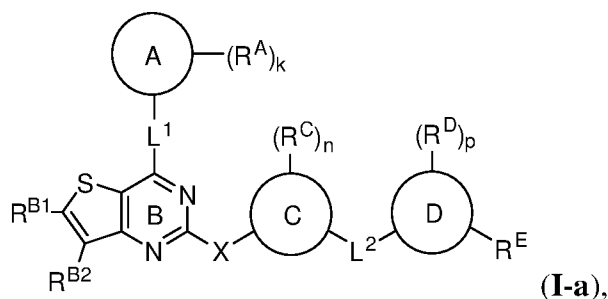


[00197] In certain embodiments,  $R^E$  is of the formula:  $\text{---}L^3\text{---}Cl$  (i-36). In certain



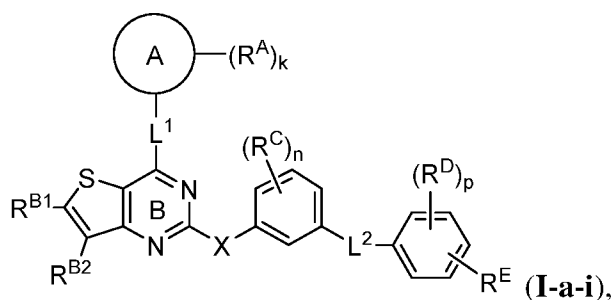
embodiments,  $R^E$  is of the formula:

[00198] In certain embodiments, the compound of Formula (I) is of Formula (I-a):



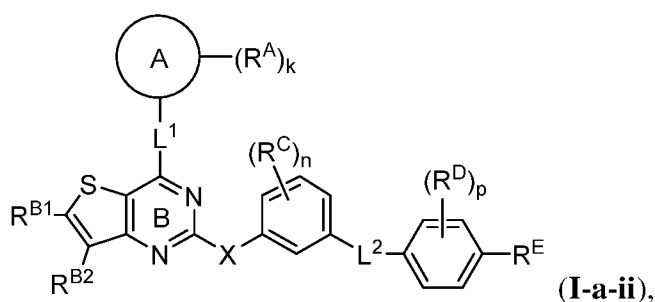
or a pharmaceutically acceptable salt thereof.

[00199] In certain embodiments, the compound of Formula (I) is of Formula (I-a-i):



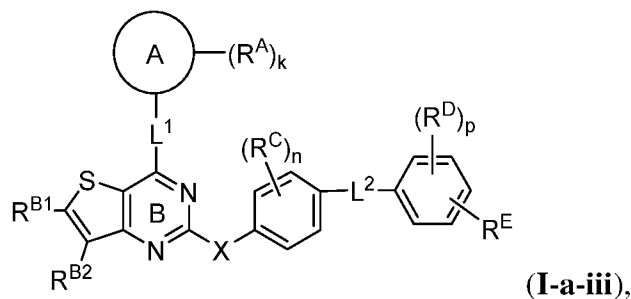
or a pharmaceutically acceptable salt thereof.

[00200] In certain embodiments, the compound of Formula (I) is of Formula (I-a-ii):



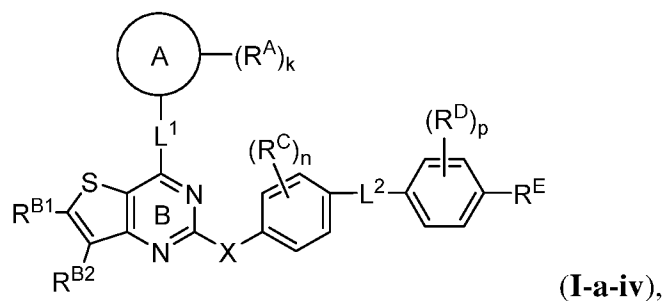
or a pharmaceutically acceptable salt thereof.

[00201] In certain embodiments, the compound of Formula (I) is of Formula (I-a-iii):



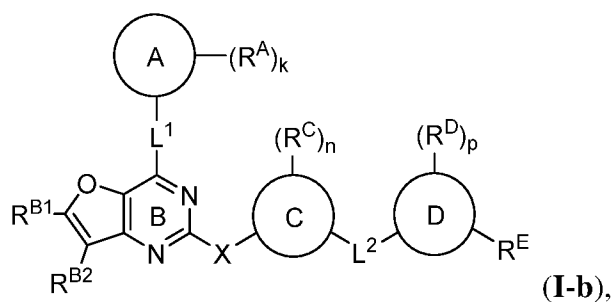
or a pharmaceutically acceptable salt thereof.

[00202] In certain embodiments, the compound of Formula (I) is of Formula (I-a-iv):



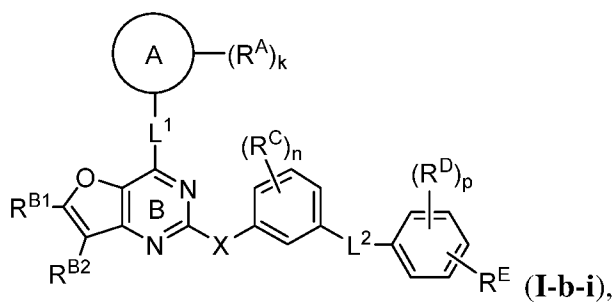
or a pharmaceutically acceptable salt thereof.

[00203] In certain embodiments, the compound of Formula (I) is of Formula (I-b):



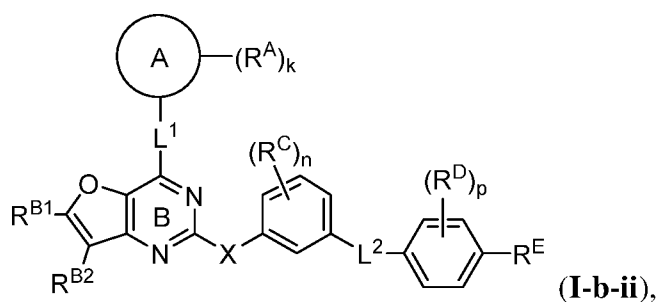
or a pharmaceutically acceptable salt thereof.

[00204] In certain embodiments, the compound of Formula (I) is of Formula (I-b-i):



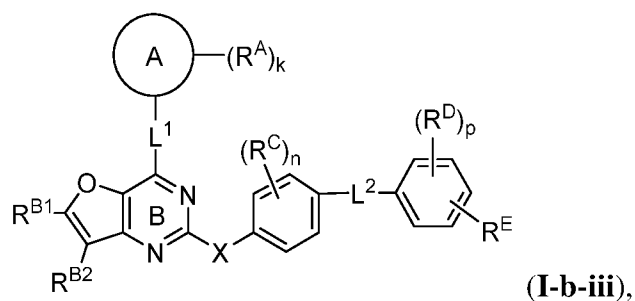
or a pharmaceutically acceptable salt thereof.

[00205] In certain embodiments, the compound of Formula (I) is of Formula (I-b-ii):



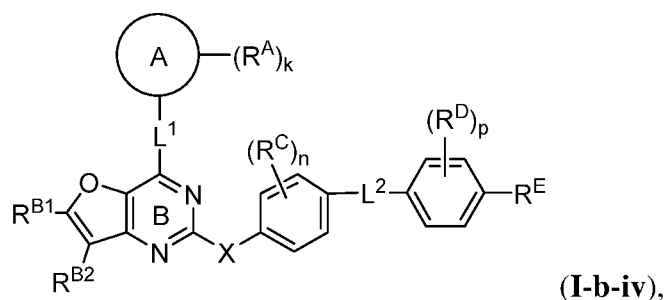
or a pharmaceutically acceptable salt thereof.

[00206] In certain embodiments, the compound of Formula (I) is of Formula (I-b-iii):



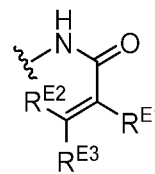
or a pharmaceutically acceptable salt thereof.

[00207] In certain embodiments, the compound of Formula (I) is of Formula (I-b-iv):

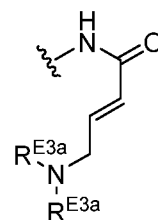


or a pharmaceutically acceptable salt thereof.

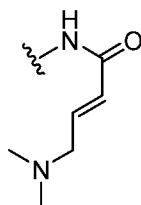
[00208] In certain embodiments of Formulae (I), and (I-a)-(I-c),  $R^E$  is of Formula (i-1); and  $L^3$  is  $-NR^{L3a}-$ . In certain embodiments of Formulae (I)-(VI),  $R^E$  is of Formula (i-1); and



$L^3$  is  $-NH-$ . In certain embodiments of Formulae (I)-(VI),  $R^E$  is of the formula:

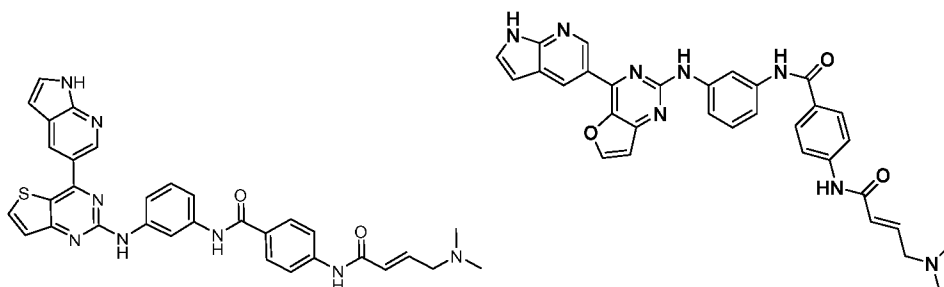


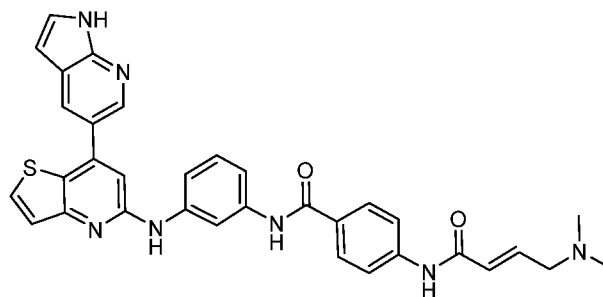
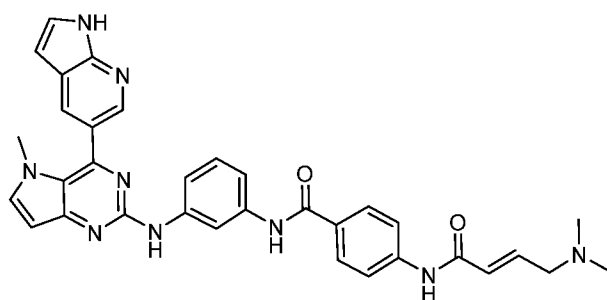
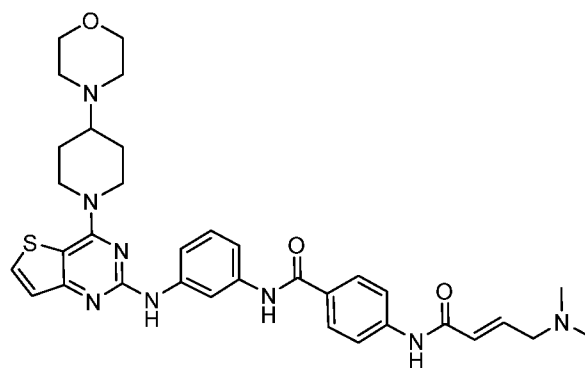
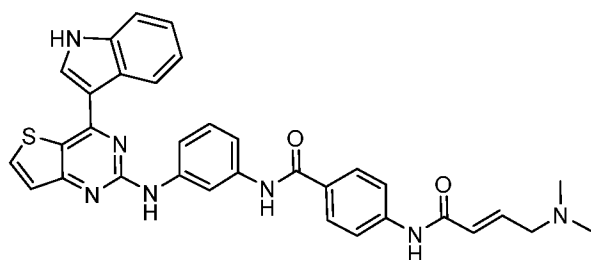
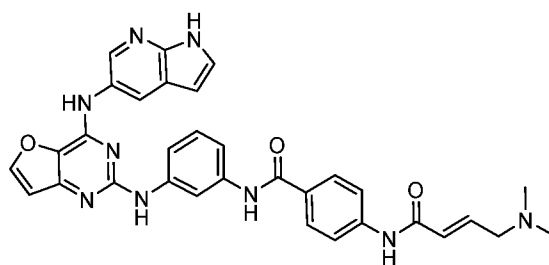
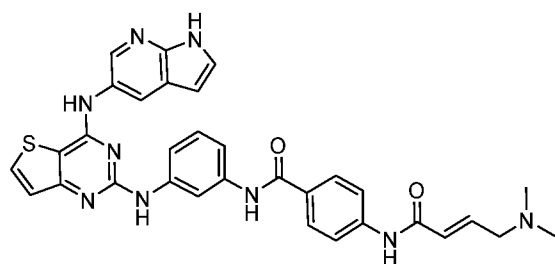
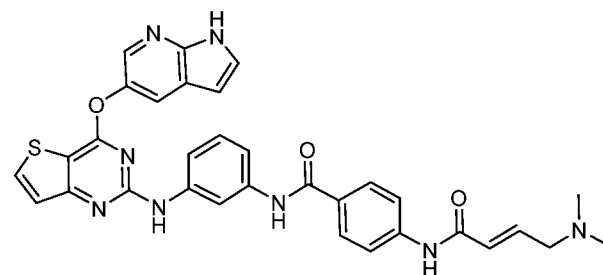
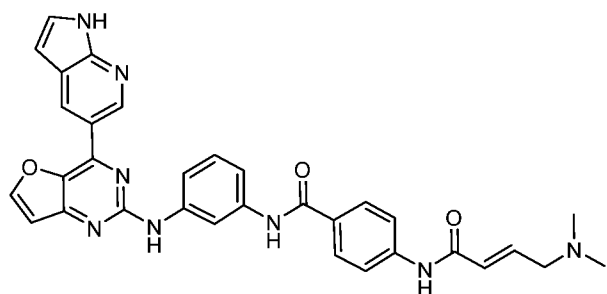
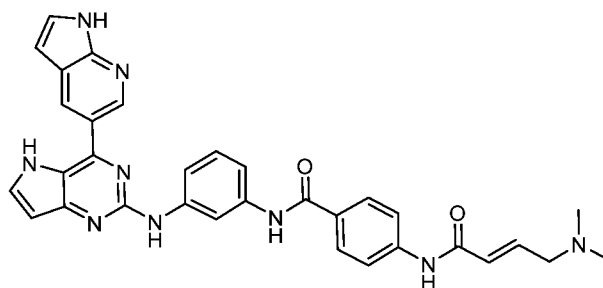
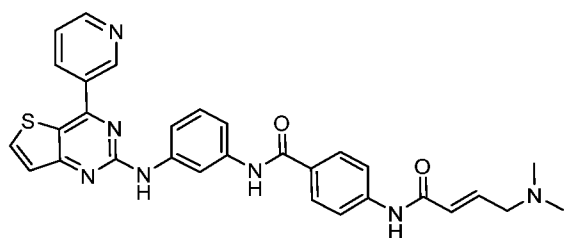
In certain embodiments of Formulae (I)-(VI),  $R^E$  is of the formula: . In certain

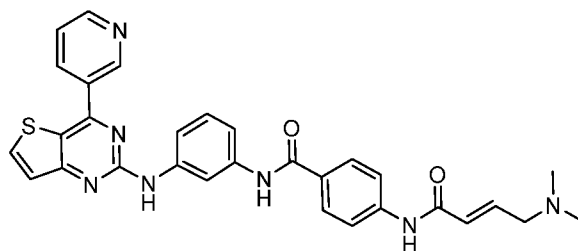
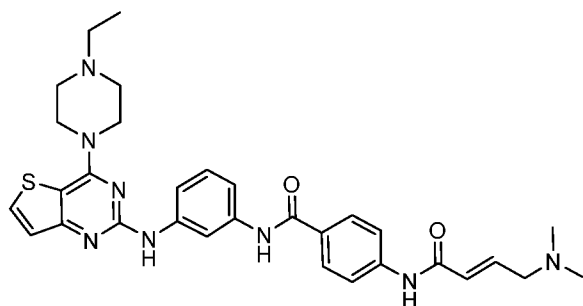
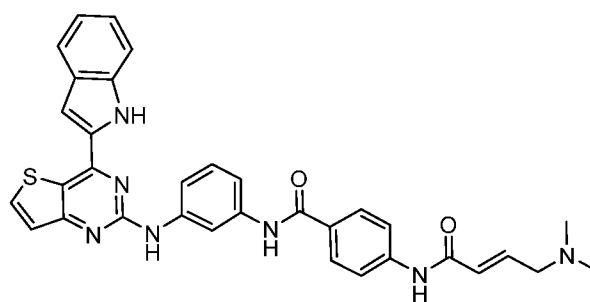
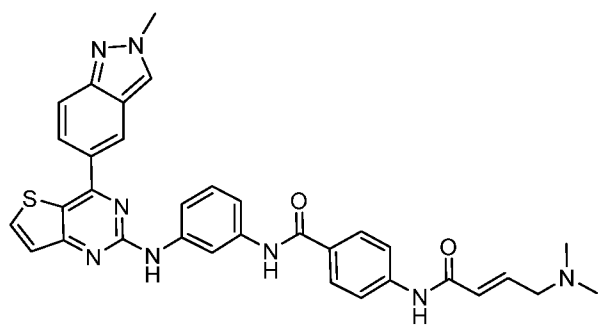


embodiments,  $R^E$  is of the formula: .

