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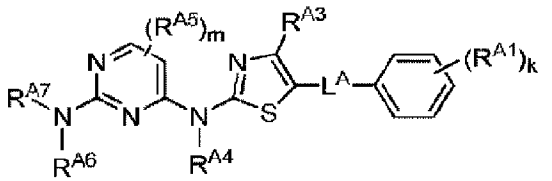
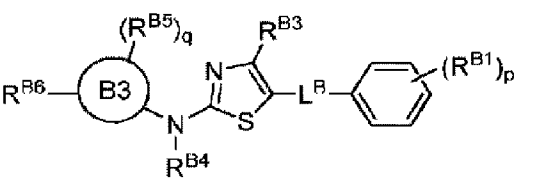
(54) Titre : COMPOSES CONTENANT DES GROUPES THIAZOLYLE POUR LE TRAITEMENT DE MALADIES PROLIFERATIVES

(54) Title: THIAZOLYL-CONTAINING COMPOUNDS FOR TREATING PROLIFERATIVE DISEASES



(I)



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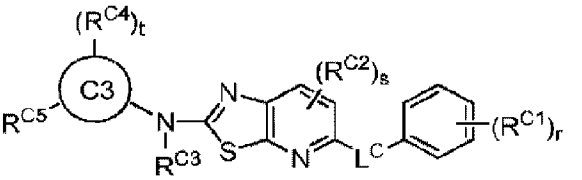

(III)

(57) Abrégé/Abstract:
The present disclosure provides thiazolyl-containing compounds of Formula (I), (II), or (III). The compounds described herein may be able to inhibit protein kinases (e.g., Src family kinases (e.g., hemopoietic cell kinase (HCK)), Bruton' s tyrosine kinase (BTK)) and may be useful in treating and/or preventing proliferative diseases (e.g., myelodysplasia, leukemia, lymphoma (e.g., Waldenstrom's macroglobulinemia)) and in inducing apoptosis in a cell (e.g., malignant blood cell). Also provided in the present disclosure are pharmaceutical compositions, kits, methods, and uses including or using a compound described herein.

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

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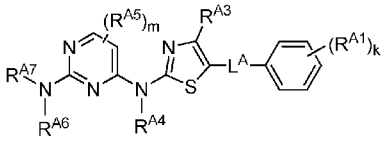
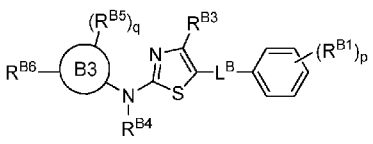
(54) Title: THIAZOLYL-CONTAINING COMPOUNDS FOR TREATING PROLIFERATIVE DISEASES



(I)



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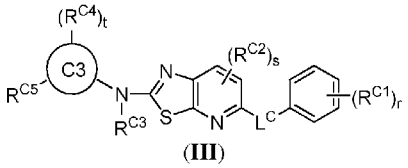

(III)

(57) Abstract: The present disclosure provides thiazolyl-containing compounds of Formula (I), (II), or (III). The compounds described herein may be able to inhibit protein kinases (e.g., Src family kinases (e.g., hemopoietic cell kinase (HCK)), Bruton' s tyrosine kinase (BTK)) and may be useful in treating and/or preventing proliferative diseases (e.g., myelodysplasia, leukemia, lymphoma (e.g., Waldenstrom's macroglobulinemia)) and in inducing apoptosis in a cell (e.g., malignant blood cell). Also provided in the present disclosure are pharmaceutical compositions, kits, methods, and uses including or using a compound described herein.

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THIAZOLYL-CONTAINING COMPOUNDS FOR TREATING PROLIFERATIVE DISEASES

[0001]

[0002]

BACKGROUND OF THE INVENTION

[0003] Hematological malignancies are types of cancers that affect the blood, the bone marrow, and/or the lymph nodes. Hematological malignancies derive from either of the two major blood cell lineages: the myeloid and lymphoid lineages. The myeloid lineage normally produces granulocytes, erythrocytes, thrombocytes, macrophages, and mast cells; and the lymphoid lineage produces B, T, Natural Killer (NK), and plasma cells. Acute and chronic myelogenous leukemia, myelodysplasia, and myeloproliferative diseases are examples of hematological malignancies of myeloid origin; and lymphomas, lymphocytic leukemias, and myeloma are examples of hematological malignancies of the lymphoid lineage.

[0004] Myelodysplasia, also known as myelodysplastic syndrome (MDS), is a hematological malignancy with ineffective production (or dysplasia) of the myeloid class of blood cells.

[0005] Lymphomas include Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma, and immunoproliferative diseases. Waldenström's macroglobulinemia (WM) is a rare, slow-growing, non-Hodgkin lymphoma. WM is also called lymphoplasmacytic lymphoma. Lymphoplasmacytic cells are cells that are in the process of maturing from B cells to plasma cells. In WM, abnormal lymphoplasmacytic cells multiply out of control, producing large amounts of a protein called monoclonal immunoglobulin M (IgM or "macroglobulin") antibody. High levels of IgM in the blood cause hyperviscosity (thickness or gumminess).

[0006] Diffuse large B-cell lymphoma (DLBCL or DLBL) is a malignancy of B cells. Usually DLBCL arises from normal B cells, but it can also represent a malignant transformation of other types of lymphoma or leukemia. An underlying immunodeficiency is a significant risk factor.

[0007] Central nervous system (CNS) lymphoma is a rare non-Hodgkin lymphoma in which malignant cells from lymph tissue form in the brain, spinal cord, meninges, and/or eye

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(primary CNS lymphoma) or spread from other parts of the body to the brain and/or spinal cord (secondary CNS lymphoma).

[0008] Lymphomas of an immune privileged site include, but are not limited to, cerebral lymphoma, ocular lymphoma, lymphoma of the placenta, lymphoma of the fetus, and testicular lymphoma.

[0009] Marginal zone lymphomas are a group of slow-growing, non-Hodgkin B-cell lymphomas presenting primarily in the marginal zone. There are three types of marginal zone lymphomas: Splenic marginal zone lymphoma, extranodal marginal zone B cell lymphoma (mucosa-associated lymphoid tissue (MALT) lymphoma), and nodal marginal zone B cell lymphoma (NMZL).

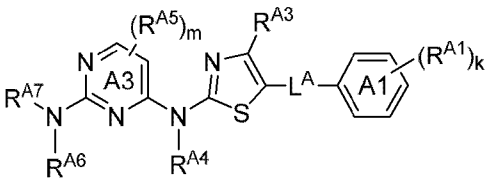
[0010] Leukemias are malignancies of the white blood cells (leukocytes). Chronic lymphoid leukemia (CLL) is the most common type of leukemia in adults. CLL affects B cell lymphocytes. In a subject with CLL, B cells grow out of control, accumulate in the bone marrow and blood, and crowd out healthy blood cells.

[0011] There is a need for novel therapies of hematological malignancies.

SUMMARY OF THE INVENTION

[0012] The present disclosure provides thiazolyl-containing compounds, such as compounds of Formula (**I**), (**II**), or (**III**). In certain embodiments, the compounds described herein are able to inhibit of protein kinases (*e.g.*, Src family kinases (*e.g.*, hemopoietic cell kinase (HCK)), Bruton's tyrosine kinase (BTK)). The compounds may be useful in treating and/or preventing proliferative diseases (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)). Without wishing to be bound by any particular theory, the compounds may act by inducing apoptosis of a cell (*e.g.*, malignant blood cell). Also provided in the present disclosure are pharmaceutical compositions, kits, methods, and uses including a compound described herein.

[0013] In one aspect, the present disclosure provides compounds of Formula (**I**):



(**I**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring A1, R^{A1}, k, L^A, R^{A3}, Ring A3, R^{A4}, R^{A5}, m, R^{A6}, and R^{A7} are described herein.

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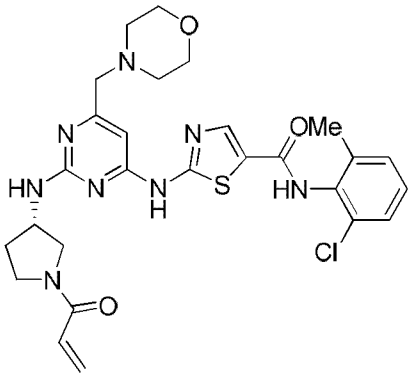
[0014] Exemplary compounds of Formula (**I**) include, but are not limited to:



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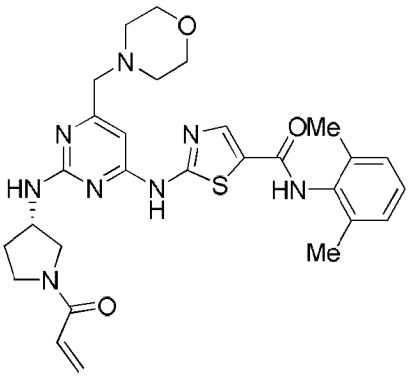

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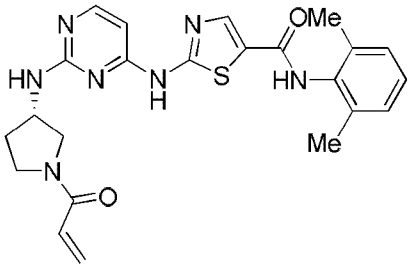
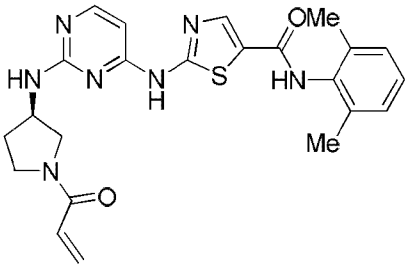
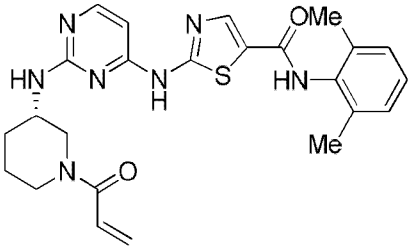


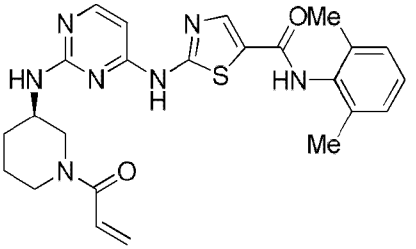
(**I-3**),



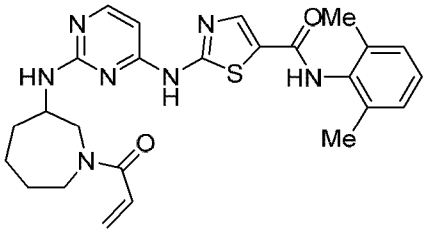
(**I-4**),



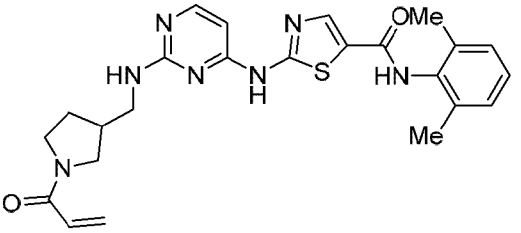
(**I-5**),



(**I-6**),



(**I-7**),



(**I-8**),

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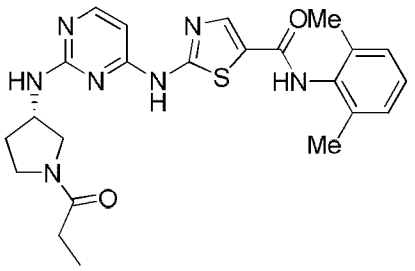

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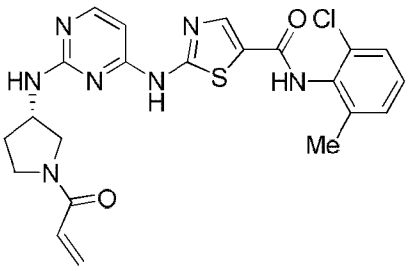

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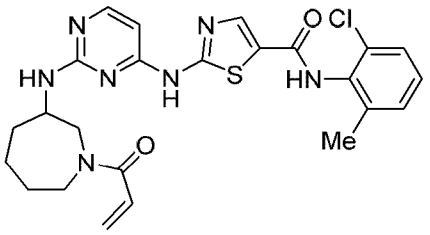

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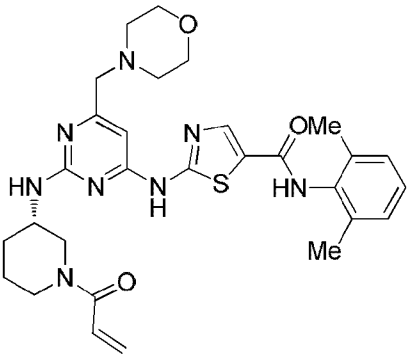
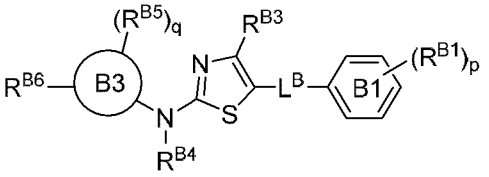


(I-12),

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

[0015] In one aspect, the present disclosure provides compounds of Formula (**II**):



(II),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring B1, R^{B1}, p, L^B, R^{B3}, R^{B4}, Ring B3, R^{B5}, q, and R^{B6} are described herein.

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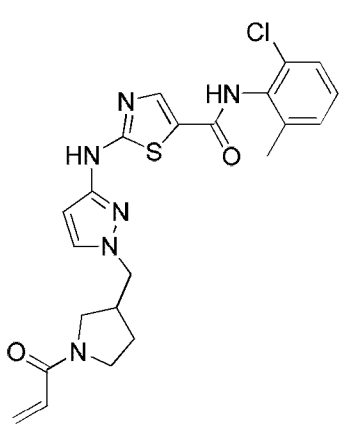
[0016] Exemplary compounds of Formula (**II**) include, but are not limited to:



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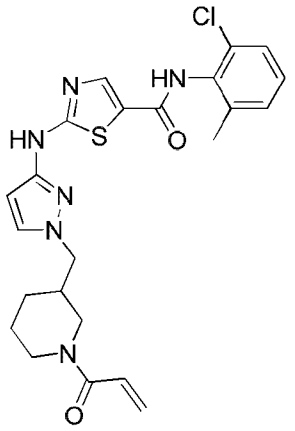

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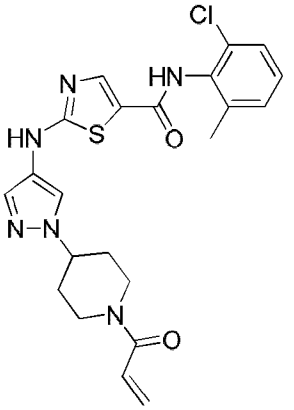
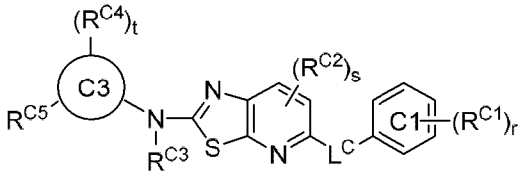


(**II-3**),

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

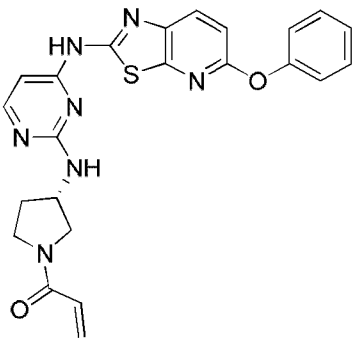
[0017] In one aspect, the present disclosure provides compounds of Formula (**III**):



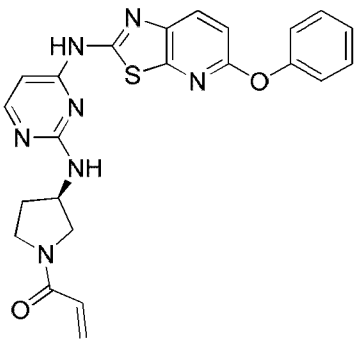
(**III**),

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein Ring C1, R^{C1}, r, L^C, R^{C2}, s, R^{C3}, Ring C3, R^{C4}, t, and R^{C5} are described herein..

[0018] Exemplary compounds of Formula (**III**) include, but are not limited to:



(**III-1**),



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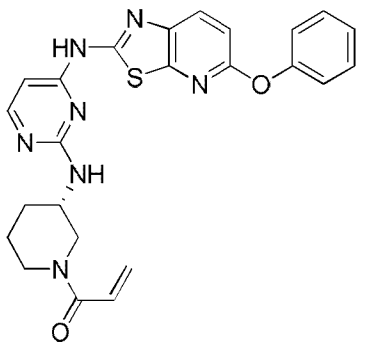

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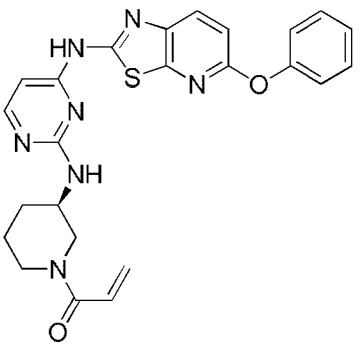

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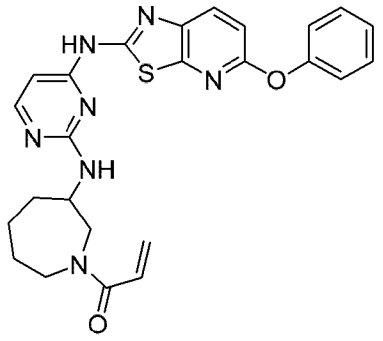

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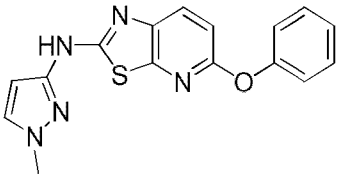

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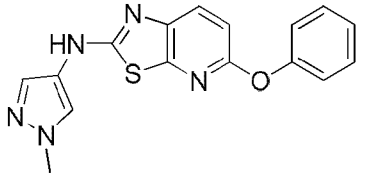

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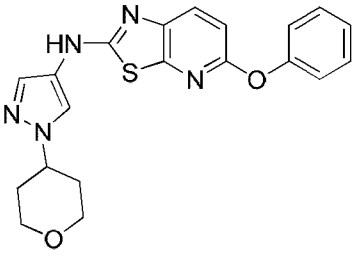

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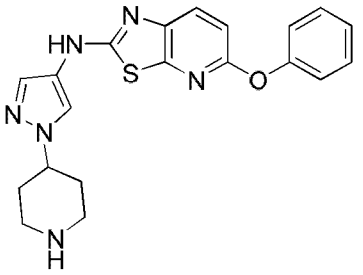

(III-9),

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

[0019] In still another aspect, the present disclosure provides pharmaceutical compositions including a compound described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include

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an effective amount of a compound described herein. An effective amount described herein may be a therapeutically effective amount or prophylactically effective amount. The pharmaceutical composition may be useful for treating a proliferative disease in a subject in need thereof, preventing a proliferative disease in a subject in need thereof, inhibiting the activity of a protein kinase in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell.