[00209] In certain embodiments, the compound of Formula (I) is of the formula:

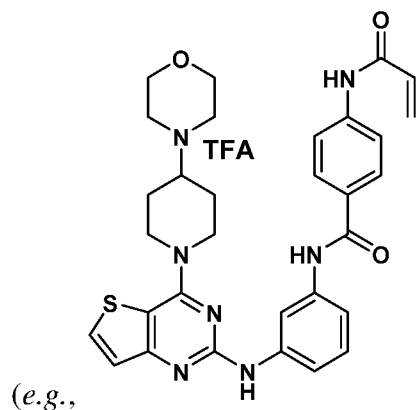
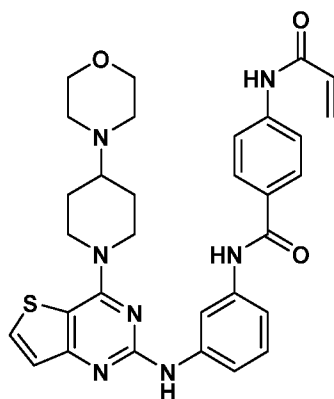
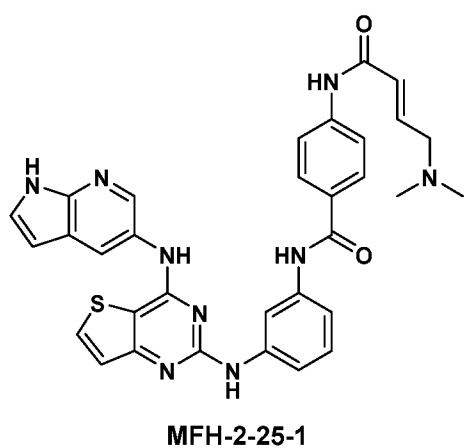




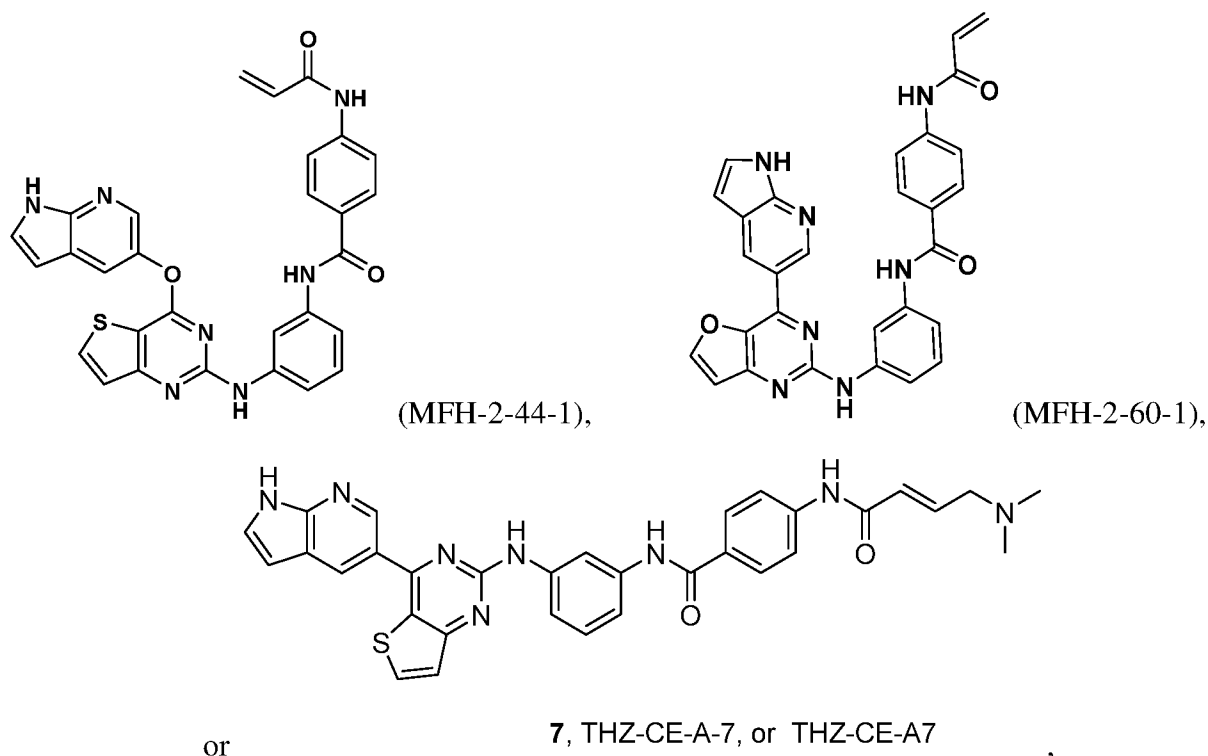


or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

**[00210]** In certain embodiments, the compound of Formula (I) is of the formula:

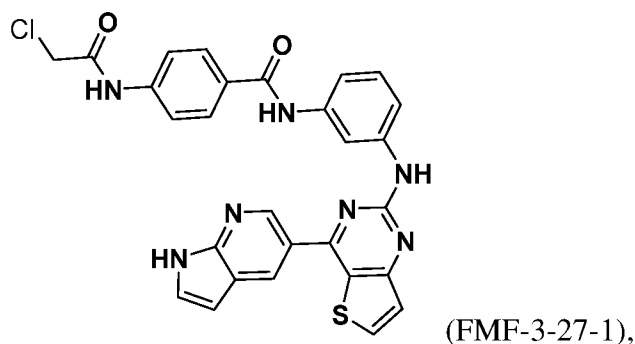


(MFH-2-40-1)),



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

**[00211]** In certain embodiments, the compound of Formula (I) is of the formula:



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

**[00212]** In certain embodiments, a compound of Formula (I) is substantially pure. In certain embodiments, a compound of Formula (I) is a substantially pure stereoisomer. In certain embodiments, the compounds of the present invention are compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof. In certain embodiments, the compounds of the present invention are compounds of Formula (I), and pharmaceutically acceptable salts and stereoisomers thereof. In certain embodiments, the compounds of the present invention are compounds of Formula (I), and pharmaceutically acceptable salts

thereof. In certain embodiments, the compounds of the present invention are a stereoisomeric mixture of compounds of Formula (I), and pharmaceutically acceptable salts thereof. In certain embodiments, the compounds of the present invention are a racemic stereoisomeric mixture of compounds of Formula (I), and pharmaceutically acceptable salts thereof.

**[00213]** The compounds of the present invention may bear multiple binding motifs for binding to a kinase. The compounds of the present invention may also inhibit a kinase. In certain embodiments, the kinase is a protein kinase. In certain embodiments, the protein kinase is a CDK (*e.g.*, CDK7, CDK12, and/or CDK13). In certain embodiments, the kinase is a lipid kinase. In certain embodiments, the protein kinase is a PIP4K. In certain embodiments, the PIP4K is a PIP4K2. In certain embodiments, the PIP4K2 is PIP4K2A protein. In certain embodiments, the PIP4K2 is PIP4K2B protein. In certain embodiments, the PIP4K2 is PIPK2C protein. Ring A of the inventive compounds may be accommodated by a hydrophobic pocket in the ATP-binding site of the kinase (*e.g.*, a lipid kinase such as PIP4K2 enzyme). Functionalities on Rings A and B may bind to residues of the kinase (*e.g.*, a lipid kinase such as PIP4K2 enzyme). For example, Ring A may form a hydrogen bond with a Cys residue of PIP4K (*e.g.* Cys293 of PIP4K2A enzyme or Cys307 and/or Cys318 of PIP4K2B enzyme). Functional groups of R<sup>E</sup> may form one or more hydrogen bonds with the kinase (*e.g.*, a lipid kinase such as PIP4K2 enzyme). Moreover, the Michael acceptor moiety of R<sup>E</sup> may react with a cysteine residue of the kinase (*e.g.*, a lipid kinase such as PIP4K2 enzyme) to allow covalent attachment of the compound to the kinase (*e.g.*, a lipid kinase such as a PIP4K2 enzyme).

**[00214]** In certain embodiments, the provided compound is capable of covalently modifying Cys293 of PI5P4K $\alpha$ . In certain embodiments, the provided compound is capable of covalently modifying Cys307 and/or Cys318 of PI5P4K $\beta$ . In certain embodiments, the provided compound is capable of covalently modifying Cys313 of PI5P4K $\gamma$  while Cys313 is based on the sequence alignment.

**[00215]** The compounds of the present invention are thought to be kinase inhibitors. In certain embodiments, the inventive compounds are inhibitors of protein kinases. In certain embodiments, the inventive compounds are CDK inhibitors. In certain embodiments, the inventive compounds are CDK7 inhibitors. In certain embodiments, the inventive compounds are CDK12 inhibitors. In certain embodiments, the inventive compounds are CDK13 inhibitors. In certain embodiments, the inventive compounds are inhibitors of lipid kinases. In certain embodiments, the inventive compounds are PIPK inhibitors. In certain embodiments,

the inventive compounds are PIP4K2 inhibitors. In certain embodiments, the inventive compounds are PIP4K2A inhibitors. In certain embodiments, the inventive compounds are PIP4K2B inhibitors. In certain embodiments, the inventive compounds are PIP4K2C inhibitors. In certain embodiments, the inventive compounds are selective CDK inhibitors (*e.g.*, being more active in inhibiting a CDK than a non-CDK kinase). In certain embodiments, the inventive compounds are selective CDK7 inhibitors (*e.g.*, being more active in inhibiting CDK7 than a non-CDK7 kinase). In certain embodiments, the inventive compounds are selective CDK12 inhibitors. In certain embodiments, the inventive compounds are selective CDK13 inhibitors. In certain embodiments, the inventive compounds are selective PIPK inhibitors (*e.g.*, being more active in inhibiting a PIPK than a non-PIPK kinase). In certain embodiments, the inventive compounds are selective PIP4K2 inhibitors (*e.g.*, being more active in inhibiting PIP4K2 than a non-PIP4K2 kinase). In certain embodiments, the inventive compounds are selective PIP4K2A inhibitors. In certain embodiments, the inventive compounds are selective PIP4K2B inhibitors. In certain embodiments, the inventive compounds are selective PIP4K2C inhibitors.

**[00216]** The selectivity of an inventive compound for a first kinase (*e.g.*, lipid kinase) over a second kinase (*e.g.*, a non-lipid kinase) may be measured by the quotient of the  $IC_{50}$  (half maximal inhibitory concentration) value of the inventive compound in inhibiting the activity of the second kinase over the  $IC_{50}$  value of the inventive compound in inhibiting the activity of the first kinase. The selectivity of an inventive compound for a first kinase over a second kinase may also be measured by the quotient of the  $K_d$  (dissociation constant) value of an adduct (covalent or non-covalent) of the inventive compound and the second kinase over the  $K_d$  value of an adduct of the inventive compound and the first kinase. In certain embodiments, the selectivity is at least about 1-fold, at least about 2-fold, at least about 5-fold, at least about 10-fold, at least about 30-fold, at least about 100-fold, at least about 300-fold, at least about 1,000-fold, at least about 3,000-fold, at least about 10,000-fold, at least about 30,000-fold, or at least about 100,000-fold. In certain embodiments,  $IC_{50}$  values are measured by a functional antagonist assay. In certain embodiments,  $IC_{50}$  values are measured by a competition binding assay. In certain embodiments,  $IC_{50}$  values are measured by a method described herein. In certain embodiments,  $K_d$  values are measured by a nuclear magnetic resonance method (*e.g.*, a linearization method and a curve fitting method). In certain embodiments,  $K_d$  values are measured by a mass spectrometry method (*e.g.*, a one-ligand one-binding-site ESI-MS method).

*Pharmaceutical Compositions, Kits, and Administration*

**[00217]** The present invention provides pharmaceutical compositions comprising a compound of Formula (I), *e.g.*, a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, as described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

**[00218]** Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of Formula (I) (the “active ingredient”) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

**[00219]** 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, for example, one-half or one-third of such a dosage.

**[00220]** Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

**[00221]** 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.

**[00222]** 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.

**[00223]** 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.

**[00224]** Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, 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), carbomers (*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 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor™), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether (Brij 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-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

**[00225]** 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.

**[00226]** Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal 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.

**[00227]** Exemplary antioxidants include alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

**[00228]** 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.

**[00229]** 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.

**[00230]** Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

**[00231]** 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.

**[00232]** Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (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.

**[00233]** Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, 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.

**[00234]** Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

**[00235]** 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, macademia nut, mallow, mango seed, meadowfoam seed, mint, 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.

**[00236]** 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 of the invention are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

**[00237]** 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 diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

**[00238]** 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.

**[00239]** In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a

parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

**[00240]** Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention 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.

**[00241]** 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.

**[00242]** 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 embedding 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.

**[00243]** 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 embedding compositions which can be used include polymeric substances and waxes.

**[00244]** Dosage forms for topical and/or transdermal administration of a compound of this invention 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 and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention 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.

**[00245]** 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. Jet injection devices which deliver liquid vaccines 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. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

**[00246]** 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.

**[00247]** A pharmaceutical composition of the invention 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.

**[00248]** 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).

**[00249]** Pharmaceutical compositions of the invention 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.

**[00250]** Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition of the invention. 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.

**[00251]** 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 of the invention 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.

**[00252]** A pharmaceutical composition of the invention 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. 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 contemplated as being within the scope of this invention.

**[00253]** 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.

**[00254]** 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 of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

**[00255]** 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).

**[00256]** The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00257] 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 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 tissue or cell, the frequency of administering the multiple doses to the subject or applying the multiple doses to the 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 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 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 tissue or cell is three doses per day. In certain embodiments, when multiple doses are administered to a subject or applied to a 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  $\mu$ g and 1  $\mu$ g, 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.

**[00258]** In certain embodiments, a dose described herein is a dose to an adult human whose body weight is 70 kg. In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

**[00259]** In certain embodiments, the compounds of Formula (I) may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

**[00260]** It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

**[00261]** It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

**[00262]** The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the

additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents 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.

**[00263]** Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, immunosuppressant agents, and a pain-relieving agent. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is selected from the group consisting of cytotoxic agents, epigenetic or transcriptional modulators (*e.g.*, DNA methyltransferase inhibitors, histone deacetylase inhibitors (HDAC inhibitors), lysine methyltransferase inhibitors), antimetabolic 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.

**[00264]** Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a proliferative disease (*e.g.*, cancer (*e.g.*, leukemia, lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, neuroblastoma, lung cancer), benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a

pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

**[00265]** Thus, in one aspect, provided are kits including a first container comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the kit of the invention includes a first container comprising a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a proliferative disease in a subject. In certain embodiments, the kits further include instructions for administering the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrug thereof, or a pharmaceutical composition thereof, to a subject to prevent and/or treat a proliferative disease.

#### *Methods of Treatment and Uses*

**[00266]** The present invention also provides methods for the treatment or prevention of a proliferative disease (*e.g.*, cancer, benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease) or an infectious disease (*e.g.*, a viral disease) in a subject.

**[00267]** 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.

**[00268]** The proliferative disease to be treated or prevented using the compounds of Formula (I) may be associated with overexpression of a kinase. The proliferative disease to be treated or prevented using the compounds of Formula (I) may be associated with aberrant activity of a kinase. In certain embodiments, the kinase is a lipid kinase. In certain

embodiments, the lipid kinase is a PIP kinase. In certain embodiments, the PIPK is PIP4K, catalyzing phosphorylation of lipid phosphatidylinositol-5-phosphate (PI-5-P) at the 4-position to generate phosphatidylinositol-4,5-bisphosphate (PI-4,5-P<sub>2</sub>). In some embodiments, the PIP4K is class I PIP4K, *i.e.* PIP4K1. In some embodiments, the PIP4K is class II PIP4K, *i.e.* PIP4K2. In some embodiments, the PIP4K2 is PIP4K2A protein. In some embodiments, the PIP4K2 is PIP4K2B protein. In some embodiments, the PIP4K2 is PIP4K2C protein.

**[00269]** In certain embodiments, the kinase is a protein kinase. In certain embodiments, the protein kinase is a 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. In certain embodiments, the CDK is CDK7. In certain embodiments, the CDK is CDK12. In certain embodiments, the CDK is CDK13.

**[00270]** In certain embodiments, a proliferative disease may be associated with aberrant activity of a CDK (*e.g.*, CDK7). Aberrant activity of a CDK (*e.g.*, CDK7) 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.*, CDK7) activity, frequently through elevated and/or inappropriate CDK activation. Inhibition of the catalytic activity of CDK7 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, CDK7 is not overexpressed, and the activity of CDK7 is elevated and/or inappropriate. In certain other embodiments, CDK7 is overexpressed, and the activity of CDK7 is elevated and/or inappropriate. The compounds of Formula (I), 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.

**[00271]** In other embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (I) will typically be associated with aberrant activity of CDK12. Aberrant activity of CDK12 may be an elevated and/or an inappropriate (*e.g.*, abnormal) activity of CDK12. In certain embodiments, CDK12 is not overexpressed, and the activity of CDK12 is elevated and/or inappropriate. In certain other embodiments, CDK12 is overexpressed, and the activity of CDK12 is elevated and/or inappropriate. The compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK12 and be useful in treating and/or preventing proliferative diseases.

**[00272]** In other embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (I) will typically be associated with aberrant activity of CDK13. Aberrant activity of CDK13 may be an elevated and/or an inappropriate (*e.g.*, abnormal) activity of CDK13. In certain embodiments, CDK13 is not overexpressed, and the activity of CDK13 is elevated and/or inappropriate. In certain other embodiments, CDK13 is overexpressed, and the activity of CDK13 is elevated and/or inappropriate. The compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, tautomers, stereoisomers, isotopically labeled derivatives, and compositions thereof, may inhibit the activity of CDK13 and be useful in treating and/or preventing proliferative diseases.

**[00273]** In certain embodiments, the proliferative disease to be treated or prevented using the compounds of Formula (I) is cancer. All types of cancers disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the cancer has one or more mutations. In certain embodiments, the cancer has EGFR mutation. In certain embodiments, the cancer has TP53 mutation. In certain embodiments, the cancer has loss of TP53 mutation. In certain embodiments, the cancer has KRAS mutation. In certain embodiments, the cancer has ALK mutation. In certain embodiments, the proliferative disease is a cancer associated with dependence on BCL-2 anti-apoptotic proteins (*e.g.*, MCL-1 and/or XIAP). 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 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 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 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 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 lung cancer has one or more mutations. In certain embodiments, the lung cancer has EGFR mutation. In certain embodiments, the lung cancer has TP53 mutation. In certain embodiments, the lung cancer has loss of TP53 mutation. In certain embodiments, the lung cancer has KRAS mutation. In certain embodiments, the lung cancer has ALK mutation. 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. 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.

**[00274]** In certain embodiments, the infectious disease to be treated or prevented using the compounds of Formula (I) is a viral disease. Such viral infections are described in U.S.

Provisional Patent Application, U.S.S.N. 61/622,828, filed April 11, 2012, and international PCT application, PCT/US2013/032488, filed March 15, 2013 and published on October 17, 2011, each of which is incorporated herein in its entirety by reference.

**[00275]** The cell described herein may be an abnormal cell. The cell may be *in vitro* or *in vivo*. In certain embodiments, the cell is a proliferative cell. In certain embodiments, the cell is a blood cell. In certain embodiments, the cell is a lymphocyte. In certain embodiments, the cell is a B-cell. In certain embodiments, the cell is a T-cell. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cell is a leukemia cell. In certain embodiments, the cell is a CLL cell. In certain embodiments, the cell is a melanoma cell. In certain embodiments, the cell is a multiple myeloma cell. In certain embodiments, the cell is a benign neoplastic cell. In certain embodiments, the cell is an endothelial cell. In certain embodiments, the cell is an immune cell.

**[00276]** In another aspect, the present invention provides methods of modulating the activity of a kinase (*e.g.* a lipid kinase such as PIPK (*e.g.* PIP4K2A, PIP4K2B, or PIP4K2C protein) enzyme or a protein kinase such as CDK (*e.g.*, CDK7, CDK1, CDK2, CDK5, CDK8, CDK9, CDK12, CDK13) enzyme ) in a biological sample or subject. In certain embodiments, the activity of the kinase is aberrant 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 attaching a compound of Formula (I) to the kinase.

**[00277]** Also provided in the present invention are methods of inhibiting transcription in a biological sample or subject.

**[00278]** The present invention also provides methods of inhibiting cell growth in a biological sample or subject.

**[00279]** In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound of Formula (I), 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 of Formula (I), 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.

**[00280]** 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. 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 (mechlorethamine hydrochloride), MYLERAN (busulfan), NEOSAR (cyclophosphamide), ONCASPAR (Pegaspargase), PURINETHOL (mercaptopurine), PURIXAN (mercaptopurine), Rubidomycin (daunorubicin hydrochloride), SPRYCEL (dasatinib), SYNRIPO (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 an anti-myelodysplasia agent. In certain embodiments, the additional pharmaceutical agent is REVLIMID (lenalidomide), DACOGEN (decitabine), VIDAZA (azacitidine), CYTOSAR-U (cytarabine), IDAMYCIN (idarubicin), CERUBIDINE (daunorubicin), or a combination thereof.