[0020] In certain embodiments, a proliferative disease described herein is myelodysplasia, leukemia (*e.g.*, chronic lymphocytic leukemia (CLL)), lymphoma (*e.g.*, Waldenström's macroglobulinemia, activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), central nervous system (CNS) lymphoma, lymphoma of an immune privileged site, testicular lymphoma, or marginal zone lymphoma).

[0021] In certain embodiments, the subject is a mammal (*e.g.*, human or non-human mammal). In certain embodiments, the cell is *in vitro* or *in vivo*. In certain embodiments, the cell is a malignant blood cell.

[0022] In certain embodiments, the protein kinase is a Src family kinase (*e.g.*, HCK) or BTK.

[0023] Another aspect of the present disclosure relates to methods of treating a proliferative disease in a subject in need thereof.

[0024] In another aspect, the present disclosure provides methods of preventing a proliferative disease in a subject in need thereof.

[0025] In another aspect, the present disclosure provides methods of inhibiting the activity (*e.g.*, aberrant activity or increased activity) of a protein kinase in a subject, biological sample, tissue, or cell. In certain embodiments, the activity of the protein kinase is selectively inhibited, compared to the activity of a different protein kinase.

[0026] In yet another aspect, the present disclosure provides methods of inducing apoptosis in a cell.

[0027] In certain embodiments, a method described herein includes administering to the subject an effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, a method described herein includes contacting a cell with an effective amount of a compound or pharmaceutical composition described herein. In certain embodiments, a method described herein further includes administering to the subject an additional pharmaceutical agent. In certain embodiments, a method described herein further includes contacting the cell with an additional pharmaceutical agent. In certain embodiments, a method described herein further includes performing a radiotherapy, immunotherapy, and/or transplantation on the subject.

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[0028] Another aspect of the disclosure relates to methods of screening a library of compounds to identify a compound that is useful in a method of the disclosure.

[0029] Another aspect of the present disclosure relates to kits comprising a container with a compound or pharmaceutical composition described herein. The kits described herein may include a single dose or multiple doses of the compound or pharmaceutical composition. The kits may be useful in a method of the disclosure. In certain embodiments, the kit further includes instructions for using the compound or pharmaceutical composition.

[0030] In yet another aspect, the present disclosure provides compounds and pharmaceutical compositions described herein for use in a method of the disclosure.

[0031] The details of one or more embodiments of the disclosure are set forth herein. Other features, objects, and advantages of the disclosure will be apparent from the Detailed Description, the Examples, and the Claims.

DEFINITIONS

[0032] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987. The disclosure is not intended to be limited in any manner by the exemplary listing of substituents described herein.

[0033] 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*

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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.

[0034] When a range of values is listed, it is intended to encompass each value and sub–range within the range. For example "C_{1-6}" is intended to encompass, C_1, C_2, C_3, C_4, C_5, C_6, C_{1-6}, C_{1-5}, C_{1-4}, C_{1-3}, C_{1-2}, C_{2-6}, C_{2-5}, C_{2-4}, C_{2-3}, C_{3-6}, C_{3-5}, C_{3-4}, C_{4-6}, C_{4-5}, and C_{5-6}.

[0035] The term "aliphatic" includes both saturated and unsaturated, straight chain (*i.e.*, unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted 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.

[0036] 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_2-cyclopropyl, vinyl, allyl, n-butyl, sec-butyl, isobutyl, tert-butyl, cyclobutyl, -CH_2-cyclobutyl, n-pentyl, sec-pentyl, isopentyl, tert-pentyl, cyclopentyl, -CH_2-cyclopentyl, n-hexyl, sec-hexyl, cyclohexyl, -CH_2-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.

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[0037] The term "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("$C_{1–10}$ alkyl"). In some embodiments, an alkyl group has 1 to 9 carbon atoms ("$C_{1–9}$ alkyl"). In some embodiments, an alkyl group has 1 to 8 carbon atoms ("$C_{1–8}$ alkyl"). In some embodiments, an alkyl group has 1 to 7 carbon atoms ("$C_{1–7}$ alkyl"). In some embodiments, an alkyl group has 1 to 6 carbon atoms ("$C_{1–6}$ alkyl"). In some embodiments, an alkyl group has 1 to 5 carbon atoms ("$C_{1–5}$ alkyl"). In some embodiments, an alkyl group has 1 to 4 carbon atoms ("$C_{1–4}$ alkyl"). In some embodiments, an alkyl group has 1 to 3 carbon atoms ("$C_{1–3}$ alkyl"). In some embodiments, an alkyl group has 1 to 2 carbon atoms ("$C_{1–2}$ alkyl"). In some embodiments, an alkyl group has 1 carbon atom ("C_1 alkyl"). In some embodiments, an alkyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkyl"). Examples of $C_{1–6}$ alkyl groups include methyl (C_1), ethyl (C_2), propyl (C_3) (*e.g.*, n–propyl, isopropyl), butyl (C_4) (*e.g.*, n–butyl, tert–butyl, sec–butyl, iso–butyl), pentyl (C_5) (*e.g.*, n–pentyl, 3–pentanyl, amyl, neopentyl, 3–methyl–2–butanyl, tertiary amyl), and hexyl (C_6) (*e.g.*, n–hexyl). Additional examples of alkyl groups include n–heptyl (C_7), n–octyl (C_8), 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 $C_{1–10}$ alkyl (such as unsubstituted C_{1-6} alkyl, *e.g.,* $–CH_3$). In certain embodiments, the alkyl group is a substituted $C_{1–10}$ alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $–CF_3$).

[0038] "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 ("$C_{2–20}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("$C_{2–10}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("$C_{2–9}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("$C_{2–8}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("$C_{2–7}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("$C_{2–6}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("$C_{2–5}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 4 carbon atoms ("$C_{2–4}$ alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("$C_{2–3}$ alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 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 $C_{2–4}$ alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of $C_{2–6}$ alkenyl groups

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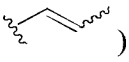
include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently 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_{2-10} alkenyl. In certain embodiments, the alkenyl group is substituted C_{2-10} alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, –CH=CHCH$_3$ or ) may be an (*E*)- or (*Z*)-double bond.

[0039] "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_{2-20} alkynyl"). In some embodiments, an alkynyl group has 2 to 10 carbon atoms ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), 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_{2-10} alkynyl. In certain embodiments, the alkynyl group is substituted C_{2-10} alkynyl.

[0040] "Carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In some embodiments, a carbocyclyl group has

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3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), 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_{3-10} carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C_{3-10} carbocyclyl.

[0041] In some embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms ("C_{5-10} cycloalkyl"). Examples of C_{5-6} cycloalkyl groups include cyclopentyl (C_5) and cyclohexyl (C_5). Examples of C_{3-6} cycloalkyl groups include the aforementioned C_{5-6} cycloalkyl groups as well as cyclopropyl (C_3) and cyclobutyl (C_4). Examples of C_{3-8} cycloalkyl groups include the aforementioned C_{3-6}

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cycloalkyl groups as well as cycloheptyl (C_7) and cyclooctyl (C_8). 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_{3-10} cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C_{3-10} cycloalkyl.

[0042] "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.

[0043] 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

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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.

[0044] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiiranyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidinyl, oxetanyl and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C_6 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.

[0045] "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 ("$C_{6–14}$ aryl"). In some embodiments, an aryl group has six ring carbon atoms ("C_6 aryl"; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms ("C_{14} 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,

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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_{6-14} aryl. In certain embodiments, the aryl group is substituted C_{6-14} aryl.

[0046] "Aralkyl" is a subset of alkyl and aryl and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group. In certain embodiments, the aralkyl is optionally substituted benzyl. In certain embodiments, the aralkyl is benzyl. In certain embodiments, the aralkyl is optionally substituted phenethyl. In certain embodiments, the aralkyl is phenethyl.

[0047] "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).

[0048] 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,

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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.

[0049] 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.

[0050] "Heteroaralkyl" is a subset of alkyl and heteroaryl and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

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[0051] "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.

[0052] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, which are divalent bridging groups, are further referred to using the suffix –ene, *e.g.*, alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene, and heteroarylene.

[0053] 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.