In certain embodiments, the additional pharmaceutical agent is an anti-macroglobulinemia agent.

In certain embodiments, the additional pharmaceutical agent is 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), JEVTANA (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), or a combination thereof. In certain embodiments, the additional pharmaceutical agent is a histone deacetylase inhibitor. In certain embodiments, the histone deacetylase inhibitor is a hydroxamic acid such as Vorinostat (SAHA), ITF2357, or PXD-101, a cyclic peptide such as depsipeptide, a benzamide such as MS-275, or an aliphatic acid such as valproic acid or AN-9.

**[00281]** In certain embodiments, the additional pharmaceutical agent is an inhibitor of a lipid kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a PIP4K. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a PIP4K2. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a PIP4K2A. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a PIP4K2B. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a PIP4K2C. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a protein kinase. In certain embodiments, the additional pharmaceutical agent is an inhibitor of a CDK. In certain embodiments, the additional pharmaceutical agent is an inhibitor of CDK7. In certain embodiments, the additional pharmaceutical agent is an inhibitor of CDK12. In certain embodiments, the additional pharmaceutical agent is an inhibitor of CDK13. In certain embodiments, the additional pharmaceutical agent is flavopiridol, triptolide, SNS-032 (BMS-387032), PHA-767491, PHA-793887, BS-181, (*S*)-CR8, (*R*)-CR8, or NU6140. In certain embodiments, the additional pharmaceutical agent is an 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 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. In certain embodiments, the additional pharmaceutical agent is an inhibitor of one or more protein kinases selected from the group consisting of IRAK1, IRAK4, BMX, and PI3K. In

certain embodiments, the additional pharmaceutical agent is an inhibitor of one or more protein kinases selected from the group consisting of BUB1B, CDK2, CDK9, CHEK2, FGR, HIPK4, PRKCQ, RET, SRC, or MELK. In certain embodiments, the additional pharmaceutical agent is an inhibitor of one or more protein kinases selected from the group consisting of ABL, ARG, BLK, CSK, EphB1, EphB2, FGR, FRK, FYN, SRC, YES, LCK, LYN, MAP2K5, NLK, p38a, SNRK, and TEC. In certain embodiments, the additional pharmaceutical agent is an inhibitor of one or more protein kinases selected from the group consisting of ABL1(H396P)-phosphorylated, ABL1-phosphorylated, BLK, EPHA4, EPHB2, EPHB3, EPHB4, FGR, JAK3(JH1domain-catalytic), KIT, KIT(L576P), KIT(V559D), PDGFRB, SRC, YES, ABL1(H396P)-nonphosphorylated, ABL1(Y253F)-phosphorylated, ABL1-nonphosphorylated, FRK, LYN, ABL1(Q252H)-nonphosphorylated, DDR1, EPHB1, ERBB4, p38-alpha, ABL2, ABL1(Q252H)-phosphorylated, SIK, EPHA8, MEK5, ABL1(E255K)-phosphorylated, ABL1(F317L)-nonphosphorylated, FYN, LCK, EPHA2, ABL1(M351T)-phosphorylated, TXK, EGFR(L858R), EGFR(L861Q), ERBB2, ERBB3, EPHA5, ABL1(F317I)-nonphosphorylated, EGFR(L747-E749del, A750P), CSK, EPHA1, ABL1(F317L)-phosphorylated, BRAF(V600E), EGFR, KIT-autoinhibited, and EGFR(E746-A750del). In certain embodiments, the additional pharmaceutical agent is an inhibitor of one or more protein kinases selected from the group consisting of ABL1(F317L)-nonphosphorylated, ABL1(H396P)-nonphosphorylated, ABL1(H396P)-phosphorylated, ABL1-phosphorylated, BLK, EPHA4, EPHB2, EPHB3, EPHB4, JAK3(JH1domain-catalytic), KIT, KIT(L576P), KIT(V559D), LYN, PDGFRB, SRC, YES, ABL1-nonphosphorylated, ABL1(Y253F)-phosphorylated, ERBB3, FGR, FRK, p38-alpha, ABL1(F317I)-nonphosphorylated, DDR1, EPHA2, ABL1(Q252H)-phosphorylated, MEK5, ABL1(Q252H)-nonphosphorylated, ABL2, FYN, EPHB1, ABL1(E255K)-phosphorylated, ABL1(F317L)-phosphorylated, EPHA1, ABL1(M351T)-phosphorylated, ERBB4, TXK, LCK, EPHA8, SIK, EPHA5, EGFR(L861Q), CSF1R-autoinhibited, BRAF(V600E), BRK, CSK, KIT(D816V), KIT-autoinhibited, EGFR(L747-T751del,Sins), EGFR(L858R), EGFR(L747-E749del, A750P), and CSF1R. In certain embodiments, the additional pharmaceutical agent is an anti-angiogenesis agent, anti-inflammatory agent, immunosuppressant, anti-bacterial agent, anti-viral agent, cardiovascular agent, cholesterol-lowering agent, anti-diabetic agent, anti-allergic agent, pain-relieving agent, or a combination thereof. 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, transplantation (*e.g.*, bone marrow transplantation, stem cell transplantation), surgery, radiation therapy, immunotherapy, and chemotherapy.

**[00282]** Another aspect of the invention relates to methods of screening a library of compounds to identify one or more compounds that are useful in the treatment of a proliferative disease, in inhibiting a kinase (*e.g.*, PIPK or CDK (*e.g.* CDK7, CDK12, CDK13) enzyme), in inhibiting cell growth. In certain embodiments, the library of compounds is a library of compounds of Formula (I). The methods of screening a library include providing at least two different compounds of Formula (I), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, or prodrugs thereof, or pharmaceutical compositions thereof; and performing at least one assay using the different compounds of Formula (I), or pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, or prodrugs thereof, or pharmaceutical compositions thereof, to detect one or more characteristics associated with the proliferative disease. In certain embodiments, the methods of screening a library include providing at least two different compounds of Formula (I), or pharmaceutically acceptable salts thereof, or pharmaceutical compositions thereof; and performing at least one assay using the different compounds of Formula (I), or pharmaceutically acceptable salts thereof, or pharmaceutical compositions thereof, to detect one or more characteristics associated with the proliferative disease. The characteristic to be detected may be a desired characteristic associated with the proliferative disease. In certain embodiments, the desired characteristic is anti-proliferation. In certain embodiments, the desired characteristic is anti-cancer. In certain embodiments, the desired characteristic is inhibition of a kinase. In certain embodiments, the desired characteristic is inhibition of a lipid kinase. In certain embodiments, the desired characteristic is inhibition of PIPK. In certain embodiments, the desired characteristic is inhibition of PIP4K. In certain embodiments, the desired characteristic is inhibition of class II PIP4K, *i.e.* PIP4K2. In certain embodiments, the desired characteristic is inhibition of PIP4K2A. In certain embodiments, the desired characteristic is inhibition of PIP4K2B. In certain embodiments, the desired characteristic is inhibition of PIP4K2C. In certain embodiments, the desired characteristic is inhibition of a protein kinase. In certain embodiments, the desired characteristic is inhibition of CDK. In certain embodiments, the desired characteristic is inhibition of CDK7. In certain embodiments, the desired characteristic is inhibition of CDK12. In certain embodiments, the desired characteristic is inhibition of CDK13. In certain embodiments, the desired characteristic is down-regulation of a kinase such as PIPK or CDK.

## EXAMPLES

**[00283]** 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.

*Synthesis of the Compounds*

**[00284]** The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. See, *e.g.*, *Scheme 1* below. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

**[00285]** Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in Greene *et al.*, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

**Example 1. Synthesis of Compound 7 (Figure 2)****2-chloro-4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidine (Compound 2)**

**[00286]** To a solution of **1** (1.0 g, 2.6 mmol) in MeCN and H<sub>2</sub>O (20 mL, 4/1, v/v) was added 2,4-dichlorothieno[3,2-d]pyrimidine (0.53 g, 2.6 mmol), NaHCO<sub>3</sub> (0.21 g, 2.6 mmol) and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (91 mg, 0.013 mmol). The reaction mixture was heated to 80 °C for 12 h. Then the mixture was diluted with EtOAc (100 mL) at room temperature, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by a silica gel column to afford the title compound **2** (0.83 g, 75%). MS(ESI): m/z 427.15 (M + H)<sup>+</sup>.

**N1-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine (Compound 3)**

**[00287]** To a solution of **2** (0.83 g, 1.95 mmol) in 2-BuOH(5.0 mL) was added benzene-1,3-diamine (0.21 g, 1.95 mmol) and PTSA (0.33 mg, 1.95 mmol). The reaction mixture was heated to 120 °C for 12 h. Then the resulting mixture was diluted with EtOAc (150 mL) at room temperature, washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by a silica gel column to afford the title compound **3** (0.31 g, 32%). MS(ESI): m/z 499.21 (M + H)<sup>+</sup>.

**4-nitro-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (Compound 4)**

**[00288]** To a solution of **3** (0.31 g, 0.62 mmol) in DCM(5.0 mL) was added 4-nitrobenzoyl chloride (0.47 g, 0.93 mmol) and DIPEA (0.20 mL). The reaction mixture was stirred at room temperature for 2 h. Then the resulting mixture was concentrated and purified by a silica gel column to afford the title compound **4** (0.32 g, 81%). MS(ESI): m/z 648.30 (M + H)<sup>+</sup>.

**4-amino-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (Compound 5)**

**[00289]** To a solution of **4** (0.32 g, 0.5 mmol) in MeOH(8.0 mL) was added 10% Pd/C (120 mg) and protected by a balloon of H<sub>2</sub>. The reaction mixture was stirred at 25 °C for 12 h. Then the resulting mixture was filtered through a pad of celite. The crude product was purified by a silica gel column to afford the title compound **5** (0.25 g, 80%). MS(ESI): m/z 618.24 (M + H)<sup>+</sup>.

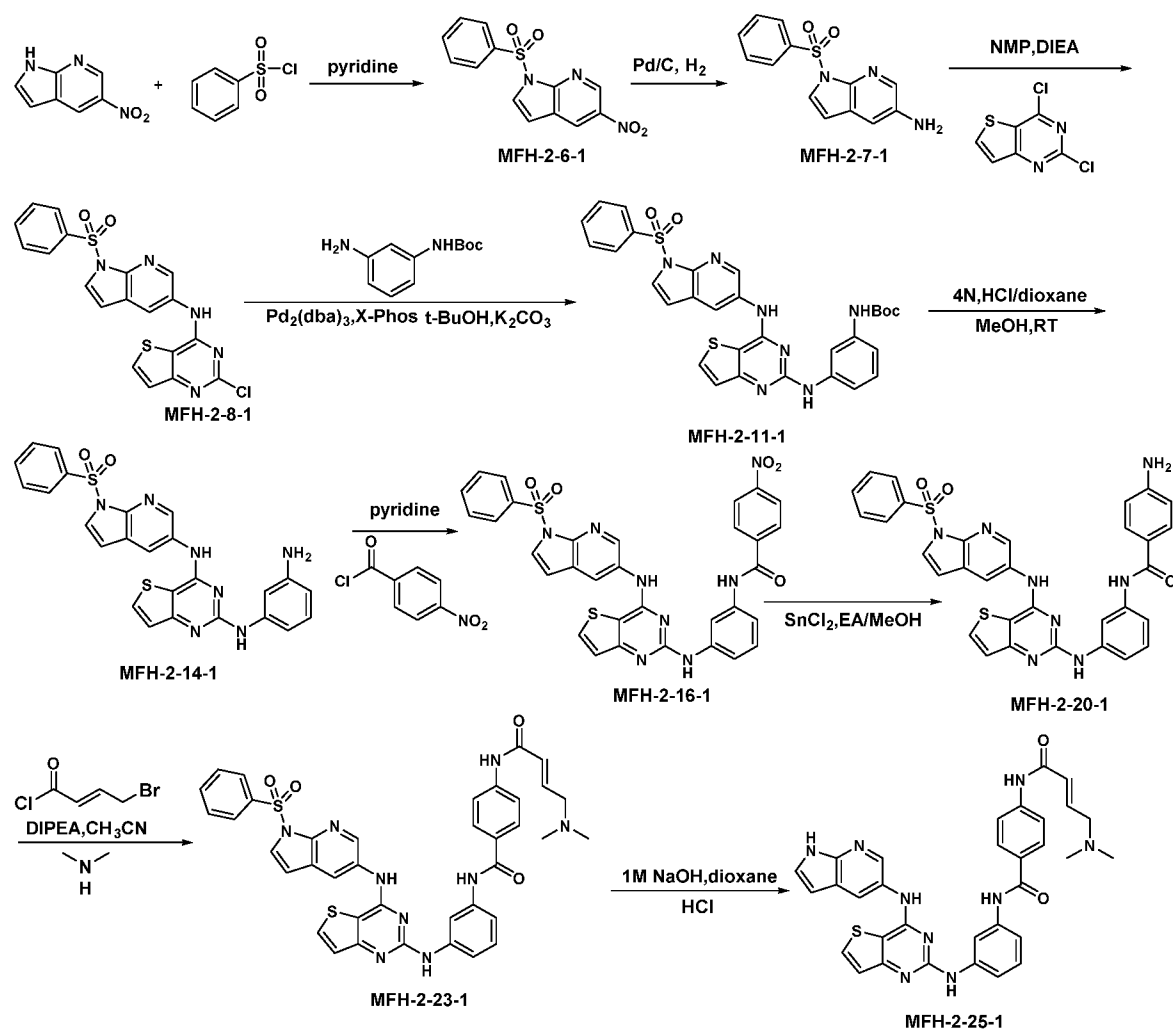
**(E)-4-(4-(dimethylamino)but-2-enamido)-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (Compound 6)**

**[00290]** To a solution of **5** (0.25 g, 0.4 mmol) in CH<sub>3</sub>CN(8.0 mL) was added (E)-4-bromobut-2-enoyl chloride (0.10 g, 0.6 mmol) and DIPEA (0.12 mL). The reaction mixture was stirred at 0 °C for 0.5 h. Then 1 mL of 2.0 M dimethylamine (in THF) was added. The resulting mixture was concentrated and purified by a silica gel column to afford the title compound **6** (0.12 g, 42%). MS(ESI): m/z 729.11 (M + H)<sup>+</sup>.

**(E)-N-(4-(5-chloro-4-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-2-ylamino)phenyl)-3-(4-(dimethylamino)but-2-enamido)benzamide(Compound 7)**

**[00291]** To a solution of **6** (100 mg, 0.13 mmol) in dioxane (4.0 mL) was 1M NaOH (1 mL). The reaction mixture was stirred at room temperature for 2 h. Then resulting mixture was concentrated and purified by a silica gel column to afford the title compound **7** (18.4 mg). MS  $m/z$  589.18 ( $M + H$ )<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  12.00(s, 1 H), 10.69 (s, 1 H), 10.13 (s, 1 H), 9.73 (s, 1 H), 9.02 (s, 1 H), 8.76 (s, 1 H), 8.37 (s, 2 H), 7.96 (d,  $J = 7.8$  Hz, 2 H), 7.80 (d,  $J = 7.8$  Hz, 2 H), 7.55-7.43 (m, 2 H), 7.42 (s, 1 H), 7.28-7.00 (m, 2 H), 6.81-6.77 (m, 1 H), 6.48 (d,  $J = 15.2$  Hz, 1 H), 3.86 (d,  $J = 15.2$  Hz, 2 H), 2.71 (s, 6 H).

**Example 2. Synthesis of compound MFH-2-25-1**



**5-nitro-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (MFH-2-6-1)**

**[00292]** A mixture of 5-nitro-1H-pyrrolo[2,3-b]pyridine (300 mg, 1.84 mmol) and benzenesulfonyl chloride (812 mg, 4.6 mmol) in pyridine (3 mL) was refluxed for 6 hours.

Then the reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel (PE/EA = 0-50%) to obtain **MFH-2-6-1** (530 mg, yield 95%). LCMS (m/z): 304 [M + H]<sup>+</sup>.

**1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-amine (MFH-2-7-1)**

**[00293]** A mixture of **MFH-2-6-1** (530 mg, 1.75 mmol) and 10% Pd/C (50 mg) in MeOH (20 mL) was stirred overnight at room temperature with an H<sub>2</sub> balloon. The mixture was filtered through CELITE, and solvent was removed to give **MFH-2-7-1** (230 mg, yield 48%). LCMS (m/z): 274 [M + H]<sup>+</sup>.

**2-chloro-N-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-4-amine (MFH-2-8-1)**

**[00294]** A solution of **MFH-2-7-1** (230 mg, 0.84 mmol), 2,4-dichlorothieno[3,2-d]pyrimidine (173 mg, 0.84 mmol) and DIEA (163 mg, 1.26 mmol) in NMP (1 mL) was stirred at 100 °C for 10 hours. The mixture was then extracted with chloroform and isopropanol(4:1). The organic phase was washed with brine (50 mL × 2) and dried over Na<sub>2</sub>SO<sub>4</sub>. The removal of the solvent to provide the residue which was purified by silica gel (MeOH/DCM = 0-20%) to give **MFH-2-8-1** (259 mg, yield 70%). LCMS (m/z): 442 [M + H]<sup>+</sup>.

**tert-butyl 3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-ylamino)thieno[3,2-d]pyrimidin-2-ylamino)phenylcarbamate (MFH-2-11-1)**

**[00295]** A mixture of **MFH-2-8-1** (259 mg, 0.57 mmol), tert-butyl 3-aminophenylcarbamate (147 mg, 0.7 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (48 mg, 0.1 mmol), K<sub>2</sub>CO<sub>3</sub> (118 mg, 0.86 mmol), and Pd<sub>2</sub>(dba)<sub>3</sub> (91 mg, 0.1 mmol) in tert-Butanol (8 mL) was refluxed for 5 hours under N<sub>2</sub> atmosphere. After cooling down to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with chloroform and isopropanol (4:1). The organic phase was washed with brine (50 mL × 2), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM, 0-20%) to give **MFH-2-11-1** (170 mg, yield 49%). LCMS (m/z): 614 [M + H]<sup>+</sup>.

**N2-(3-aminophenyl)-N4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidine-2,4-diamine (MFH-2-14-1)**

**[00296]** To a mixture of compound **MFH-2-11-1** (170 mg, 0.28 mmol) in methanol (5 mL) was added 4 N HCl/dioxane (6 mL) and the resulted solution was stirred for 3 hours. The mixture was concentrated under reduced pressure to provide the crude which was directly used in the next step. LCMS (m/z): 514 [M + H]<sup>+</sup>.

**4-nitro-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-ylamino)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-16-1)**

**[00297]** A mixture of **MFH-2-14-1** (140 mg, 0.27 mmol) and 4-nitrobenzoyl chloride (61 mg, 0.33 mmol) in pyridine (2 mL) was refluxed overnight. Then the reaction mixture was concentrated under reduced pressure, and the residue was directly used in the next step. LCMS (m/z): 663 [M + H]<sup>+</sup>.