[0054] A group is optionally substituted 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 optionally substituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present 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,

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

[0055] Exemplary carbon atom substituents include, but are not limited to, halogen, –CN, –NO_2, –N_3, –SO_2H, –SO_3H, –OH, –OR^{aa}, –$ON(R^{bb})_2$, –$N(R^{bb})_2$, –$N(R^{bb})_3^+X^-$, –$N(OR^{cc})R^{bb}$, –SH, –SR^{aa}, –SSR^{cc}, –$C(=O)R^{aa}$, –CO_2H, –CHO, –$C(OR^{cc})_2$, –CO_2R^{aa}, –$OC(=O)R^{aa}$, –OCO_2R^{aa}, –$C(=O)N(R^{bb})_2$, –$OC(=O)N(R^{bb})_2$, –$NR^{bb}C(=O)R^{aa}$, –$NR^{bb}CO_2R^{aa}$, –$NR^{bb}C(=O)N(R^{bb})_2$, –$C(=NR^{bb})R^{aa}$, –$C(=NR^{bb})OR^{aa}$, –$OC(=NR^{bb})R^{aa}$, –$OC(=NR^{bb})OR^{aa}$, –$C(=NR^{bb})N(R^{bb})_2$, –$OC(=NR^{bb})N(R^{bb})_2$, –$NR^{bb}C(=NR^{bb})N(R^{bb})_2$, –$C(=O)NR^{bb}SO_2R^{aa}$, –$NR^{bb}SO_2R^{aa}$, –$SO_2N(R^{bb})_2$, –$SO_2R^{aa}$, –$SO_2OR^{aa}$, –$OSO_2R^{aa}$, –$S(=O)R^{aa}$, –$OS(=O)R^{aa}$, –$Si(R^{aa})_3$, –$OSi(R^{aa})_3$ –$C(=S)N(R^{bb})_2$, –$C(=O)SR^{aa}$, –$C(=S)SR^{aa}$, –$SC(=S)SR^{aa}$, –$SC(=O)SR^{aa}$, –$OC(=O)SR^{aa}$, –$SC(=O)OR^{aa}$, –$SC(=O)R^{aa}$, –$P(=O)(R^{aa})_2$, –$P(=O)(OR^{cc})_2$, –$OP(=O)(R^{aa})_2$, –$OP(=O)(OR^{cc})_2$, –$P(=O)(N(R^{bb})_2)_2$, –$OP(=O)(N(R^{bb})_2)_2$, –$NR^{bb}P(=O)(R^{aa})_2$, –$NR^{bb}P(=O)(OR^{cc})_2$, –$NR^{bb}P(=O)(N(R^{bb})_2)_2$, –$P(R^{cc})_2$, –$P(OR^{cc})_2$, –$P(R^{cc})_3^+X^-$, –$P(OR^{cc})_3^+X^-$, –$P(R^{cc})_4$, –$P(OR^{cc})_4$, –$OP(R^{cc})_2$, –$OP(R^{cc})_3^+X^-$, –$OP(OR^{cc})_2$, –$OP(OR^{cc})_3^+X^-$, –$OP(R^{cc})_4$, –$OP(OR^{cc})_4$, –$B(R^{aa})_2$, –$B(OR^{cc})_2$, –$BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X– is a counterion;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, $=NN(R^{bb})_2$, $=NNR^{bb}C(=O)R^{aa}$, $=NNR^{bb}C(=O)OR^{aa}$, $=NNR^{bb}S(=O)_2R^{aa}$, $=NR^{bb}$, or $=NOR^{cc}$;

each instance of R^{aa} is, independently, selected from $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from 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}, –$C(=NR^{cc})OR^{aa}$, –$C(=NR^{cc})N(R^{cc})_2$, –$SO_2N(R^{cc})_2$, –SO_2R^{cc}, –SO_2OR^{cc}, –SOR^{aa}, –$C(=S)N(R^{cc})_2$, –$C(=O)SR^{cc}$, –$C(=S)SR^{cc}$, –$P(=O)(R^{aa})_2$, –$P(=O)(OR^{cc})_2$, –$P(=O)(N(R^{cc})_2)_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl,

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carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3^+X^-$, $–N(OR^{ee})R^{ff}$, –SH, $–SR^{ee}$, $–SSR^{ee}$, $–C(=O)R^{ee}$, $–CO_2H$, $–CO_2R^{ee}$, $–OC(=O)R^{ee}$, $–OCO_2R^{ee}$, $–C(=O)N(R^{ff})_2$, $–OC(=O)N(R^{ff})_2$, $–NR^{ff}C(=O)R^{ee}$, $–NR^{ff}CO_2R^{ee}$, $–NR^{ff}C(=O)N(R^{ff})_2$, $–C(=NR^{ff})OR^{ee}$, $–OC(=NR^{ff})R^{ee}$, $–OC(=NR^{ff})OR^{ee}$, $–C(=NR^{ff})N(R^{ff})_2$, $–OC(=NR^{ff})N(R^{ff})_2$, $–NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$–NR^{ff}SO_2R^{ee}$, $–SO_2N(R^{ff})_2$, $–SO_2R^{ee}$, $–SO_2OR^{ee}$, $–OSO_2R^{ee}$, $–S(=O)R^{ee}$, $–Si(R^{ee})_3$, $–OSi(R^{ee})_3$, $–C(=S)N(R^{ff})_2$, $–C(=O)SR^{ee}$, $–C(=S)SR^{ee}$, $–SC(=S)SR^{ee}$, $–P(=O)(OR^{ee})_2$, $–P(=O)(R^{ee})_2$, $–OP(=O)(R^{ee})_2$, $–OP(=O)(OR^{ee})_2$, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S; wherein X^- is a counterion;

each instance of R^{ee} is, independently, selected from $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, $C_{6–10}$ aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, $C_{1–6}$ alkyl, $C_{1–6}$ perhaloalkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–10 membered heterocyclyl, $C_{6–10}$ aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, –CN, $–NO_2$, $–N_3$, $–SO_2H$, $–SO_3H$, –OH, $–OC_{1–6}$ alkyl, $–ON(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_2$, $–N(C_{1–6}$ alkyl$)_3^+X^-$, $–NH(C_{1–6}$ alkyl$)_2^+X^-$, $–NH_2(C_{1–6}$ alkyl$)^+X^-$, $–NH_3^+X^-$, $–N(OC_{1–6}$ alkyl$)(C_{1–6}$ alkyl), $–N(OH)(C_{1–6}$ alkyl), –NH(OH), –SH, $–SC_{1–6}$ alkyl, $–SS(C_{1–6}$ alkyl), $–C(=O)(C_{1–6}$ alkyl), $–CO_2H$, $–CO_2(C_{1–6}$

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alkyl), –OC(=O)(C_{1-6} alkyl), –OCO_2(C_{1-6} alkyl), –C(=O)NH_2, –C(=O)N(C_{1-6} alkyl)$_2$, –OC(=O)NH(C_{1-6} alkyl), –NHC(=O)(C_{1-6} alkyl), –N(C_{1-6} alkyl)C(=O)(C_{1-6} alkyl), –$NHCO_2$(C_{1-6} alkyl), –NHC(=O)N(C_{1-6} alkyl)$_2$, –NHC(=O)NH(C_{1-6} alkyl), –NHC(=O)NH_2, –C(=NH)O(C_{1-6} alkyl),–OC(=NH)(C_{1-6} alkyl), –OC(=NH)OC_{1-6} alkyl, –C(=NH)N(C_{1-6} alkyl)$_2$, –C(=NH)NH(C_{1-6} alkyl), –C(=NH)NH_2, –OC(=NH)N(C_{1-6} alkyl)$_2$, –OC(NH)NH(C_{1-6} alkyl), –OC(NH)NH_2, –NHC(NH)N(C_{1-6} alkyl)$_2$, –NHC(=NH)NH_2, –$NHSO_2$(C_{1-6} alkyl), –SO_2N(C_{1-6} alkyl)$_2$, –SO_2NH(C_{1-6} alkyl), –SO_2NH_2,–SO_2C_{1-6} alkyl, –SO_2OC_{1-6} alkyl, –OSO_2C_{1-6} alkyl, –SOC_{1-6} alkyl, –Si(C_{1-6} alkyl)$_3$, –OSi(C_{1-6} alkyl)$_3$ –C(=S)N(C_{1-6} alkyl)$_2$, C(=S)NH(C_{1-6} alkyl), C(=S)NH_2, –C(=O)S(C_{1-6} alkyl), –C(=S)SC_{1-6} alkyl, –SC(=S)SC_{1-6} alkyl, –P(=O) (OC_{1-6} alkyl)$_2$, –P(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(C_{1-6} alkyl)$_2$, –OP(=O)(OC_{1-6} alkyl)$_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S; wherein X^- is a counterion.

[0056] A "counterion" or "anionic counterion" is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (*e.g.*, F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HCO_3^-, HSO_4^-, sulfonate ions (*e.g.*, methansulfonate, trifluoromethanesulfonate, *p*–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), carboxylate ions (*e.g.*, acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), 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.

[0057] "Halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0058] "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)N$R^{bb}SO_2R^{aa}$, –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.

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[0059] 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, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, 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.

[0060] 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, $–OR^{aa}$, $–N(R^{cc})_2$, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $C_{1–10}$ alkyl (*e.g.*, aralkyl, heteroaralkyl), $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ 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^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} 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, 3rd edition, John Wiley & Sons, 1999.

[0061] For example, nitrogen protecting groups such as amide groups (*e.g.*, $–C(=O)R^{aa}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3–phenylpropanamide, picolinamide, 3–pyridylcarboxamide, *N*–benzoylphenylalanyl derivative, benzamide, *p*–phenylbenzamide, *o*–nitophenylacetamide, *o*–nitrophenoxyacetamide, acetoacetamide, (*N'*–dithiobenzyloxyacylamino)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.

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[0062] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethylcarbamate, 9–fluorenylmethyl carbamate (Fmoc), 9–(2–sulfo)fluorenylmethyl carbamate, 9–(2,7–dibromo)fluoroenylmethyl carbamate, 2,7–di–*t*–butyl–[9–(10,10–dioxo–10,10,10,10–tetrahydrothioxanthyl)]methyl carbamate (DBD–Tmoc), 4–methoxyphenacyl carbamate (Phenoc), 2,2,2–trichloroethyl carbamate (Troc), 2–trimethylsilylethyl carbamate (Teoc), 2–phenylethyl carbamate (hZ), 1–(1–adamantyl)–1–methylethyl carbamate (Adpoc), 1,1–dimethyl–2–haloethyl carbamate, 1,1–dimethyl–2,2–dibromoethyl carbamate (DB–*t*–BOC), 1,1–dimethyl–2,2,2–trichloroethyl carbamate (TCBOC), 1–methyl–1–(4–biphenylyl)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, alkyldithio carbamate, benzyl carbamate (Cbz), *p*–methoxybenzyl carbamate (Moz), *p*–nitobenzyl carbamate, *p*–bromobenzyl carbamate, *p*–chlorobenzyl carbamate, 2,4–dichlorobenzyl carbamate, 4–methylsulfinylbenzyl carbamate (Msz), 9–anthrylmethyl carbamate, diphenylmethyl carbamate, 2–methylthioethyl carbamate, 2–methylsulfonylethyl carbamate, 2–(*p*–toluenesulfonyl)ethyl carbamate, [2–(1,3–dithianyl)]methyl carbamate (Dmoc), 4–methylthiophenyl carbamate (Mtpc), 2,4–dimethylthiophenyl carbamate (Bmpc), 2–phosphonioethyl carbamate (Peoc), 2–triphenylphosphonioisopropyl carbamate (Ppoc), 1,1–dimethyl–2–cyanoethyl carbamate, *m*–chloro–*p*–acyloxybenzyl carbamate, *p*–(dihydroxyboryl)benzyl carbamate, 5–benzisoxazolylmethyl carbamate, 2–(trifluoromethyl)–6–chromonylmethyl carbamate (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–dimethoxyacylvinyl 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–

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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.

[0063] Nitrogen protecting groups such as sulfonamide groups (*e.g.*, $–S(=O)_2R^{aa}$) 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 phenacylsulfonamide.

[0064] 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–acetoxypropylamine, *N*–(1–isopropyl–4–nitro–2–oxo–3–pyroolin–3–yl)amine, quaternary ammonium salts, *N*–benzylamine, *N*–di(4–methoxyphenyl)methylamine, *N*–5–dibenzosuberylamine, *N*–triphenylmethylamine (Tr), *N*–[(4–methoxyphenyl)diphenylmethyl]amine (MMTr), *N*–9–phenylfluorenylamine (PhF), *N*–2,7–dichloro–9–fluorenylmethyleneamine, *N*–ferrocenylmethylamino (Fcm), *N*–2–picolylamino *N*′–oxide, *N*–1,1–dimethylthiomethyleneamine, *N*–benzylideneamine, *N*–*p*–methoxybenzylideneamine, *N*–diphenylmethyleneamine, *N*–[(2–pyridyl)mesityl]methyleneamine, *N*–(*N*′,*N*′–dimethylaminomethylene)amine, *N*,*N*′–isopropylidenediamine, *N*–*p*–nitrobenzylideneamine, *N*–salicylideneamine, *N*–5–chlorosalicylideneamine, *N*–(5–chloro–2–hydroxyphenyl)phenylmethyleneamine, *N*–cyclohexylideneamine, *N*–(5,5–dimethyl–3–oxo–1–cyclohexenyl)amine, *N*–borane derivative, *N*–diphenylborinic acid derivative, *N*–

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[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).

[0065] Exemplary oxygen atom substituents include, but are not limited to, $–R^{aa}$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R^{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3{}^+X^-$, $–P(OR^{cc})_2$, $–P(OR^{cc})_3{}^+X^-$, $–P(=O)(R^{aa})_2$, $–P(=O)(OR^{cc})_2$, and $–P(=O)(N(R^{bb})_2)_2$, wherein X^-, R^{aa}, R^{bb}, and R^{cc} are as defined herein. 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, 3rd edition, John Wiley & Sons, 1999. Exemplary oxygen protecting groups include, but are not limited to, methyl, *t*-butyloxycarbonyl (BOC or Boc), methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (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, α–naphthyldiphenylmethyl, *p*–

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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), dimethylthexylsilyl, *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–napththyl 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–butenoate, *o*–(methoxyacyl)benzoate, α–naphthoate, nitrate, alkyl *N,N,N′,N′*–tetramethylphosphorodiamidate, alkyl *N*–phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4–dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0066] Exemplary sulfur atom substituents include, but are not limited to, $–R^{aa}$, $–C(=O)SR^{aa}$, $–C(=O)R^{aa}$, $–CO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–S(=O)R^{aa}$, $–SO_2R^{aa}$, $–Si(R^{aa})_3$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–P(=O)_2R^{aa}$, –

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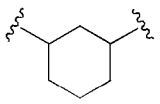
$P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein. In certain embodiments, the sulfur atom substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur 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, 3rd edition, John Wiley & Sons, 1999.

[0067] 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 $-C^AH(C^BH_2C^CH_3)-$ includes one chain atom C^A, one hydrogen atom on C^A, and non-chain substituent $-(C^BH_2C^CH_3)$. The term "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, $-CH(C_2H_5)-$ is a C_1 hydrocarbon chain, and  is a C_3 hydrocarbon chain. When a range of values is used, the meaning of the range is as described herein. For example, a 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.*, $-(CH_2)_4-$). A hydrocarbon chain may also be unsaturated and include one or more C=C and/or C≡C bonds anywhere in the hydrocarbon chain. For instance, $-CH=CH-(CH_2)_2-$, $-CH_2-C\equiv C-CH_2-$, and $-C\equiv C-CH=CH-$ are all examples of a unsubstituted and unsaturated hydrocarbon chain. In certain embodiments, the hydrocarbon chain is unsubstituted (*e.g.*, $-C\equiv C-$ or $-(CH_2)_4-$). In certain embodiments, the hydrocarbon chain is substituted (*e.g.*, $-CH(C_2H_5)-$ and $-CF_2-$). Any two substituents on the hydrocarbon chain may be joined to form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl ring.

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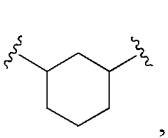
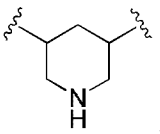
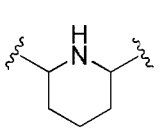
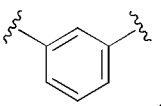
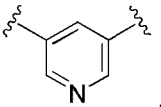
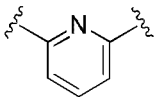
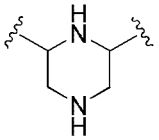
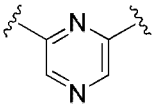
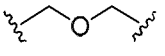
For instance,  ,  ,  ,  ,  , and  are all examples of a hydrocarbon chain. In contrast, in certain embodiments,  and  are not within the scope of the hydrocarbon chains described herein. When a chain atom of a C_x hydrocarbon chain is replaced with a heteroatom, the resulting group is referred to as a C_x hydrocarbon chain wherein a chain atom is replaced with a heteroatom, as opposed to a C_{x-1} hydrocarbon chain. For example,  is a C_3 hydrocarbon chain wherein one chain atom is replaced with an oxygen atom.

[0068] 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, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, *N*,*O*-dimethylhydroxylamino, pixyl, and haloformates. Exemplary leaving groups include, but are not limited to, activated substituted hydroxyl groups (*e.g.*, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-OP(=O)_2R^{aa}$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-OP(=O)_2N(R^{bb})_2$, and $-OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein). In some cases, the leaving group is a sulfonic acid ester, such as toluenesulfonate (tosylate, –OTs), methanesulfonate (mesylate, –OMs), *p*-bromobenzenesulfonyloxy (brosylate, –OBs), $-OS(=O)_2(CF_2)_3CF_3$ (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. In some embodiments, the leaving group is a sulfonate-containing group. In some embodiments, the leaving group is a tosylate group. The leaving group may also be a phosphineoxide (*e.g.*, formed during a Mitsunobu reaction) or an internal leaving group such as an epoxide or cyclic sulfate. Other non-limiting examples of leaving groups are water, ammonia, alcohols, ether moieties, thioether moieties, zinc halides, magnesium moieties, diazonium salts, and copper moieties.

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[0069] The term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19. Pharmaceutically acceptable salts of the compounds 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 $N^+(C_{1-4}\ alkyl)_4^-$ 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.

[0070] 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"

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encompasses both solution-phase and isolatable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0071] 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 ($R \cdot 6\ H_2O$)).