**4-amino-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-ylamino)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-20-1)**

**[00298]** To a solution of **MFH-2-16-1** (179 mg, 0.27 mmol) in ethyl acetate and methanol (1:1) were added Tin(II) chloride dehydrate (183 mg, 0.81 mmol) and conc. HCl (0.1 mL). After stirring for 3 hours at 80 °C, the reaction mixture was diluted with chloroform and iso-propanol (4:1), neutralized with saturated NaHCO<sub>3</sub>, and filtered. The filtrate was extracted with chloroform and iso-propanol(4:1) and concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (MeOH/DCM = 0-20%) to give **MFH-2-20-1** (90 mg, yield 53%). LCMS (m/z): 633 [M + H]<sup>+</sup>.

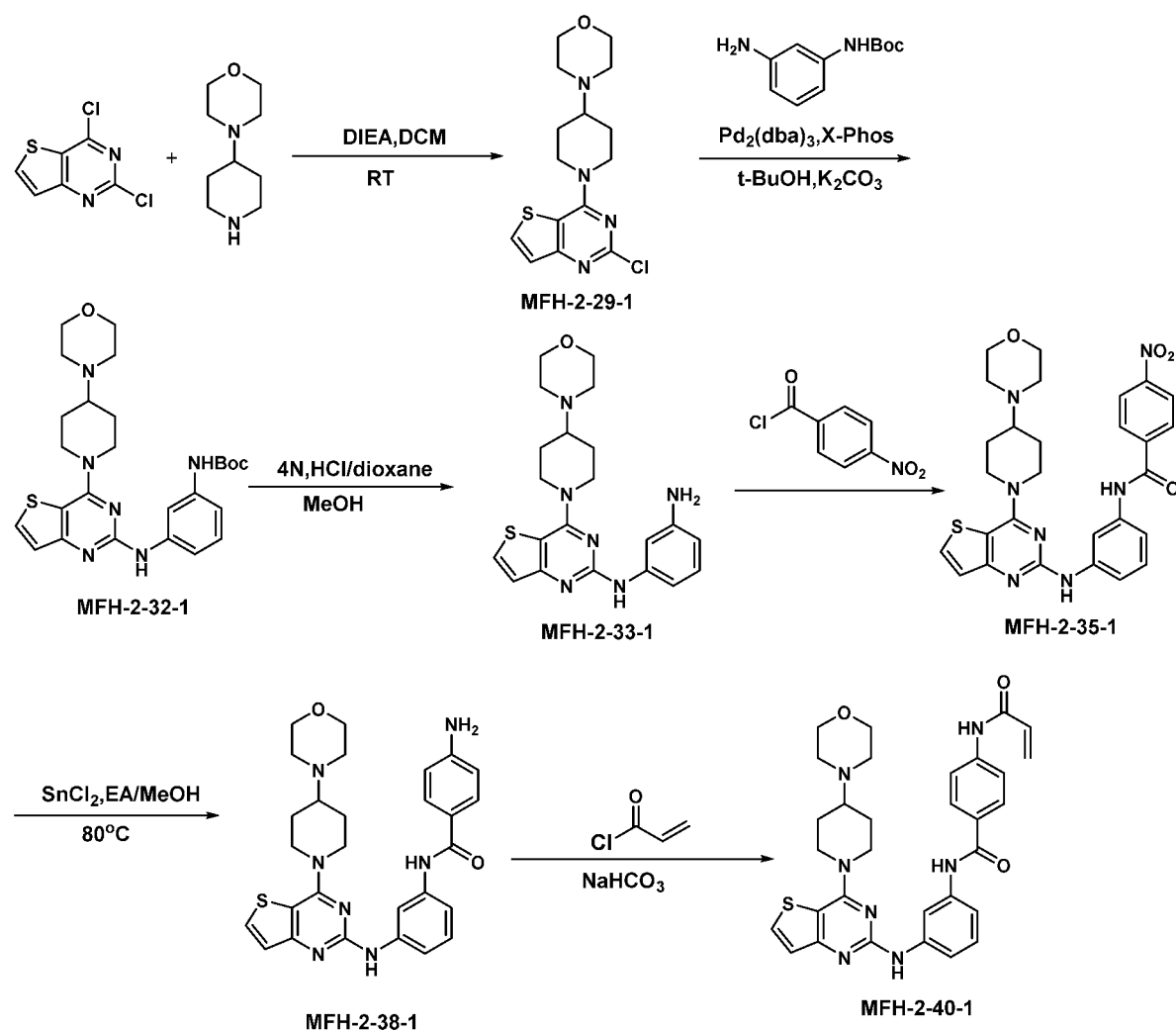
**(E)-4-(4-bromobut-2-enamido)-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-ylamino)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide(MFH-2-23-1)**

**[00299]** A solution of (E)-4-bromobut-2-enoic acid (12 mg, 0.07 mmol) in SOCl<sub>2</sub> (0.2 mL) was stirred at 70 °C for 1 hour under N<sub>2</sub> atmosphere. The mixture was cooled to room temperature and then was concentrated under reduced pressure. The residue was diluted with dichloromethane, and the resulted solution was added dropwise to a solution of **MFH-2-20-1** (30 mg, 0.05 mmol) and DIPEA (0.2 mL) in CH<sub>3</sub>CN (2 mL) at 0 °C. After stirring for 1 hour at 0 °C, a solution of dimethylamine in THF (2 mol/L, 0.05 mL, 0.1 mmol) was added, and the reaction mixture was stirred at room temperature for 1 hour. The removal of the solvent under

reduced pressure provided the residue which was purified by HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to obtain **MFH-2-23-1** (30 mg, yield 86%). LCMS (m/z): 744 [M + H]<sup>+</sup>.

**(E)-N-(3-(4-(1H-pyrrolo[2,3-b]pyridin-5-ylamino)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)-4-(4-(dimethylamino)but-2-enamido)benzamide (MFH-2-25-1):**

**[00300]** A solution of **MFH-2-23-1** (30 mg, 0.04mmol) in 1 M NaOH (5 ml) and dioxane (5 mL) was stirred at room temperature for 2 hours. The solution was then neutralized (1 M HCl) and concentrated under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to obtain **MFH-2-25-1** (off-white solid, 6.8 mg, yield 28%). LCMS (m/z): 604 [M + H]<sup>+</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.78 (s, 1H), 10.77 (s, 1H), 10.64 (s, 1H), 10.32 (s, 1H), 10.22 (s, 1H), 10.05 (s, 1H), 8.37 (s, 1H), 8.27 (s, 2H), 7.93 (t, J = 10.6 Hz, 3H), 7.80 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.40 (s, 1H), 7.31 (d, J = 5.2 Hz, 1H), 7.19 (s, 1H), 6.84 – 6.73 (m, 1H), 6.50 (d, J = 15.3 Hz, 1H), 6.46 (s, 1H), 3.18 (d, 2H) 2.81 (s, 6H).

**Example 3. Synthesis of compound MFH-2-40-1****4-(1-(2-chlorothieno[3,2-d]pyrimidin-4-yl)piperidin-4-yl)morpholine (MFH-2-29-1)**

**[00301]** To a solution of 2,4-dichlorothieno[3,2-d]pyrimidine (300 mg, 1.46 mmol) and DIPEA (227 mg, 1.76 mmol) in DCM (5 mL) was added 4-(piperidin-4-yl)morpholine (274 mg, 1.61 mmol) in DCM (3 mL) dropwise at room temperature. The mixture was stirred at room temperature for 3 hours and then was concentrated under reduced pressure. The residue was purified by silica gel (NH<sub>3</sub>/MeOH(1.75N)/DCM = 0-20%) to obtain **MFH-2-29-1** (496 mg, yield 100%). LCMS (m/z): 339 [M + H]<sup>+</sup>.

**tert-butyl 3-(4-(4-morpholinopiperidin-1-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenylcarbamate (MFH-2-32-1)**

**[00302]** A solution of **MFH-2-29-1** (496 mg, 1.46 mmol), tert-butyl 3-aminophenylcarbamate (335 mg, 1.61 mmol), 2-Dicyclohexylphosphino-2',4',6'-

triisopropylbiphenyl (105 mg, 0.22 mmol),  $K_2CO_3$  (243 mg, 1.76 mmol), and  $Pd_2(dba)_3$  (201 mg, 0.22 mmol) in tert-Butanol (10 mL) was refluxed for 5 hours under  $N_2$  atmosphere. The mixture was cooled to room temperature, diluted with water (20 mL), and extracted with chloroform and iso-propanol(4:1). The organic phase was washed with brine (50 mL  $\times$  2), dried over  $Na_2SO_4$ , and filtered, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography ( $NH_3/MeOH(1.75N)/DCM$  20%) to give **MFH-2-32-1** (700 mg, yield 94%). LCMS (m/z): 511  $[M + H]^+$ .

**N1-(4-(4-morpholinopiperidin-1-yl)thieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine (MFH-2-33-1)**

**[00303]** To a mixture of compound **MFH-2-32-1** (700 mg, 1.37 mmol) in methanol (6 mL) was added 4 N HCl/dioxane (12 mL), and the reaction was stirred for 3 hours at room temperature. The solution was concentrated under reduced pressure, and the residue was used directly in the next step. LCMS (m/z): 411  $[M + H]^+$ .

**N-(3-(4-(4-morpholinopiperidin-1-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)-4-nitrobenzamide (MFH-2-35-1)**

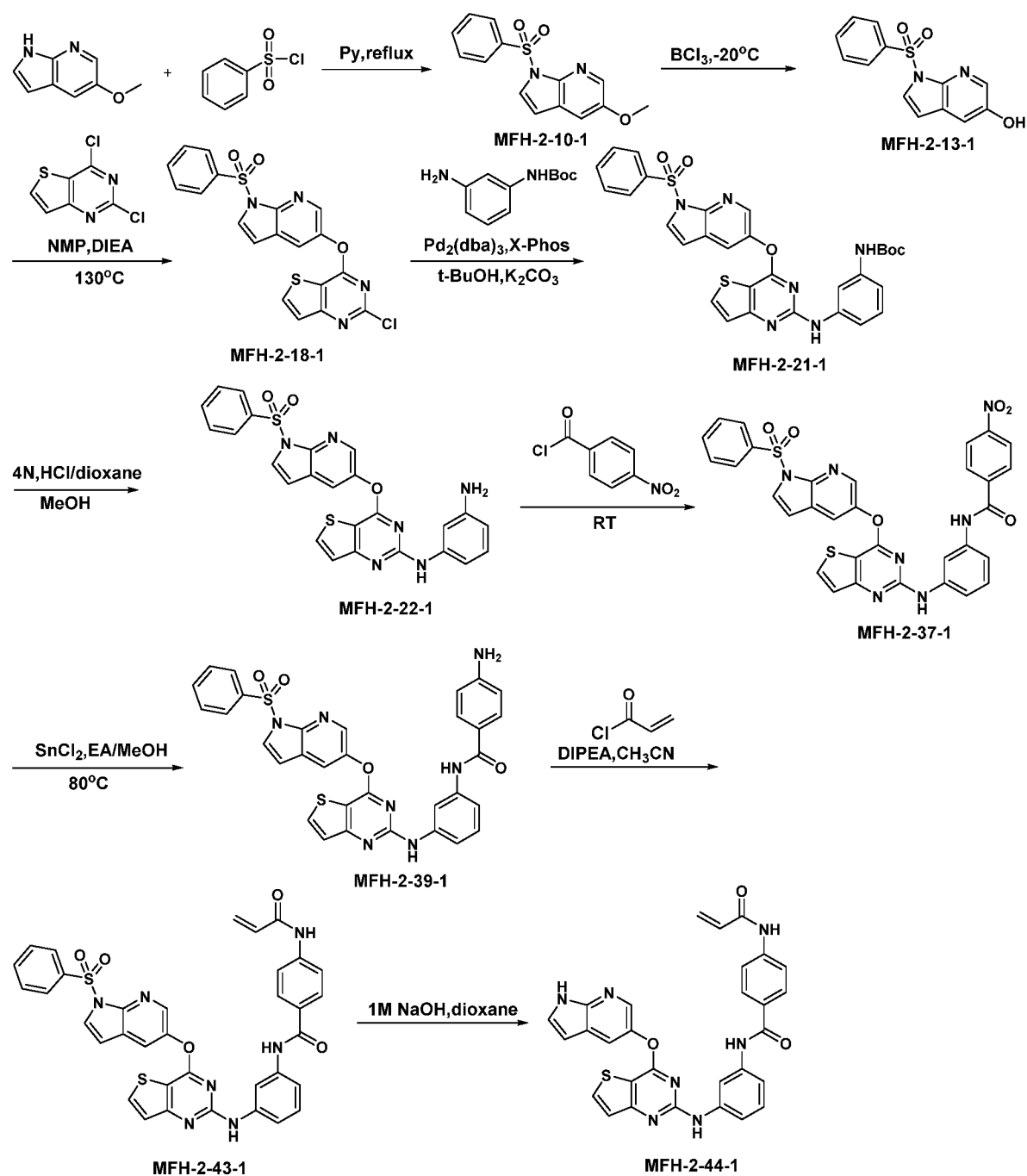
**[00304]** A mixture of **MFH-2-33-1** (570 mg, 1.39 mmol), 4-nitrobenzoyl chloride (322 mg, 1.74 mmol), and pyridine (3 mL) was refluxed overnight. Then the reaction mixture was concentrated under reduced pressure, and the residue was directly used in the next step. LCMS (m/z): 560  $[M + H]^+$ .

**4-amino-N-(3-(4-(4-morpholinopiperidin-1-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-38-1)**

**[00305]** To a solution of **MFH-2-35-1** (430 mg, 0.77 mmol) in ethyl acetate and methanol (1:1) were added Tin(II) chloride dehydrate (522 mg, 2.31 mmol) and conc. HCl (0.2 mL). After stirring for 3 hours at 80 °C, the reaction mixture was diluted with chloroform and iso-propanol (4:1) and neutralized with saturated  $NaHCO_3$ . The solution was then filtered, and the filtrate was extracted with chloroform and iso-propanol (4:1). Concentration under reduced pressure provided the crude which was purified by silica gel column chromatography ( $NH_3/MeOH(1.75N)/DCM = 0-20\%$ ) to give **MFH-2-38-1** (200 mg, yield 49%). LCMS (m/z): 530  $[M + H]^+$ .

**4-acrylamido-N-(3-(4-(4-morpholinopiperidin-1-yl)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-40-1)**

**[00306]** To a solution of **MFH-2-38-1** (50 mg, 0.09 mmol) in sat. NaHCO<sub>3</sub> (3 mL) and THF (3 mL) was added acryloyl chloride (11 mg, 0.12 mmol) in DCM (0.5 mL) dropwise at 0 °C. The mixture was stirred for 1 hour and then was concentrated under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to obtain **MFH-2-40-1** (off-white solid, 14 mg, yield 25%). LCMS (m/z): 584 [M + H]<sup>+</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 10.47 (s, 1H), 10.13 (s, 1H), 9.95 (s, 1H), 9.46 (s, 1H), 8.32 (s, 1H), 8.17 (d, J = 5.4 Hz, 1H), 7.98 (d, J = 8.7 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 7.3 Hz, 1H), 7.28 (s, 1H), 7.26 (d, J = 1.0 Hz, 1H), 7.24 (s, 1H), 6.49 (dd, J = 17.0, 10.2 Hz, 1H), 6.32 (dd, J = 17.0, 1.9 Hz, 1H), 5.82 (dd, J = 10.1, 1.9 Hz, 1H), 3.97 (s, 4H), 3.08 (s, 4H), 3.03 (s, 1H), 2.21 (d, J = 10.8 Hz, 4H), 1.71 (d, J = 9.1 Hz, 4H).

**Example 4. Synthesis of compound MFH-2-44-1****5-methoxy-1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridine (MFH-2-10-1)**

**[00307]** A mixture of 5-methoxy-1H-pyrrolo[2,3-b]pyridine (800 mg, 5.4 mmol) and benzenesulfonyl chloride (1.9 g, 10.8 mmol) in pyridine (8 mL) was refluxed overnight. Then the reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel (PE/EA = 0-50%) to obtain **MFH-2-10-1** (646 mg, yield 42%). LCMS (m/z): 289 [M + H]<sup>+</sup>.

**1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-ol (MFH-2-13-1)**

**[00308]** To a solution of **MFH-2-10-1** (646 mg, 2.25 mmol) in DCM (20 mL) was added boron trichloride in hexane (1 mol/L, 22.5 ml, 22.5 mmol) dropwise at -15 °C. The mixture was warmed to room temperature and the mixture was stirred overnight. After completion, water (50 ml) was added at 0 °C and the aqueous layer was extracted with DCM. The combined organic layers was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by silica gel column chromatography (PE/EA = 0-50%) to give **MFH-2-13-1** (353 mg, yield 57%). LCMS (m/z): 275 [M + H]<sup>+</sup>.

**2-chloro-4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidine (MFH-2-18-1)**

**[00309]** A mixture of **MFH-2-13-1** (353 mg, 1.29 mmol), 2,4-dichlorothieno[3,2-d]pyrimidine (205 mg, 1.00 mmol), and DIEA (259 mg, 2.00 mmol) in NMP (2 mL) was stirred at 130 °C for 10 hours. The residue was extracted with chloroform and iso-propanol (4:1). The organic phase was washed with brine (50 mL × 2) and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the residue was purified by silica gel (MeOH/DCM = 0-20%) to obtain **MFH-2-18-1** (290 mg, yield 51%). LCMS (m/z): 443 [M + H]<sup>+</sup>.

**tert-butyl 3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-ylamino)phenylcarbamate (MFH-2-21-1)**

**[00310]** A mixture of **MFH-2-18-1** (290 mg, 0.66 mmol), tert-butyl 3-aminophenylcarbamate (164 mg, 0.79 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (63 mg, 0.13 mmol), K<sub>2</sub>CO<sub>3</sub> (109 mg, 0.79 mmol), and Pd<sub>2</sub>(dba)<sub>3</sub> (120 mg, 0.13 mmol) in tert-Butanol (8 mL). The mixture was stirred at reflux for 5 hours under N<sub>2</sub> atmosphere. The mixture was cooled to room temperature and diluted with water (20 ml) and extracted with chloroform and iso-propanol (4:1). The organic phase was washed with brine (50 mL × 2). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give the crude which was purified by silica gel column chromatography (MeOH/DCM = 0-20%) to give **MFH-2-21-1** (400 mg, yield 99%). LCMS (m/z): 615 [M + H]<sup>+</sup>.

**N1-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine (MFH-2-22-1)**

[00311] To a solution of **MFH-2-21-1** (400 mg, 0.65 mmol) in methanol (5 mL) was added 4 N HCl/dioxane (12 mL). The solution was then stirred for 3 hours at room temperature, and the solvent was removed under reduced pressure to provide a crude which was directly used in the next step. LCMS (m/z): 515 [M + H]<sup>+</sup>.

**4-nitro-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-37-1)**

[00312] The mixture of **MFH-2-22-1** (200.0 mg, 0.39 mmol) and 4-nitrobenzoyl chloride (72.0 mg, 0.39 mmol) in pyridine (3.0 mL) was refluxed overnight. Then the reaction mixture was concentrated under reduced pressure, and the residue was directly used in the next step. LCMS (m/z): 664 [M + H]<sup>+</sup>.