[0072] 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 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.

[0073] 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".

[0074] 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".

[0075] 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

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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.

[0076] 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_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds described herein may be preferred.

[0077] 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.

[0078] 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

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"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.

[0079] The term "aberrant activity" refers to activity deviating from normal activity. The term "increased activity" refers to activity higher than normal activity.

[0080] The terms "composition" and "formulation" are used interchangeably.

[0081] 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. The subject may also be a plant. In certain embodiments, the plant is a land plant. In certain embodiments, the plant is a non-vascular land plant. In certain embodiments, the plant is a vascular land plant. In certain embodiments, the plant is a seed plant. In certain embodiments, the plant is a cultivated plant. In certain embodiments, the plant is a dicot. In certain embodiments, the plant is a monocot. In certain embodiments, the plant is a flowering plant. In some embodiments, the plant is a cereal plant, *e.g.*, maize, corn, wheat, rice, oat, barley, rye, or millet. In some embodiments, the plant is a legume, *e.g.*, a bean plant, *e.g.*, soybean plant. In some embodiments, the plant is a tree or shrub.

[0082] 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

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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 a first biological sample.

[0083] The terms "administer," "administering," or "administration" refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing a compound described herein, or a composition thereof, in or on a subject.

[0084] 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.

[0085] The terms "condition," "disease," and "disorder" are used interchangeably.

[0086] 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.

[0087] 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.

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[0088] 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.

[0089] A "proliferative disease" refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as the matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) the pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, "malignant neoplasms"), benign neoplasms, angiogenesis, inflammatory diseases, and autoimmune diseases.

[0090] 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.

[0091] 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 with the growth of a normal tissue. A neoplasm or tumor may be "benign" or "malignant," depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A "benign

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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.

[0092] 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); 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.*,

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adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma); familiar hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); 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 neuroendoctrine 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 andenocarcinoma, 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).

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[0093] 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 lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma, such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL, such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma (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 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).

[0094] 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, arthrosteitis, rheumatoid arthritis, inflammatory arthritis, Sjogren's syndrome, giant cell arteritis, progressive systemic sclerosis

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(scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto's thyroiditis, Graves' disease, Goodpasture's disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener's granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis. An ocular inflammatory disease includes, but is not limited to, post-surgical inflammation.

[0095] 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 erythematosis, rheumatoid arthritis, psoriatic arthritis,

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systemic lupus erythematosis, 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.

[0096] 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. One of the largest groups of kinases are protein kinases, which act on and modify the activity of specific proteins. 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. These 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,

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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, PIP4K2C, 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,

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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. In certain embodiments, the protein kinase is a protein kinase shown in *Table 2 or Table 3*.

[0097] The term "SRC family kinase" refers to a family of non-receptor tyrosine protein kinases that includes nine members: SRCA subfamily that includes c-SRC (proto-oncogene tyrosine-protein kinase SRC), YES (proto-oncogene tyrosine-protein kinase Yes), FYN (proto-oncogene tyrosine-protein kinase FYN), and FGR (Gardner-Rasheed feline sarcoma viral (v-FGR) oncogene homolog); SRCB subfamily that includes LCK (lymphocyte-specific protein tyrosine kinase), HCK (tyrosine-protein kinase HCK, hemopoietic cell kinase), BLK (tyrosine-protein kinase BLK), and LYN (tyrosine-protein kinase LYN); and FRK (Fyn-related kinase).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

[0098] The present disclosure provides thiazolyl-containing compounds, such as compounds of Formula (**I**), (**II**), or (**III**). In certain embodiments, the compounds described herein are able to inhibit protein kinases (*e.g.*, Src family kinases (*e.g.*, hemopoietic cell kinase (HCK)), Bruton's tyrosine kinase (BTK)). Therefore, the compounds may be useful in treating and/or preventing proliferative diseases (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)). The compounds may act by inducing apoptosis in a cell (*e.g.*, malignant blood cell). Also provided in the present disclosure are pharmaceutical compositions, kits, methods, and uses including a compound described herein.

Compounds

[0099] One aspect of the present disclosure relates to the compounds described herein. The compounds described herein are thiazolyl-containing compounds that may be useful in treating and/or preventing proliferative diseases in a subject, inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell. In certain embodiments, a compound described herein is a compound of Formula (**I**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, a compound described herein is a compound of Formula (**I**), or a

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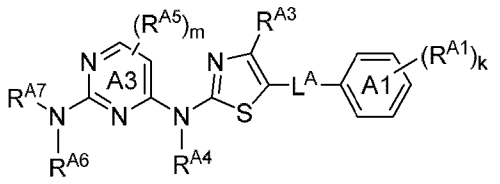
pharmaceutically acceptable salt thereof. In certain embodiments, a compound described herein is a compound of Formula (**II**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, a compound described herein is a compound of Formula (**II**), or a pharmaceutically acceptable salt thereof. In certain embodiments, a compound described herein is a compound of Formula (**III**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiments, a compound described herein is a compound of Formula (**III**), or a pharmaceutically acceptable salt thereof.

Compounds of Formula (I)

[00100] In certain embodiments, a compound described herein is of Formula (**I**):



(**I**),

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

each instance of R^{A1} 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 $–OC(=O)N(R^a)_2$;

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, or 5;

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L^A is –C(=O)–NR^{A2}– or –NR^{A2}–C(=O)–, wherein R^{A2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

R^{A3} 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 –$OC(=O)N(R^a)_2$;

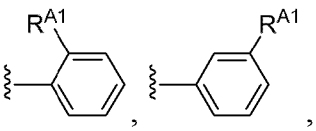
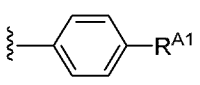
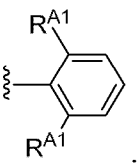
R^{A4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

each instance of R^{A5} 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 –$OC(=O)N(R^a)_2$;

m is 0, 1, or 2;

R^{A6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group; and

R^{A7} 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 heteroaryl, –$C(=O)R^a$, –$C(=O)OR^a$, –$C(=O)N(R^a)_2$, or a nitrogen protecting group.

[00101] Formula (**I**) includes as Ring A1 a phenyl ring that is unsubstituted (*e.g.*, when k is 0) or substituted (*e.g.*, when k is 1, 2, 3, 4, or 5) with one or more substituents R^{A1}. In certain embodiments, Ring A1 is of the formula:  , , or  . In certain embodiments, Ring A1 is of the formula:  . In certain

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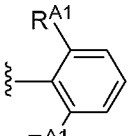
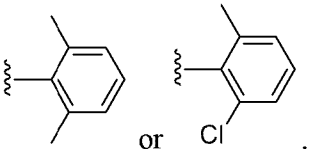
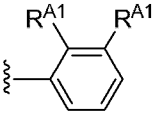
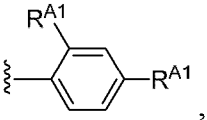
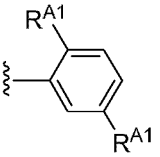
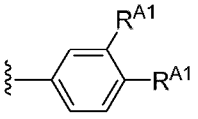
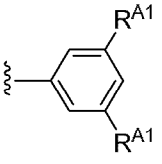
embodiments, Ring A1 is of the formula:  , wherein each instance of R^{A1} is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, Ring A1 is of the formula:  or . In certain embodiments, Ring A1 is of the formula:  ,  ,  ,  , or  .

[00102] In Formula (**I**), Ring A1 may include one or more substituents R^{A1}. In certain embodiments, all instances of R^{A1} are the same. In certain embodiments, two instances of R^{A1} are different from each other. In certain embodiments, at least one instance of R^{A1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A1} is $–CH_3$. In certain embodiments, at least one instance of R^{A1} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently

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nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{A1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A1} is $–OR^a$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{A1} is $–SR^a$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{A1} is $–N(R^a)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{A1} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{A1} is $–C(=NR^a)R^a$, $–C(=NR^a)OR^a$, or $–C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{A1} is $–C(=O)R^a$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^a$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^a)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{A1} is $–NR^aC(=O)R^a$, $–NR^aC(=O)OR^a$, or $–NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{A1} is $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^a)_2$.

[00103] When Formula (**I**) includes two or more instances of substituent R^a, any two instances of R^a may be the same or different from each other. In certain embodiments, at least one instance of R^a is H. In certain embodiments, each instance of R^a is H. In certain embodiments, at least one instance of R^a is substituted or unsubstituted acyl (*e.g.*, acetyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^a is $–CH_3$. In certain embodiments, at least one instance of R^a is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkenyl

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(*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^a is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^a is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^a is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^a is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts) when attached to a nitrogen atom. In certain embodiments, R^a is an oxygen protecting group (*e.g.*, 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^a is a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom. In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted, heterocyclic ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heterocyclic ring comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^a are joined to form a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00104] 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 4. In certain embodiments, k is 5.

[00105] In certain embodiments, k is 1; and R^{A1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl,

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perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, k is 2; and each of the two instances of R^{A1} is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I).

[00106] Formula (**I**) includes divalent linker L^A connecting Ring A1 to the thiazolyl ring. In certain embodiments, L^A is $–C(=O)–N(R^{A2})–$ (*e.g.*, $–C(=O)–NH–$). In certain embodiments, L^A is $–N(R^{A2})–C(=O)–$ (*e.g.*, $–NH–C(=O)–$).