**4-amino-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-39-1)**

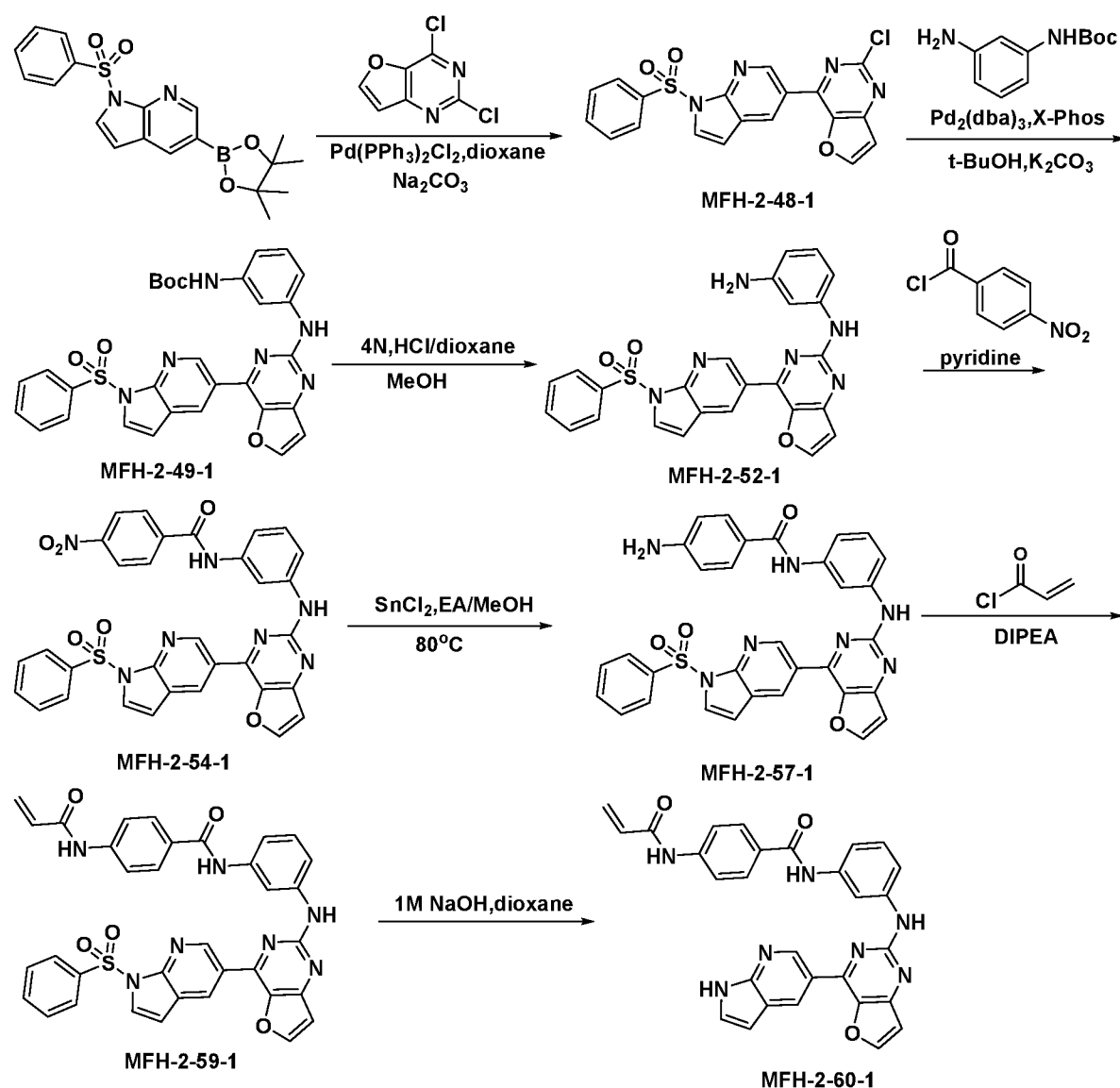
[00313] To a solution of **MFH-2-37-1** (258 mg, 0.39 mmol) in ethyl acetate and methanol (1:1) was added Tin(II) chloride dehydrate (271 mg, 1.2 mmol). After stirring for 3 hours at 80 °C, the reaction mixture was diluted with chloroform and iso-propanol (4:1) and neutralized with saturated NaHCO<sub>3</sub>. The mixture was then filtered, and the filtrate was extracted with chloroform and iso-propanol (4:1). The solvent was then removed under reduced pressure, and the resulting residue was purified by silica gel column chromatography (MeOH/DCM = 0-20%) to give **MFH-2-39-1** (120 mg, yield 48%). LCMS (m/z): 634 [M + H]<sup>+</sup>.

**4-acrylamido-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-43-1)**

[00314] To a solution of **MFH-2-39-1** (25 mg, 0.04 mmol) and DIPEA (0.2 mL) in CH<sub>3</sub>CN (2 mL) was added acryloyl chloride (5 mg, 0.05 mmol) in DCM (0.2 mL) dropwise. The mixture was then stirred at 0 °C for 1 hour. The solution was then concentrated under reduced pressure, and the residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to provide **MFH-2-43-1** (22 mg, yield 80%). LCMS (m/z): 688 [M + H]<sup>+</sup>.

**N-(3-(4-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)thieno[3,2-d]pyrimidin-2-ylamino)phenyl)-4-acrylamidobenzamide (MFH-2-44-1):**

**[00315]** To a solution of **MFH-2-43-1** (22 mg, 0.03mmol) in 1M NaOH (3 ml) and dioxane (3 mL) was stirred at room temperature for 2 hours. The solution was neutralized (1 M HCl) and concentrated under reduced pressure. The residue was purified by prep-HPLC (MeOH/H<sub>2</sub>O, 0.05% TFA) to obtain **MFH-2-44-1** (3.8 mg, yield 22%). LCMS (m/z): 548 [M + H]<sup>+</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.82 (s, 1H), 10.44 (d, J = 10.0 Hz, 1H), 10.05 (s, 1H), 9.44 (s, 1H), 8.30 (d, J = 5.4 Hz, 1H), 8.26 (d, J = 2.5 Hz, 1H), 8.03 (t, J = 4.9 Hz, 1H), 7.99 (d, J = 7.0 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.80 (d, J = 8.8 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.38 (dd, J = 13.7, 6.8 Hz, 2H), 7.28 – 7.19 (m, 1H), 6.93 (t, J = 8.1 Hz, 1H), 6.51 (dd, J = 3.4, 1.8 Hz, 1H), 6.49 – 6.43 (m, 1H), 6.31 (dd, J = 17.0, 1.9 Hz, 1H), 5.81 (dd, J = 10.1, 1.9 Hz, 1H).

**Example 5. Synthesis of compound MFH-2-60-1****2-chloro-4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidine (MFH-2-48-1)**

**[00316]** A mixture of 2,4-dichlorofuro[3,2-d]pyrimidine (300 mg, 1.59 mmol), 1-(phenylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (640 mg, 1.67 mmol), Sat.  $\text{Na}_2\text{CO}_3$  (3 mL), and  $\text{Pd(PPh}_3)_2\text{Cl}_2$  (167 mg, 0.24 mmol) in dioxane (6 mL) was stirred at  $80^\circ\text{C}$  for 2 hours under  $\text{N}_2$  atmosphere. The mixture was then cooled to room temperature and diluted with water (30 mL). The residue was extracted with chloroform and iso-propanol (4:1), and the organic phase was washed with brine (50 mL  $\times$  2) and dried with  $\text{Na}_2\text{SO}_4$ . The solvent was then removed, and the residue was purified by silica

gel (MeOH/DCM = 0-10%) to obtain **MFH-2-48-1** (520 mg, yield 79%). LCMS (m/z): 411 [M + H]<sup>+</sup>.

**tert-butyl3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-ylamino)phenylcarbamate (MFH-2-49-1)**

[00317] A mixture of **MFH-2-48-1** (520 mg, 1.27 mmol), tert-butyl 3-aminophenylcarbamate (277 mg, 1.33 mmol), 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (91 mg, 0.19 mmol) K<sub>2</sub>CO<sub>3</sub> (210 mg, 1.52 mmol), and Pd<sub>2</sub>(dba)<sub>3</sub> (174 mg, 0.19 mmol) in tert-Butanol (8 mL) was refluxed for 5 hours under N<sub>2</sub> atmosphere. The mixture was cooled to room temperature and diluted with water (20 mL) and extracted with chloroform and iso-propanol (4:1). The organic phase was washed with brine (50 mL × 2) and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM = 0-20%) to give **MFH-2-49-1** (310 mg, yield 42%). LCMS (m/z): 583 [M + H]<sup>+</sup>.

**N1-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-yl)benzene-1,3-diamine (MFH-2-52-1)**

[00318] To a mixture of compound **MFH-2-49-1** (310 mg, 0.53 mmol) in methanol (5 mL) was added 4 N HCl/dioxane (8 mL). The mixture was stirred for 3 hours at room temperature and then was concentrated under reduced pressure to give a crude which was used directly in the next step. LCMS (m/z): 483 [M + H]<sup>+</sup>.

**4-nitro-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-54-1)**

[00319] A mixture of **MFH-2-52-1** (220 mg, 0.46 mmol), 4-nitrobenzoyl chloride (101 mg, 0.55 mmol), and pyridine (2 mL) was refluxed for overnight. Then the reaction mixture was concentrated under reduced pressure, and the residue was used directly in the next step. LCMS (m/z): 632 [M + H]<sup>+</sup>.

**4-amino-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-57-1)**

[00320] To a solution of **MFH-2-54-1** (290 mg, 0.46 mmol) in ethyl acetate and methanol (1:1) were added tin(II) chloride dehydrate (312 mg, 1.38 mmol) and conc. HCl (0.1 mL).

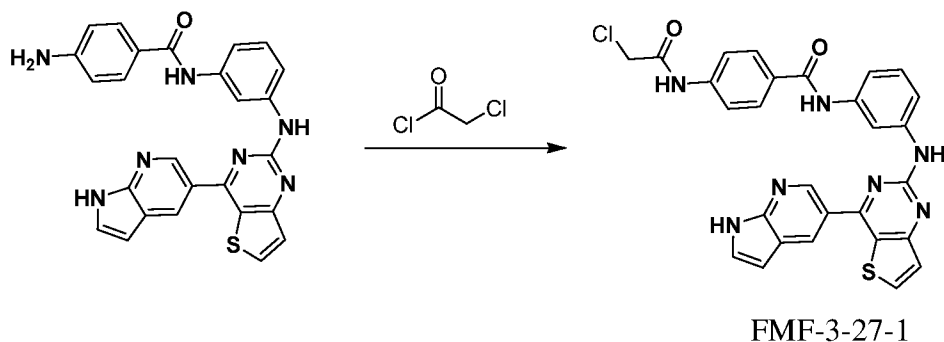
After stirring for 3 hours at 80 °C, the reaction mixture was diluted with chloroform and iso-propanol (4:1), neutralized with saturated NaHCO<sub>3</sub>, and filtered. The filtrate was extracted with chloroform and iso-propanol (4:1) and concentrated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (MeOH/DCM = 0-20%) to give **MFH-2-57-1** (140 mg, yield 51%). LCMS (m/z): 602 [M + H]<sup>+</sup>.

**4-acrylamido-N-(3-(4-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-ylamino)phenyl)benzamide (MFH-2-59-1)**

**[00321]** To a solution of **MFH-2-57-1** (40 mg, 0.07 mmol) and DIPEA (0.2 mL) in CH<sub>3</sub>CN (2 mL) was added acryloyl chloride (8 mg, 0.09 mmol) in DCM (0.2 mL) dropwise. The mixture was then stirred at 0 °C for 1 hour and then was concentrated under reduced pressure. The residue was purified by prep-HPLC (C18 column, MeOH/H<sub>2</sub>O, containing 0.05% TFA) to obtain **MFH-2-59-1** (off-white solid, 40 mg, yield 87%). LCMS (m/z): 656 [M + H]<sup>+</sup>.

**N-(3-(4-(1H-pyrrolo[2,3-b]pyridin-5-yl)furo[3,2-d]pyrimidin-2-ylamino)phenyl)-4-acrylamidobenzamide (MFH-2-60-1):**

**[00322]** To a solution of **MFH-2-59-1** (40 mg, 0.06mmol) in 1 M NaOH (4 mL) and dioxane (4 mL) was stirred at room temperature for 2 hours. The reaction solution was neutralized (1 M HCl), concentrated under reduced pressure. The residue was purified by prep-HPLC (C<sub>18</sub> column, MeOH/H<sub>2</sub>O, containing 0.05% TFA) to obtain **MFH-2-60-1** (off-white solid, 6.8 mg, yield 22%), LCMS (m/z): 516 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 12.02 (s, 1H), 10.44 (s, 1H), 10.14 (d, J = 15.8 Hz, 1H), 9.61 (s, 1H), 9.35 (s, 1H), 9.09 (d, J = 1.7 Hz, 1H), 8.48 (d, J = 2.2 Hz, 1H), 8.43 (s, 1H), 7.99 (dd, J = 18.6, 8.6 Hz, 2H), 7.82 (t, J = 12.7 Hz, 2H), 7.62 – 7.59 (m, 1H), 7.58 – 7.55 (m, 1H), 7.33 – 7.26 (m, 2H), 7.06 (d, J = 2.2 Hz, 1H), 6.62 (dd, J = 3.3, 1.7 Hz, 1H), 6.49 (dd, J = 16.9, 10.1 Hz, 1H), 6.33 (dd, J = 17.0, 1.8 Hz, 1H), 5.83 (dd, J = 10.1, 1.8 Hz, 1H).

**Example 6. Synthesis of compound FMF-3-27-1****N-(3-((4-(1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-yl)amino)phenyl)-4-(2-chloroacetamido)benzamide**

**[00323]** N-(3-((4-(1H-pyrrolo[2,3-b]pyridin-5-yl)thieno[3,2-d]pyrimidin-2-yl)amino)phenyl)-4-aminobenzamide (30 mg, 0.06 mmol) was dissolved in 5 mL THF and 5 mL saturated aqueous solution of NaHCO<sub>3</sub>. The reaction mixture was cooled to 0 °C. A 1.3 mM solution of 2-chloroacetyl chloride in THF was added drop-wise until the reaction was complete as analyzed by LC/MS. The reaction mixture was diluted with water and extracted with dichloromethane (3 × 20 mL), dried over MgSO<sub>4</sub>, concentrated, and purified by HPLC to give the title compound (10 mg, 0.02 mmol) as a TFA salt. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.04 (s, 1H), 10.60 (s, 1H), 10.17 (s, 1H), 9.77 (s, 1H), 9.07 (d, *J* = 2.0 Hz, 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.48 – 8.29 (m, 2H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.47 (d, *J* = 5.5 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 6.64 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.32 (s, 2H). MS (ESI) *m/z*: 555 Da (M + H)<sup>+</sup>.

*Biological Evaluation***Example 7. Kinase assay**

**[00324]** PIP4K *in vitro* kinase assay was carried out as described in Rameh *et al* (Nature, 1997). Briefly, 0.1 ug of GST-PI5P4Ka or 0.4ug of GST-PI5P4Ka resuspended in 70uL of kinase buffer containing 20 mM HEPES pH 7.4, 100 mM NaCl, 0.5mM EGTA was stabilized at room temperature for 10 minutes and incubated with 1uM of DMSO or indicated compound for 30 minutes. Then the kinase reaction was carried out in a total volume of 100uL for 10 minutes by adding 20 uL of lipid substrates (4ug of phosphatidylserine and 2ug of PI5P) in buffer containing 30 mM HEPES pH7.4 and 1 mM EGTA, and 10 uL of ATP mix (500 uM non-radiolabeled ATP, 10 uCi [<sup>32</sup>P]-ATP, 65 mM HEPES pH7.4 and 100 mM

MgCl<sub>2</sub>). The reaction was terminated by adding 50 uL of HCl. Phosphoinositides were extracted by adding 100 uL methanol/chloroform (1:1, vol:vol) mix and subjected to thin layer chromatography separation using heat-activated 1% potassium oxalate-coated silica gel 60 plates (EMD Chemicals Inc., Billerica, MA, USA) and a 1-propanol/2 M acetic acid (65:35, vol:vol) solvent system. The radiolabeled PI(4,5)P<sub>2</sub> was quantified with a Phosphorimager (Molecular Dynamics, STORM840, GE Healthcare, Waukesha, WI, USA).

#### **Example 8. Cell proliferation assay**

**[00325]** To determine cell proliferation, cells were plated at  $2 \times 10^3$  cells per well of 96-well plate. Cells were incubated and assayed at indicated times using Cell Titer-Glo Luminescent Cell Viability assay (Promega). Cells were allowed to equilibrate to room temperature for 15 minutes, then an equal volume of the Cell Titer-Glo reagent was added to wells and incubated for 15 minutes on an orbital shaker. Luminescence was recorded according to the manufacturer's protocol.