[00107] In certain embodiments, R^{A2} is H. In certain embodiments, R^{A2} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $–CH_3$, Bn, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{A2} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00108] The thiazolyl ring of Formula (**I**) includes substituent R^{A3}. In certain embodiments, R^{A3} is H. In certain embodiments, R^{A3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{A3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{A3} is $–CH_3$. In certain embodiments, R^{A3} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{A3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, R^{A3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{A3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{A3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{A3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{A3} is substituted or unsubstituted phenyl. In certain embodiments, R^{A3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{A3} is $–OR^a$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –

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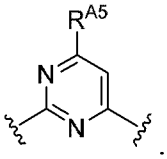
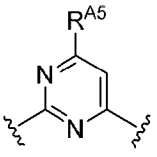
O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, R^{A3} is $–SR^a$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, R^{A3} is $–N(R^a)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, R^{A3} is –CN, –SCN, or $–NO_2$. In certain embodiments, R^{A3} is $–C(=NR^a)R^a$, $–C(=NR^a)OR^a$, or $–C(=NR^a)N(R^a)_2$. In certain embodiments, R^{A3} is $–C(=O)R^a$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^a$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^a)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{A3} is $–NR^aC(=O)R^a$, $–NR^aC(=O)OR^a$, or $–NR^aC(=O)N(R^a)_2$. In certain embodiments, R^{A3} is $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^a)_2$.

[00109] Formula (**I**) includes substituent R^{A4} on a nitrogen atom attached to the thiazolyl ring. In certain embodiments, R^{A4} is H. In certain embodiments, R^{A4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $–CH_3$, Bn, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{A4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00110] Formula (**I**) includes as Ring A3 a pyrimidinyl ring that is unsubstituted (*e.g.*, when m is 0) or substituted (*e.g.*, when m is 1 or 2) with one or more substituents R^{A5}. In certain embodiments, Ring A3 is of the formula: 

. In certain embodiments, Ring A3 is of the formula: 

, wherein R^{A5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl).

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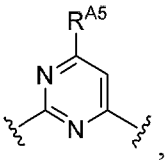
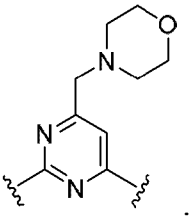
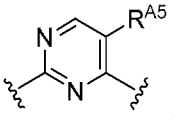
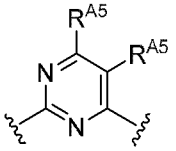
In certain embodiments, Ring A3 is of the formula:  , wherein R^{A5} is C_{1-6} alkyl substituted independently with at least one substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, Ring A3 is of the formula:  . In certain embodiments, Ring A3 is of the formula:  . In certain embodiments, Ring A3 is of the formula:  .

[00111] In Formula (**I**), Ring A3 may include one or two substituents R^{A5}. In certain embodiments, two instances of R^{A5} are the same. In certain embodiments, two instances of R^{A5} are different from each other. In certain embodiments, at least one instance of R^{A5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A5} is $-CH_3$. In certain embodiments, at least one instance of R^{A5} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{A5} is C_{1-6} alkyl substituted with at least one substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A5} is methyl substituted at least with substituted or unsubstituted oxetanyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted pyrrolidinyl, substituted or

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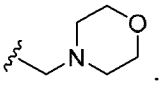
unsubstituted tetrahydropyranyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl. In certain embodiments, at least one instance of R^{A5} is of the formula:  . In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{A5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{A5} is $-OR^a$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{A5} is $-SR^a$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{A5} is $-N(R^a)_2$ (*e.g.*, $-NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $-NMe_2$)). In certain embodiments, at least one instance of R^{A5} is –CN, –SCN, or $-NO_2$. In certain embodiments, at least one instance of R^{A5} is $-C(=NR^a)R^a$, $-C(=NR^a)OR^a$, or $-C(=NR^a)N(R^a)_2$. In certain embodiments, at least one instance of R^{A5} is $-C(=O)R^a$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $-C(=O)OR^a$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $-C(=O)N(R^a)_2$ (*e.g.*, $-C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted

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or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{A5} is $–NR^aC(=O)R^a$, $–NR^aC(=O)OR^a$, or $–NR^aC(=O)N(R^a)_2$. In certain embodiments, at least one instance of R^{A5} is $–OC(=O)R^a$, $–OC(=O)OR^a$, or $–OC(=O)N(R^a)_2$.

[00112] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2.

[00113] Formula (**I**) includes substituent R^{A6} on a nitrogen atom attached to Ring A3. In certain embodiments, R^{A6} is H. In certain embodiments, R^{A6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $–CH_3$, Bn, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{A6} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00114] Formula (**I**) includes substituent R^{A7} on a nitrogen atom attached to Ring A3. In certain embodiments, R^{A7} is H. In certain embodiments, R^{A7} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{A7} is $–CH_3$. In certain embodiments, R^{A7} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{A7} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, R^{A7} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{A7} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{A7} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{A7} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{A7} is $–C(=O)R^a$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^a$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^a)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or

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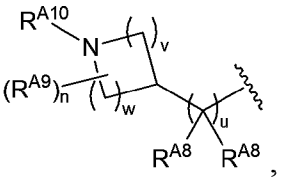
unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{A7} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{A7} is of the formula:



wherein:

each instance of R^{A8} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

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

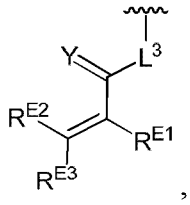
v is 1, 2, or 3;

w is 1, 2, or 3;

each instance of R^{A9} is independently halogen, or substituted or unsubstituted C_{1-6} alkyl;

n is an integer between 0 and 13, inclusive; and

R^{A10} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted carbocyclyl, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^a)_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-42**):



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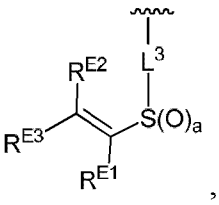

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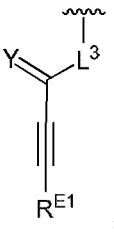

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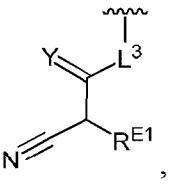

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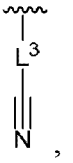

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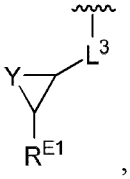

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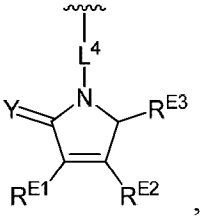

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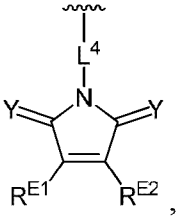

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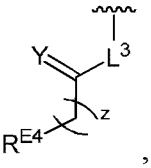

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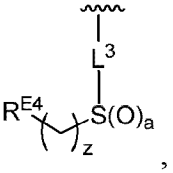

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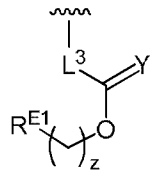
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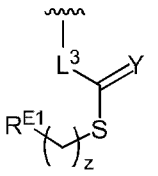
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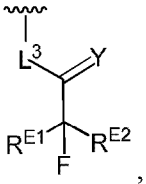
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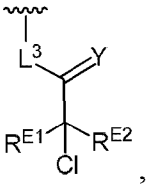
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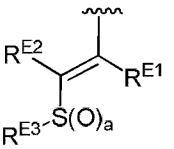
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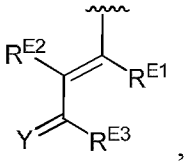
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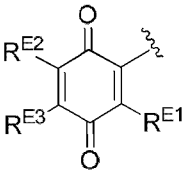
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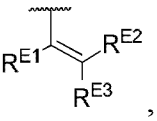
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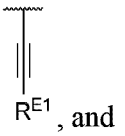
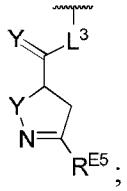
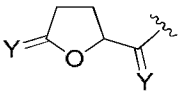
(ii-18)


, and

(ii-19)


;

(ii-20)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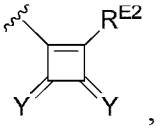
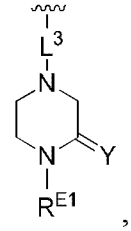
(ii-21)