#### **EQUIVALENTS AND SCOPE**

**[00326]** 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.

**[00327]** 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.

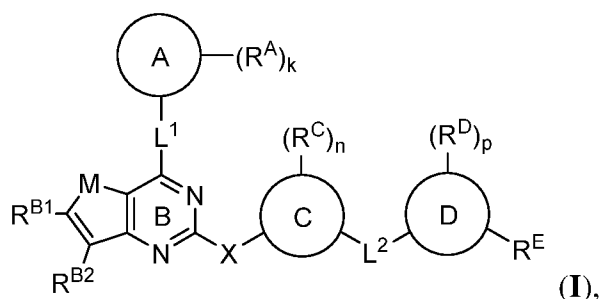
**[00328]** This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

**[00329]** 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 (I):



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is a substituted or unsubstituted, monocyclic or bicyclic heteroaryl ring or a substituted or unsubstituted, monocyclic heterocyclic ring;

each instance of  $R^A$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

each instance of  $R^a$  is independently hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of  $R^a$  are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring;

k is 0, 1, 2, 3, 4, 5, or 6;

M is  $NR^M$ , O, or S;

$R^M$  is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or

unsubstituted heteroaryl, or a nitrogen protecting group;

$L^1$  is a bond,  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ ;

each instance of  $R^b$  is independently hydrogen, halogen, or substituted or unsubstituted  $C_{1-6}$  alkyl;

each instance of  $R^c$  is independently hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

$R^{B1}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

$R^{B2}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

$X$  is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ , or  $-NR^cS(=O)_2-$ ;

Ring C is a substituted or unsubstituted phenyl ring;

Ring D is a substituted or unsubstituted phenyl ring;

each instance of  $R^c$  is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ;

OC(=O)N(R<sup>a</sup>)<sub>2</sub>;

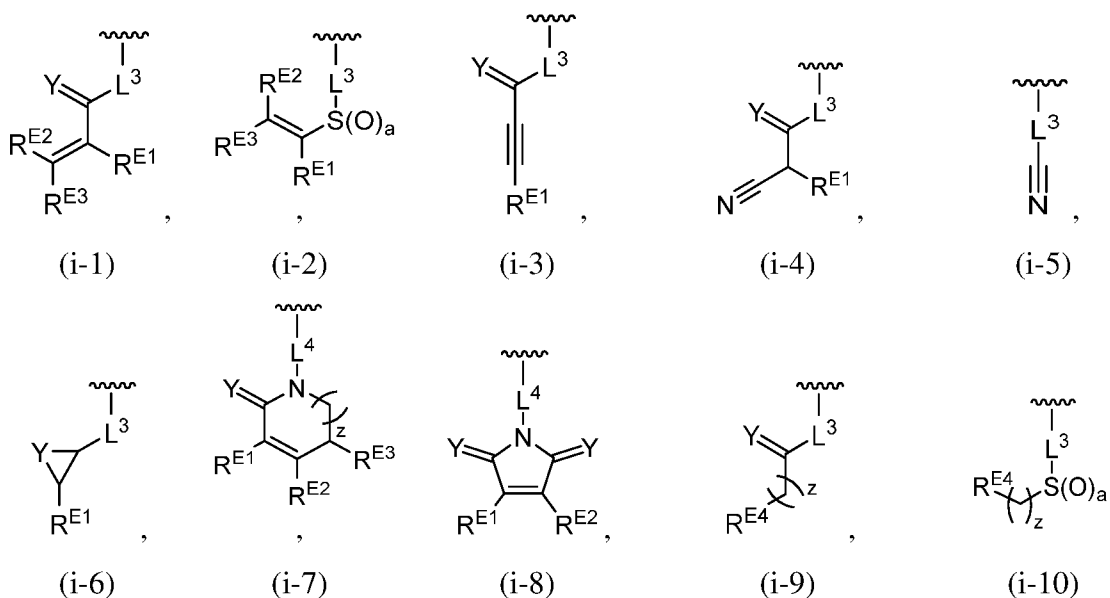
n is 0, 1, 2, 3, or 4;

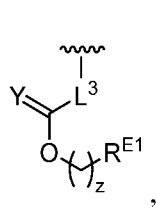
L<sup>2</sup> is -C(R<sup>b</sup>)<sub>2</sub>-, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)<sub>2</sub>-, -NR<sup>c</sup>-, -C(R<sup>b</sup>)<sub>2</sub>C(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>C(=O)-, -C(=O)C(R<sup>b</sup>)<sub>2</sub>-, (E)-CR<sup>b</sup>=CR<sup>b</sup>-, (Z)-CR<sup>b</sup>=CR<sup>b</sup>-, -C≡C-, -OC(=O)-, -C(=O)O-, -SC(=O)-, -C(=O)S-, -NR<sup>c</sup>C(=O)-, -C(=O)NR<sup>c</sup>-, -OC(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>O-, -SC(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>S-, -NR<sup>c</sup>C(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>NR<sup>c</sup>-, -S(=O)O-, -OS(=O)-, -S(=O)NR<sup>c</sup>-, -NR<sup>c</sup>S(=O)-, -S(=O)<sub>2</sub>O-, -OS(=O)<sub>2</sub>-, -S(=O)<sub>2</sub>NR<sup>c</sup>-, -NR<sup>c</sup>S(=O)<sub>2</sub>-, -OC(=O)O-, -NR<sup>c</sup>C(=O)O-, -OC(=O)NR<sup>c</sup>-, -NR<sup>c</sup>C(=O)NR<sup>c</sup>-, -C(R<sup>b</sup>)<sub>2</sub>C(=O)C(R<sup>b</sup>)<sub>2</sub>-, -OC(=O)C(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>C(=O)O-, -NR<sup>c</sup>C(=O)C(R<sup>b</sup>)<sub>2</sub>-, -C(R<sup>b</sup>)<sub>2</sub>C(=O)NR<sup>c</sup>-, or a substituted or unsubstituted 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-, -S(=O)-, -S(=O)<sub>2</sub>-, or -NR<sup>c</sup>-;

each instance of R<sup>D</sup> is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, -OR<sup>a</sup>, -N(R<sup>a</sup>)<sub>2</sub>, -SR<sup>a</sup>, -CN, -SCN, -C(=NR<sup>a</sup>)R<sup>a</sup>, -C(=NR<sup>a</sup>)OR<sup>a</sup>, -C(=NR<sup>a</sup>)N(R<sup>a</sup>)<sub>2</sub>, -C(=O)R<sup>a</sup>, -C(=O)OR<sup>a</sup>, -C(=O)N(R<sup>a</sup>)<sub>2</sub>-, -NO<sub>2</sub>-, -NR<sup>a</sup>C(=O)R<sup>a</sup>, -NR<sup>a</sup>C(=O)OR<sup>a</sup>, -NR<sup>a</sup>C(=O)N(R<sup>a</sup>)<sub>2</sub>-, -OC(=O)R<sup>a</sup>, -OC(=O)OR<sup>a</sup>, or -OC(=O)N(R<sup>a</sup>)<sub>2</sub>;

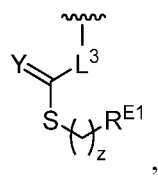
p is 0, 1, 2, 3, or 4;

R<sup>E</sup> is of the formula:

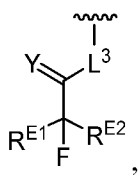




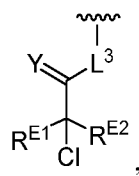
(i-11)



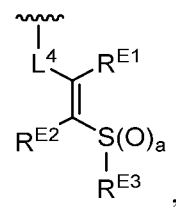
(i-12)



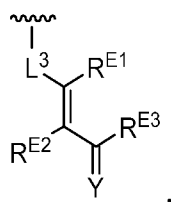
(i-13)



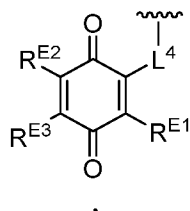
(i-14)



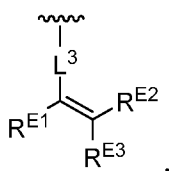
(i-15)



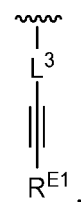
(i-16)



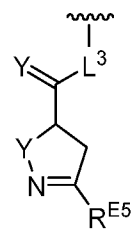
(i-17)



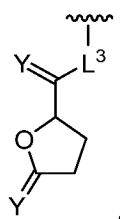
(i-18)



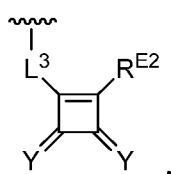
(i-19)



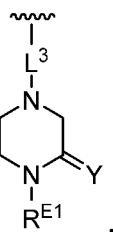
(i-20)



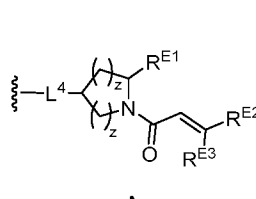
(i-21)



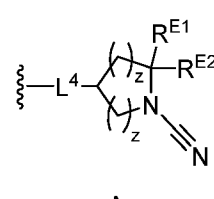
(i-22)



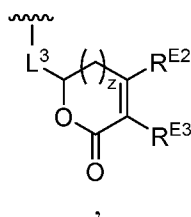
(i-23)



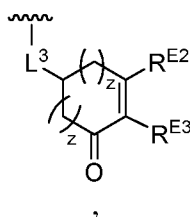
(i-24)



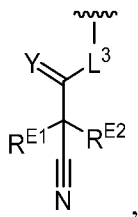
(i-25)



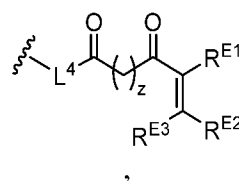
(i-26)



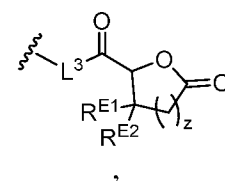
(i-27)



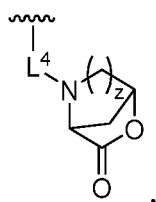
(i-28)



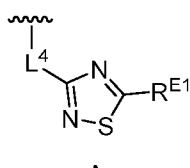
(i-29)



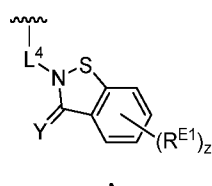
(i-30)



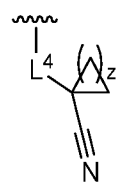
(i-31)



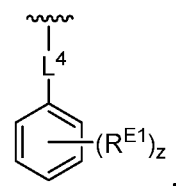
(i-32)



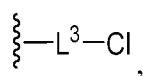
(i-33)



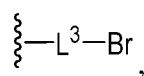
(i-34)



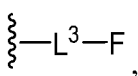
(i-35)



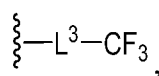
(i-36)



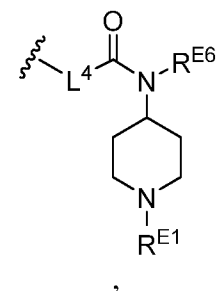
(i-37)



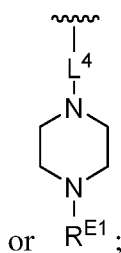
(i-38)



(i-39)



(i-40)



(i-41)

$L^3$  is  $-C(R^b)_2-$ ,  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ ,  $-NR^c-$ ,  $-C(R^b)_2C(R^b)_2-$ ,  $-C(R^b)_2C(=O)-$ ,  $-C(=O)C(R^b)_2-$ ,  $(E)-CR^b=CR^b-$ ,  $(Z)-CR^b=CR^b-$ ,  $-C\equiv C-$ ,  $-OC(=O)-$ ,  $-C(=O)O-$ ,  $-SC(=O)-$ ,  $-C(=O)S-$ ,  $-NR^cC(=O)-$ ,  $-C(=O)NR^c-$ ,  $-OC(R^b)_2-$ ,  $-C(R^b)_2O-$ ,  $-SC(R^b)_2-$ ,  $-C(R^b)_2S-$ ,  $-NR^cC(R^b)_2-$ ,  $-C(R^b)_2NR^c-$ ,  $-S(=O)O-$ ,  $-OS(=O)-$ ,  $-S(=O)NR^c-$ ,  $-NR^cS(=O)-$ ,  $-S(=O)_2O-$ ,  $-OS(=O)_2-$ ,  $-S(=O)_2NR^c-$ ,  $-NR^cS(=O)_2-$ ,  $-OC(=O)O-$ ,  $-NR^cC(=O)O-$ ,  $-OC(=O)NR^c-$ ,  $-NR^cC(=O)NR^c-$ ,  $-C(R^b)_2C(=O)C(R^b)_2-$ ,  $-OC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)O-$ ,  $-NR^cC(=O)C(R^b)_2-$ ,  $-C(R^b)_2C(=O)NR^c-$ , or a substituted or unsubstituted  $C_{1-4}$  hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with  $-C(=O)-$ ,  $-O-$ ,  $-S-$ ,  $-S(=O)-$ ,  $-S(=O)_2-$ , or  $-NR^c-$ ;

$L^4$  is a bond or substituted or unsubstituted  $C_{1-6}$  hydrocarbon chain;

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

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

$R^{E5}$  is halogen;

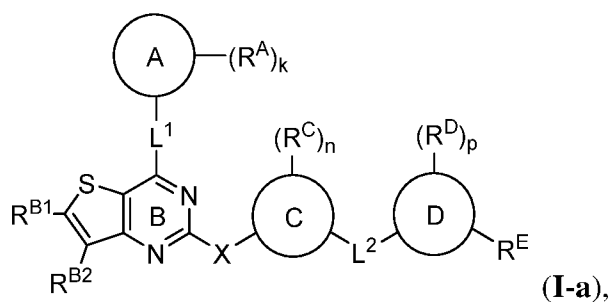
$R^{E6}$  is hydrogen, substituted or unsubstituted  $C_{1-6}$  alkyl, or a nitrogen protecting group;

each instance of  $Y$  is independently  $O$ ,  $S$ , or  $NR^c$ ;

$a$  is 1 or 2; and

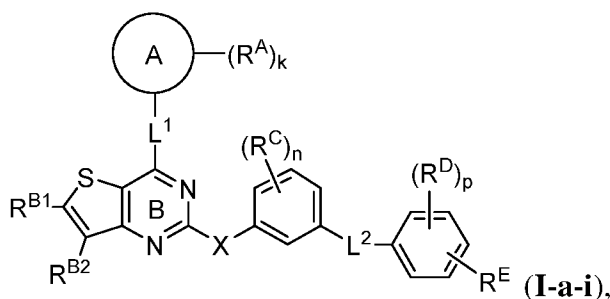
each instance of  $z$  is independently 0, 1, 2, 3, 4, 5, or 6.

2. The compound of claim 1, wherein the compound is of Formula **(I-a)**:



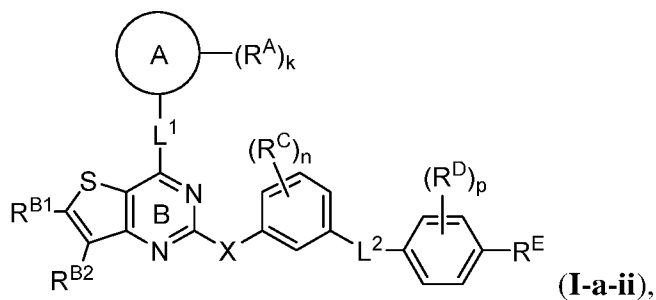
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is of Formula **(I-a-i)**:



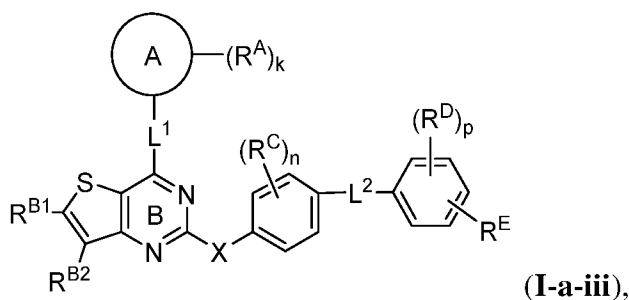
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, wherein the compound is of Formula **(I-a-ii)**:



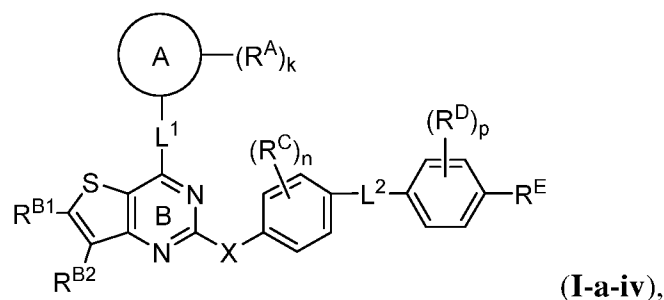
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, wherein the compound is of Formula **(I-a-iii)**:



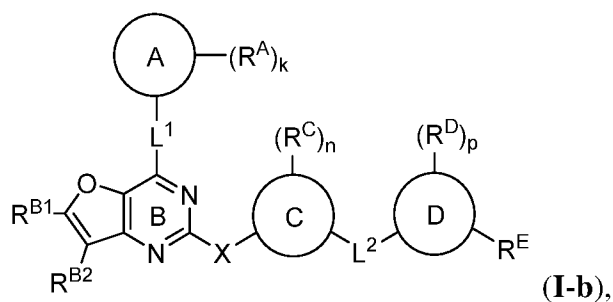
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is of Formula **(I-a-iv)**:



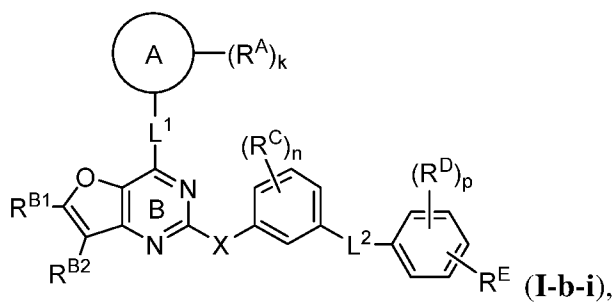
or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is of Formula **(I-b)**:



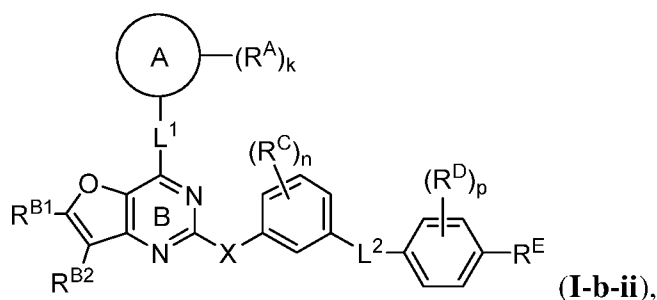
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, wherein the compound is of Formula **(I-b-i)**:



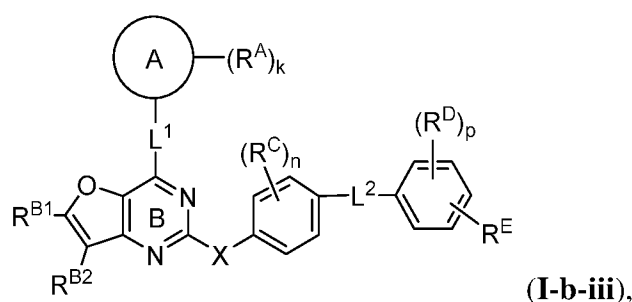
or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is of Formula **(I-b-ii)**:



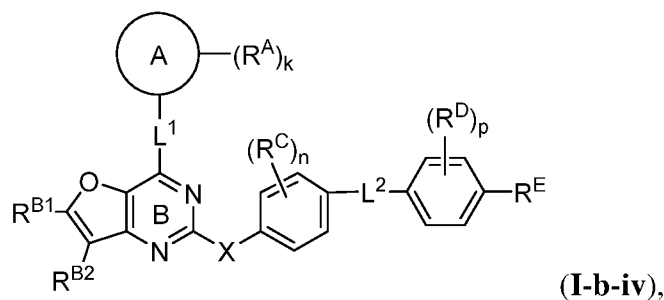
or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, wherein the compound is of Formula **(I-b-iii)**:



or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, wherein the compound is of Formula **(I-b-iv)**:



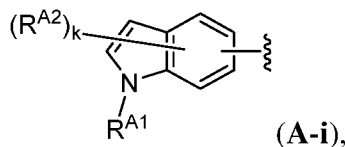
or a pharmaceutically acceptable salt thereof.

12. The compound of any one of claims 1-11, wherein Ring A is a substituted or unsubstituted, bicyclic heteroaryl ring.

13. The compound of claim 12, wherein Ring A is a substituted or unsubstituted, 9- or 10-membered, bicyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

14. The compound of claim 12, wherein Ring A is a substituted or unsubstituted, bicyclic heteroaryl ring with one nitrogen.

15. The compound of claim 12, wherein Ring A is of Formula (A-i):



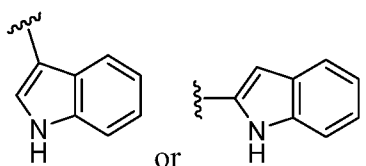
wherein:

$R^{A1}$  is selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and a nitrogen protecting group; and

each instance of  $R^{A2}$  is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-OR^{A2a}$ ,  $-N(R^{A2a})_2$ , and  $-SR^{A2a}$ , wherein each occurrence of  $R^{A2a}$  is independently selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two  $R^{A2a}$  groups are joined to form a substituted or unsubstituted heterocyclic ring.

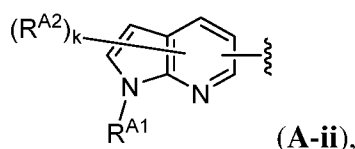
16. The compound of claim 15, wherein k is 0, 1, 2, 3, 4, or 5.

17. The compound of claim 12, wherein Ring A is of the formula:



18. The compound of claim 12, wherein Ring A is a substituted or unsubstituted, bicyclic heteroaryl ring with two nitrogen.

19. The compound of claim 12, wherein Ring A is of Formula (A-ii):



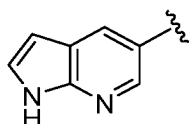
wherein:

$R^{A1}$  is selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and a nitrogen protecting group; and

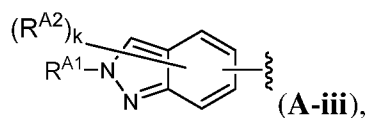
each instance of  $R^{A2}$  is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-OR^{A2a}$ ,  $-N(R^{A2a})_2$ , and  $-SR^{A2a}$ , wherein each occurrence of  $R^{A2a}$  is independently selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two  $R^{A2a}$  groups are joined to form a substituted or unsubstituted heterocyclic ring.

20. The compound of claim 19, wherein k is 0, 1, 2, 3, or 4.

21. The compound of claim 12, wherein Ring A is of the formula:



22. The compound of claim 12, wherein Ring A is of Formula (A-iii):



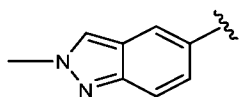
wherein:

$R^{A1}$  is selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and a nitrogen protecting group; and

each instance of  $R^{A2}$  is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-OR^{A2a}$ ,  $-N(R^{A2a})_2$ , and  $-SR^{A2a}$ , wherein each occurrence of  $R^{A2a}$  is independently selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two  $R^{A2a}$  groups are joined to form a substituted or unsubstituted heterocyclic ring.

23. The compound of claim 22, wherein  $k$  is 0, 1, 2, 3, or 4.

24. The compound of claim 12, wherein Ring A is of the formula:

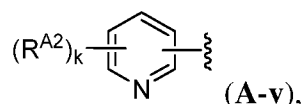


25. The compound of any one of claims 1-11, wherein Ring A is a substituted or unsubstituted, monocyclic heteroaryl ring.

26. The compound of claim 25, wherein Ring A is a substituted or unsubstituted, 5- or 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

27. The compound of claim 25, wherein Ring A is a substituted or unsubstituted, monocyclic heteroaryl ring with one nitrogen.

28. The compound of claim 25, wherein Ring A is of Formula (A-v):

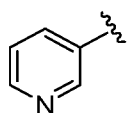


wherein:

each instance of  $R^{A2}$  is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-OR^{A2a}$ ,  $-N(R^{A2a})_2$ , and  $-SR^{A2a}$ , wherein each occurrence of  $R^{A2a}$  is independently selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two  $R^{A2a}$  groups are joined to form a substituted or unsubstituted heterocyclic ring.

29. The compound of claim 28, wherein k is 0, 1, 2, 3, or 4.

30. The compound of claim 25, wherein Ring A is of the formula:

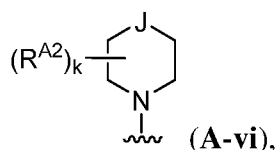


31. The compound of any one of claims 1-11, wherein Ring A is a substituted or unsubstituted, monocyclic heterocyclic ring.

32. The compound of claim 31, wherein Ring A is a substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently oxygen, nitrogen, or sulfur, as valency permits.

33. The compound of claim 31, wherein Ring A is a substituted or unsubstituted, 6-membered heterocyclic ring.

34. The compound of claim 31, wherein Ring A is of Formula (A-vi):



wherein:

J is  $C(R^{CJ})_2$  or  $NR^{NJ}$ ;

each instance of  $R^{CJ}$  is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-OR^a$ ,  $-N(R^a)_2$ ,  $-SR^a$ ,  $-CN$ ,  $-SCN$ ,  $-C(=NR^a)R^a$ ,  $-C(=NR^a)OR^a$ ,  $-C(=NR^a)N(R^a)_2$ ,  $-C(=O)R^a$ ,  $-C(=O)OR^a$ ,  $-C(=O)N(R^a)_2$ ,  $-NO_2$ ,  $-NR^aC(=O)R^a$ ,  $-NR^aC(=O)OR^a$ ,  $-NR^aC(=O)N(R^a)_2$ ,  $-OC(=O)R^a$ ,  $-OC(=O)OR^a$ , or  $-OC(=O)N(R^a)_2$ ; and

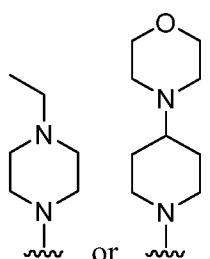
$R^{NJ}$  is hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, optionally substituted acyl, or a nitrogen protecting group; and

each instance of  $R^{A2}$  is independently selected from the group consisting of hydrogen, halogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl,  $-CN$ ,  $-OR^{A2a}$ ,  $-N(R^{A2a})_2$ , and  $-SR^{A2a}$ , wherein each occurrence of  $R^{A2a}$  is independently selected from the group consisting of hydrogen, substituted or unsubstituted acyl, substituted or unsubstituted alkyl, substituted or

unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R<sup>A2a</sup> groups are joined to form a substituted or unsubstituted heterocyclic ring.

35. The compound of claim 34, wherein k is 0, 1, 2, 3, 4, 5, or 6.

36. The compound of claim 31, wherein Ring A is of the formula:



37. The compound of any one of claims 1-36, wherein M is S.

38. The compound of any one of claims 1-36, wherein M is O.

39. The compound of any one of claims 1-36, wherein M is NR<sup>M</sup>.

40. The compound of claim 39, wherein M is NH.

41. The compound of any one of claims 1-40, wherein L<sup>1</sup> is a bond.

42. The compound of any one of claims 1-40, wherein L<sup>1</sup> is -O- or -S-.

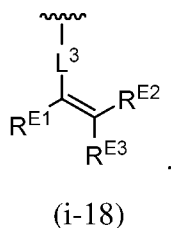
43. The compound of claim 42, wherein L<sup>1</sup> is -O-.

44. The compound of any one of claims 1-40, wherein L<sup>1</sup> is -NR<sup>c</sup>-.

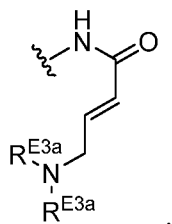
45. The compound of claim 44, wherein L<sup>1</sup> is -NH-.

46. The compound of any one of claims 1-45, wherein  $R^{B1}$  is hydrogen.
47. The compound of any one of claims 1-46, wherein  $R^{B2}$  is hydrogen.
48. The compound of any one of claims 1-47, wherein X is  $-NR^c-$ .
49. The compound of claim 48, wherein X is  $-NH-$ .
50. The compound of any one of claims 1-49, wherein n is 0.
51. The compound of any one of claims 1-50, wherein  $L^2$  is  $-NR^cC(=O)-$  or  $-C(=O)NR^c-$ .
52. The compound of claim 51, wherein  $L^2$  is  $-NR^cC(=O)-$ .
53. The compound of claim 51, wherein  $L^2$  is  $-NHC(=O)-$  or  $-C(=O)NH-$ .
54. The compound of claim 51, wherein  $L^2$  is  $-NHC(=O)-$ .
55. The compound of any one of claims 1-54, wherein X and  $L^2$  are *para* or *meta* to each other.
56. The compound of any one of claims 1-54, wherein X and  $L^2$  are *meta* to each other.
57. The compound of any one of claims 1-56, wherein  $R^E$  and  $L^2$  are *para* or *meta* to each other.
58. The compound of any one of claims 1-56, wherein  $R^E$  and  $L^2$  are *para* to each other.
59. The compound of any one of claims 1-58, wherein p is 0.

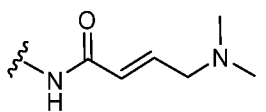
60. The compound of any one of claims 1-59, wherein  $R^E$  is of Formula (i-18):



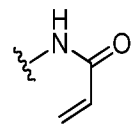
61. The compound of claim 60, wherein  $L^3$  is  $-NR^cC(=O)-$ .
62. The compound of claim 60, wherein  $L^3$  is  $-NHC(=O)-$ .
63. The compound of any one of claims 60-62, wherein  $R^{E1}$  is hydrogen.
64. The compound of any one of claims 60-63, wherein  $R^{E2}$  is hydrogen.
65. The compound of any one of claims 60-64, wherein  $R^{E3}$  is optionally substituted alkyl.
66. The compound of claim 65, wherein  $R^{E3}$  is substituted alkyl.
67. The compound of claim 65, wherein  $R^{E3}$  is  $-\text{CH}_2\text{-N}(\text{CH}_3)_2$ .
68. The compound of claim 60, wherein  $R^E$  is of the formula:



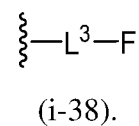
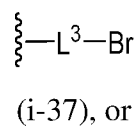
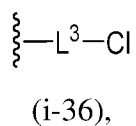
69. The compound of claim 60, wherein  $R^E$  is of the formula:



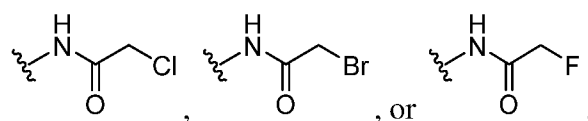
70. The compound of claim 60, wherein  $R^E$  is of the formula:



71. The compound of claim 60, wherein  $R^E$  is of the formula:

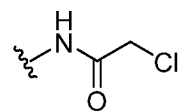


72. The compound of claim 60, wherein  $R^E$  is of the formula:

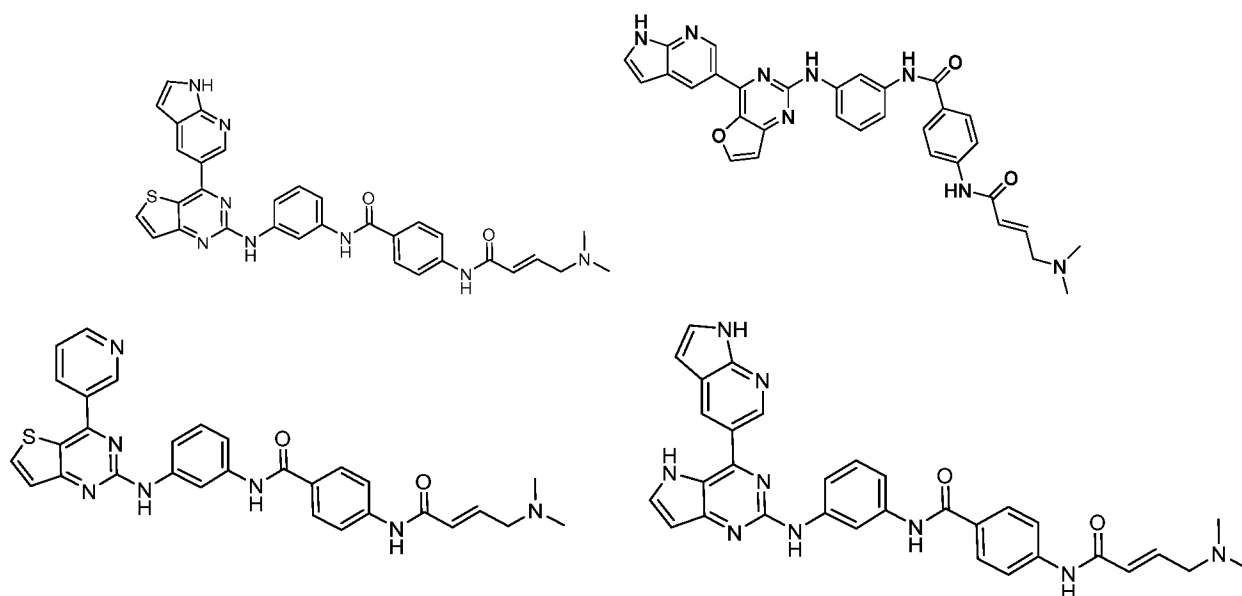


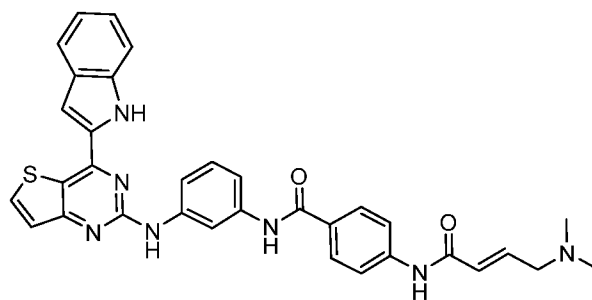
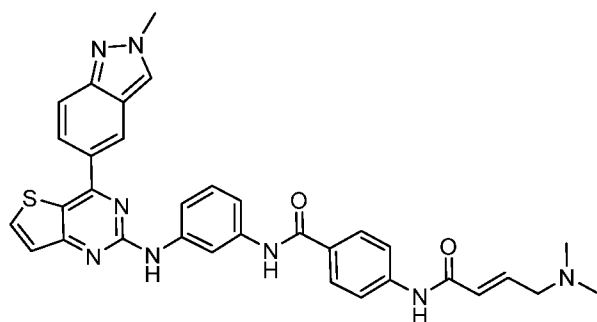
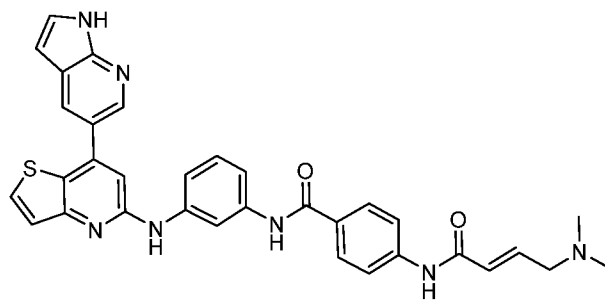
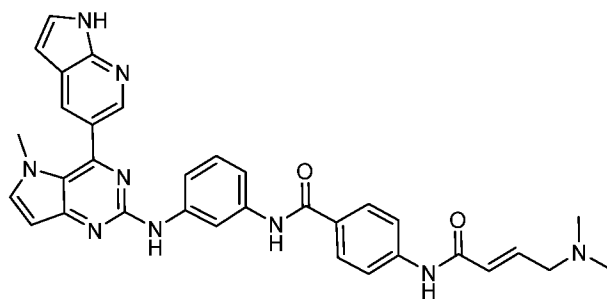
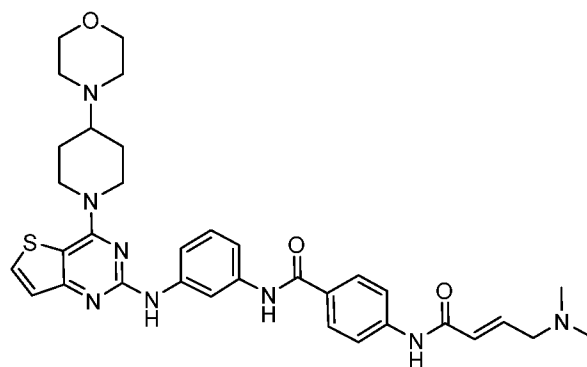
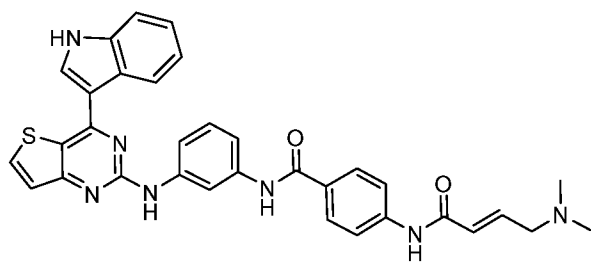
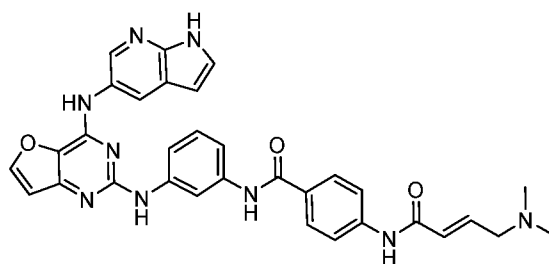
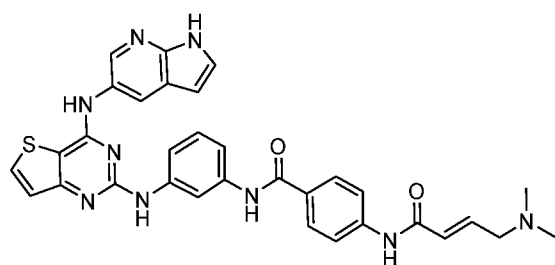
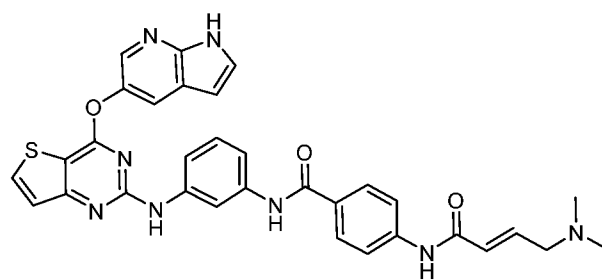
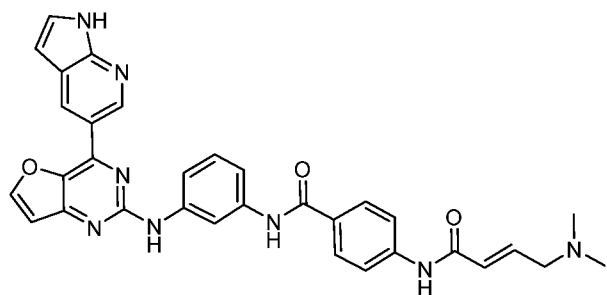
73. The compound of claim 60, wherein  $R^E$  is of the formula: (i-36).

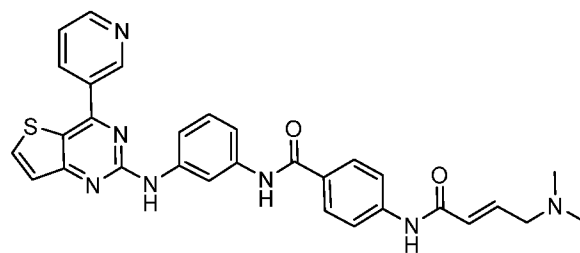
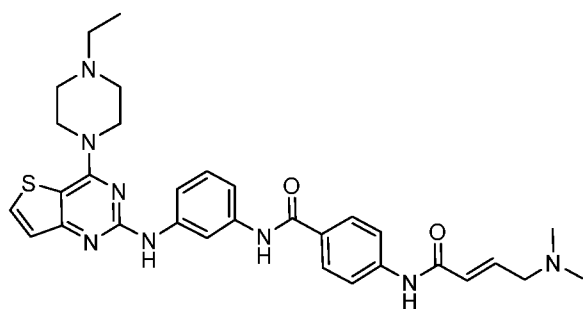
74. The compound of claim 60, wherein  $R^E$  is of the formula:



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

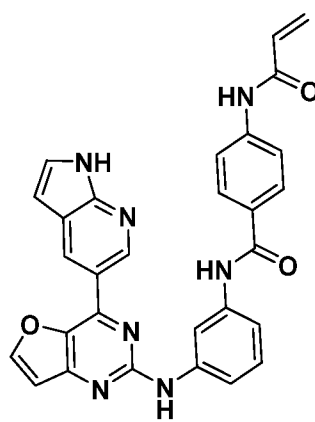
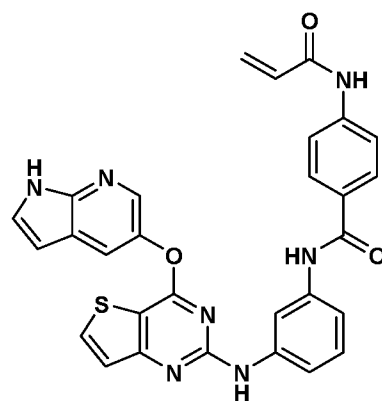
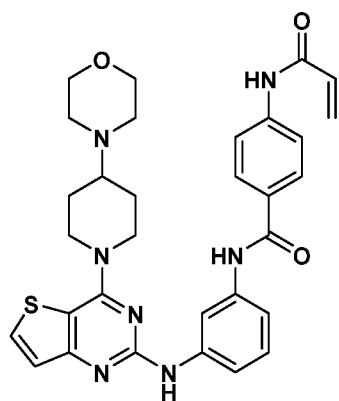






or a pharmaceutically acceptable salt thereof.

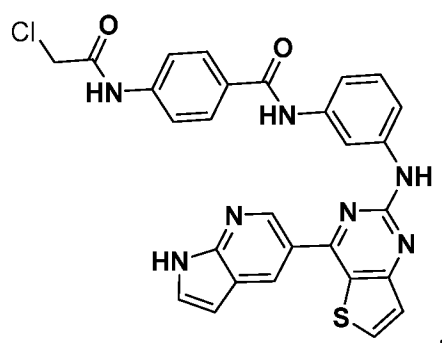
76. The compound of claim 1, wherein the compound is of the formula:



or

or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

78. A pharmaceutical composition comprising a compound of any one of claims 1-77, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

79. The pharmaceutical composition of claim 78, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound for use in treating a proliferative disease in a subject in need thereof.

80. A method of treating a proliferative disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-77, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 78 and 79.

81. The method of claim 80, wherein the subject is a mammal.

82. The method of claim 80, wherein the subject is a human.

83. The method of any one of claims 80-82, wherein the proliferative disease is associated with aberrant activities of a kinase.

84. The method of any one of claims 80-83, wherein the proliferative disease is cancer.

85. The method of claim 84, wherein the cancer is breast cancer.

86. The method of claim 84, wherein the cancer is lung cancer.
87. The method of claim 84, wherein the cancer is small cell lung cancer (SCLC).
88. The method of claim 84, wherein the cancer is non-small cell lung cancer (NSCLC).
89. A method of modulating the activity of a kinase in a biological sample or subject, the method comprising administering to the subject or contacting the biological sample with a therapeutically effective amount of a compound of any one of claims 1-77, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 78 and 79.
90. The method of any one of claims 83 and 89, wherein the kinase is a protein kinase.
91. The method of claim 90, wherein the protein kinase is a cyclin-dependent kinase (CDK).
92. The method of claim 91, wherein the protein kinase is CDK7.
93. The method of claim 91, wherein the protein kinase is CDK12.
94. The method of claim 91, wherein the protein kinase is CDK13.
95. The method of any one of claims 83 and 89, wherein the kinase is a lipid kinase.
96. The method of claim 95, wherein the lipid kinase is a phosphatidylinositol-5-phosphate 4-kinase (PIP4K).
97. The method of claim 96, wherein the PIP4K is PIP4K2.
98. The method of claim 96, wherein the PIP4K is PI5P4K $\alpha$ .
99. The method of claim 96, wherein the PIP4K is PI5P4K $\beta$ .
100. The method of claim 96, wherein the PIP4K is PI5P4K $\gamma$ .

101. The method of any one of claims 80-100, wherein the compound is capable of covalently modifying Cys293 of PI5P4K $\alpha$ .

102. The method of any one of claims 80-101, wherein the compound is capable of covalently modifying Cys307 and/or Cys318 of PI5P4K $\beta$ .

103. The method of any one of claims 80-102, wherein the compound is capable of covalently modifying Cys313 of PI5P4K $\gamma$ .

104. A method of inhibiting cell growth in a biological sample or subject, the method comprising administering to the subject or contacting the biological sample with a therapeutically effective amount of a compound of any one of claims 1-77, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 78 and 79.

105. The method of any one of claims 80-104, further comprising administering to the subject or contacting the biological sample with a therapeutically effective amount of one or more pharmaceutical agents in combination with the compound, the pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

106. The method of claim 105, wherein the pharmaceutical agent is an anti-proliferative agent.

107. The method of claim 105, wherein the pharmaceutical agent is a kinase inhibitor.

108. The method of claim 105, wherein the pharmaceutical agent is an inhibitor of a protein kinase.

109. The method of claim 105, wherein the pharmaceutical agent is an inhibitor of cyclin-dependent kinase (CDK).

110. The method of claim 105, wherein the pharmaceutical agent is an inhibitor of a lipid kinase.

111. The method of claim 105, wherein the pharmaceutical agent is an inhibitor of a phosphatidylinositol-5-phosphate 4-kinase (PIP4K).

112. A kit comprising: a compound of any one of claims 1-77, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of any one of claims 78 and 79; and instructions for administering to a subject or contacting a biological sample with the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

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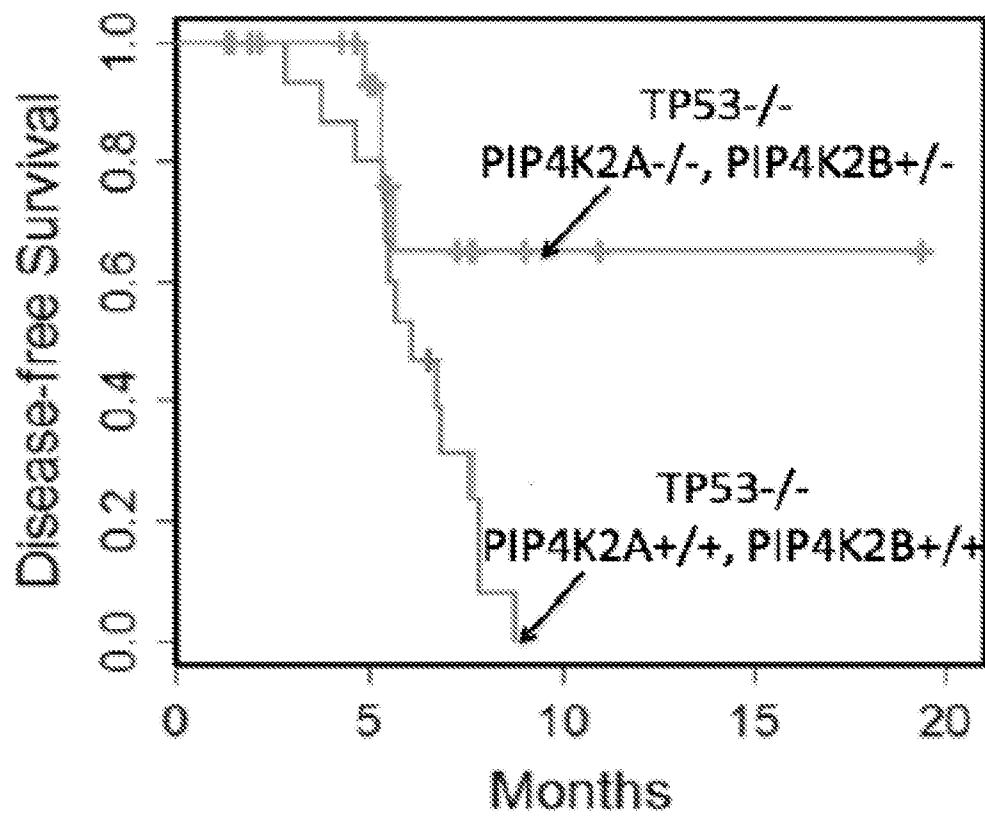
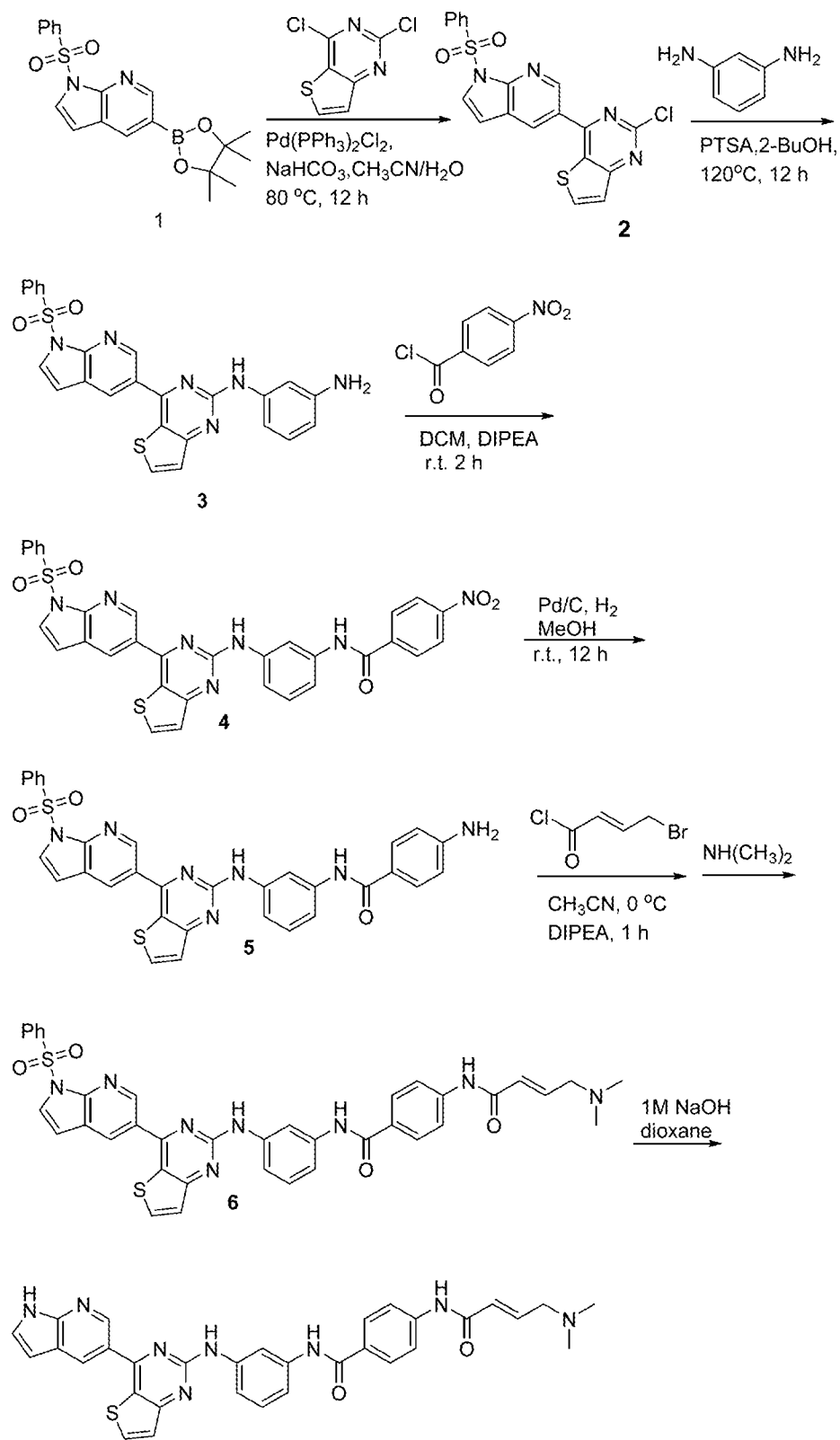


Figure 1

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7, THZ-CE-A-7, or THZ-CE-A7

Figure 2

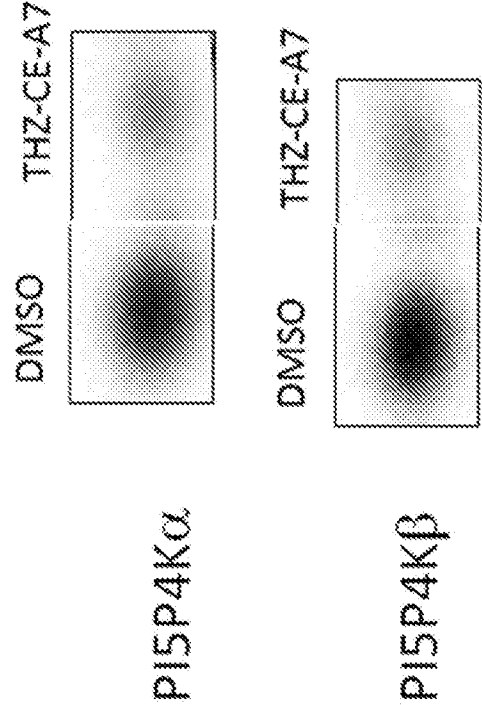
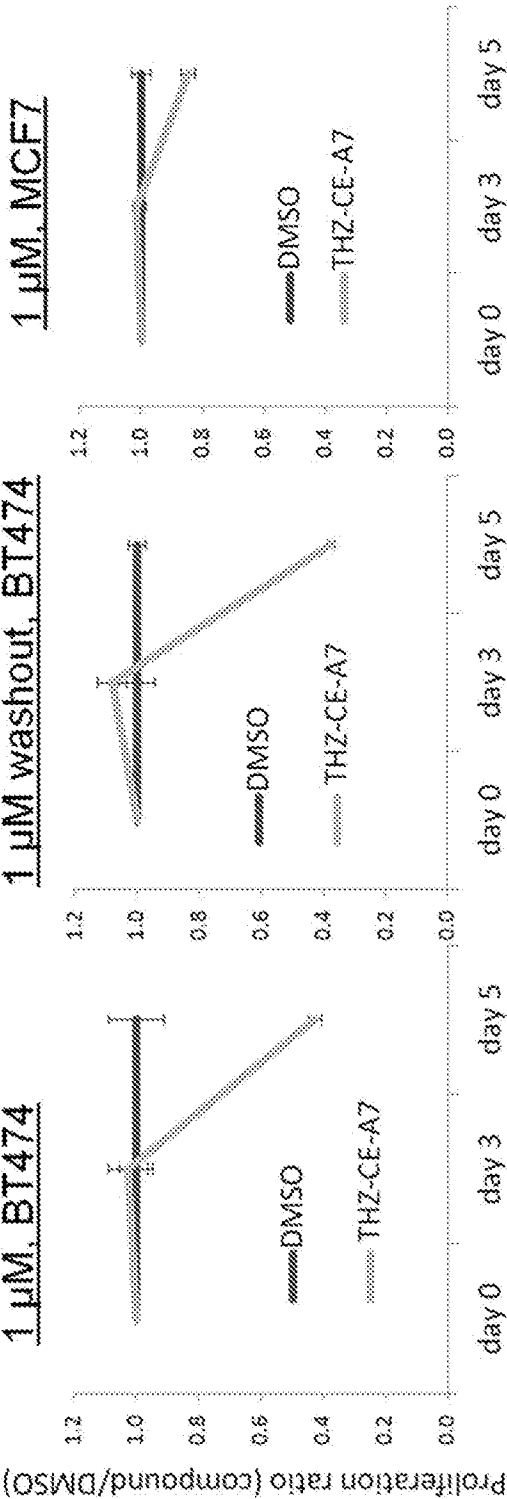


Figure 3B



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/39302

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 35/02; C07D 401/14; A61K 31/506 (2016.01)

CPC - C07D 401/14; A61K 31/53

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61P 35/02; C07D 401/14; A61K 31/506 (2016.01)

CPC: C07D 401/14; A61K 31/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO; PubMed; Google/Google Scholar; cancer, proliferative, lymphoma, CDK, PIP4K, phosphatidylinositol, cyclin, kinase, protein, lipid

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                      | Relevant to claim No.   |
|-----------|---|---|
| Y         | WO 2015/058140 A1 (DANA-FARBER CANCER INSTITUTE, INC.) 23 April 2015; paragraphs [0031], [0041], [0095] | 1-11, 12/1-11, 13/12/1-11, 14/12/1-11, 15/12/1-11, 16/15/12/1-11, 17/12/1-11, 18/12/1-11, 19/12/1-11, 20/19/12/1-11, 21/12/1-11, 22/12/1-11, 23/22/12/1-11, 24/12/1-11, 25/1-11, 26/25/1-11, 27/25/1-11, 28/25/1-11, 29/28/25/1-11, 30/25/1-11, 31/1-11, 32/31/1-11, 33/31/1-11, 34/31/1-11, 35/34/31/1-11, 36/31/1-11, 76-77 |



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

04 September 2016 (04.09.2016)

Date of mailing of the international search report

27 SEP 2016

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

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PCT OSP: 571-272-7774

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/39302

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.  |
|-----------|--|--|
| Y         | US 2013/0040949 A1 (GRAY, NS et al.) 14 February 2013; paragraphs [0011], [0013]-[0016], [0019]-[0021], [0023], [0033], [0069], [0077], [0091] | 1-11, 12/1-11,<br>13/12/1-11, 14/12/1-11,<br>15/12/1-11,<br>16/15/12/1-11,<br>17/12/1-11, 18/12/1-11,<br>19/12/1-11,<br>20/19/12/1-11,<br>21/12/1-11, 22/12/1-11,<br>23/22/12/1-11,<br>24/12/1-11, 25/1-11,<br>26/25/1-11, 27/25/1-11,<br>28/25/1-11,<br>29/28/25/1-11,<br>30/25/1-11, 31/1-11,<br>32/31/1-11, 33/31/1-11,<br>34/31/1-11,<br>35/34/31/1-11,<br>36/31/1-11, 76-77 |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/39302

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 37-75, 78-112  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

## 摘要

本發明提供新穎的式(I)的化合物及其藥學上可接受的鹽、溶劑化物、水合物、多晶型物、共晶體、互變異構體、立體異構體、同位素標記的衍生物、前藥及其組合物。還提供了涉及發明的化合物或組合物的方法和試劑盒，用於治療或預防受試者中的增殖性疾病(例如癌症(例如肺癌、乳腺癌、白血病、淋巴瘤、黑色素瘤、多發性骨髓瘤、尤文肉瘤、骨肉瘤、腦癌、神經母細胞瘤)、良性腫瘤、血管生成、炎性疾病、自身炎性疾病和自身免疫疾病)。使用本發明的化合物或組合物治療患有增殖性疾病的受試者可以抑制受試者中的激酶(例如蛋白質激酶(例如細胞周期蛋白依賴性激酶(CDK)(例如 CDK7、CDK12 或 CDK13))或脂質激酶諸如磷脂酰肌醇-5-磷酸 4-激酶(PIP4K)(例如 PI5P4K $\alpha$ 、PI5P4K $\beta$  或 PI5P4K $\gamma$ )的異常活性。