,

(ii-22)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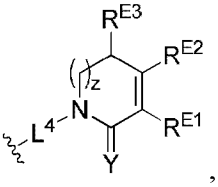
(ii-23)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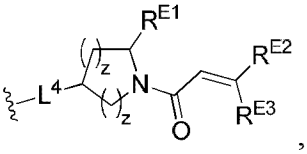
(ii–24)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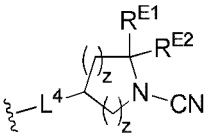
(ii–25)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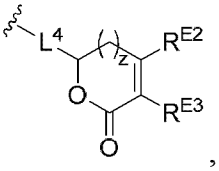
(ii–26)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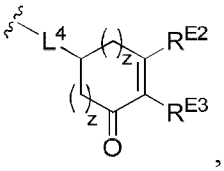
(ii–27)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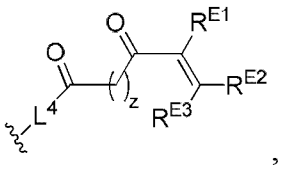
(ii–28)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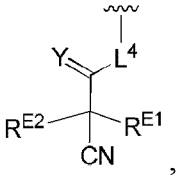
(ii–29)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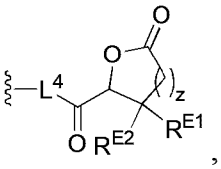
(ii–30)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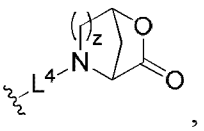
(ii–31)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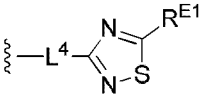
(ii–32)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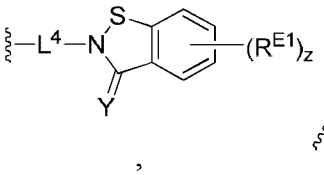
(ii–33)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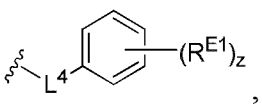
(ii–34)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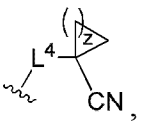
(ii–35)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(ii–36)

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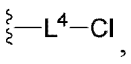
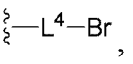
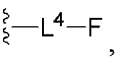
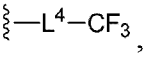
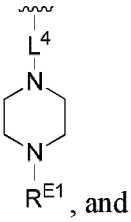
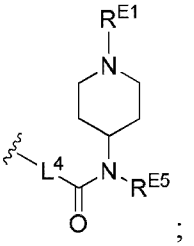

, (ii–37)


, (ii–38)


, (ii–39)


, (ii-40)


, and (ii-41)


; (ii-42)

wherein:

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

L^4 is a bond or an optionally substituted C_{1-4} hydrocarbon chain;

R^{E1} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, –CH_2OR^{E1a}, –$CH_2N(R^{E1a})_2$, –CH_2SR^{E1a}, –OR^{E1a}, –$N(R^{E1a})_2$, –$Si(R^{E1a})_3$, and –SR^{E1a}, wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E2} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted

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carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, and $–SR^{E2a}$, wherein each occurrence of R^{E2a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E3} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, and $–SR^{E3a}$, wherein each occurrence of R^{E3a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E3a} groups are joined to form an optionally substituted heterocyclic ring; or R^{E1} and R^{E3}, or R^{E2} and R^{E3}, or R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

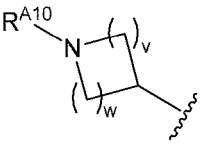
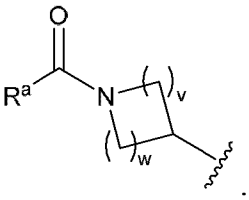
R^{E4} is a leaving group;

R^{E5} is halogen;

Y is O, S, or NR^{E6}, wherein R^{E6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

a is 1 or 2; and

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

[00115] In certain embodiments, R^{A7} is of the formula:  . In certain embodiments, R^{A7} is of the formula:  . In certain embodiments, R^{A7} is of

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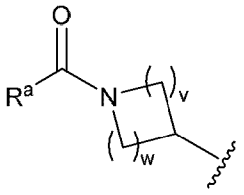
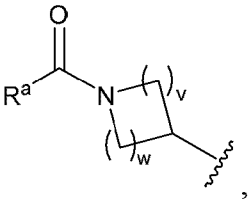
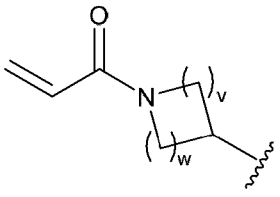
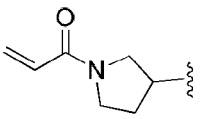
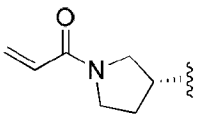
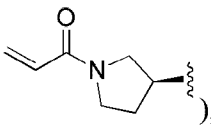
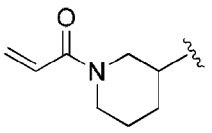
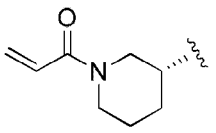
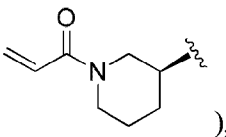
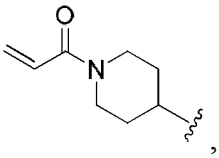
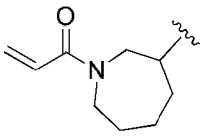
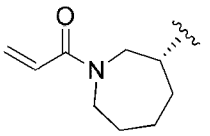
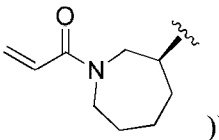
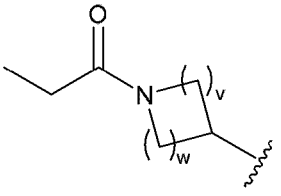
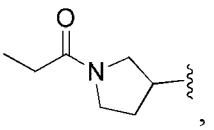
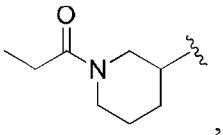
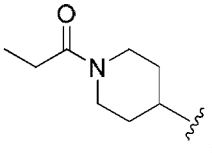
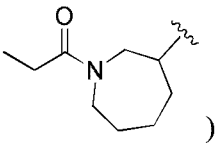
the formula:  , wherein R^a is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{A7} is of the formula:  , wherein R^a is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{A7} is of the formula:

 (*e.g.*,  (*e.g.*,  or ),

 (*e.g.*,  or ),  , or

 (*e.g.*,  or )). In certain embodiments, R^{A7} is of the formula:  (*e.g.*,  ,  ,

 , or ). In certain embodiments, R^{A7} is of the formula:

 . In certain embodiments, R^{A7} is of the formula:

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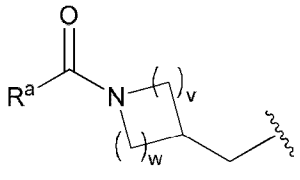
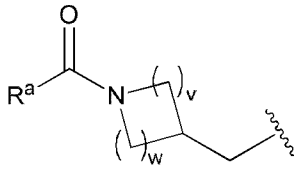
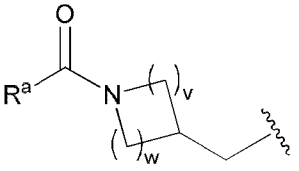
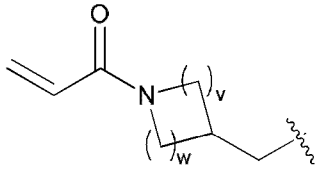
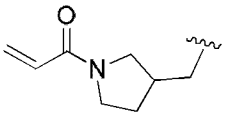
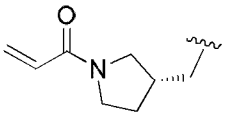
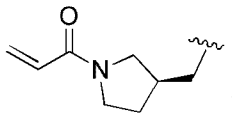
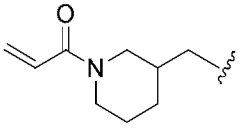
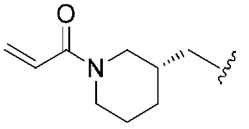
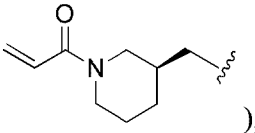
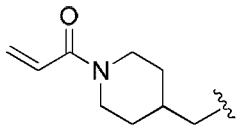
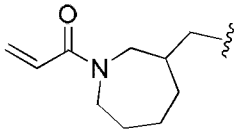
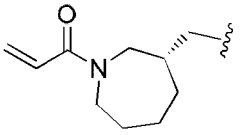
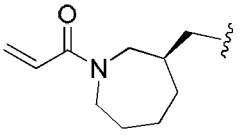
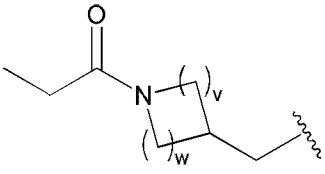
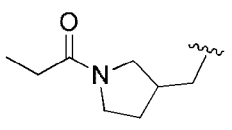
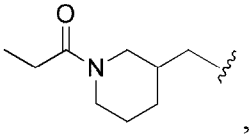
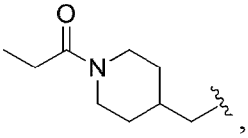
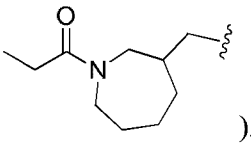
 . In certain embodiments, R^{A7} is of the formula:

 , wherein R^a is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{A7} is of the formula:  , wherein R^a is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{A7} is of the formula:

 (*e.g.*,  (*e.g.*,  or ),  (*e.g.*,  or ),  , or  (*e.g.*,  or )). In certain embodiments, R^{A7} is of the formula:  (*e.g.*,  ,  ,  , or ).

[00116] In certain embodiments, all instances of R^{A8} are the same. In certain embodiments, two instances of R^{A8} are different from each other. In certain embodiments, at least one instance of R^{A8} is H. In certain embodiments, each instance of R^{A8} is H. In certain embodiments, at least one instance of R^{A8} is halogen (*e.g.*, F, Cl, Br, or I). In certain

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embodiments, at least one instance of R^{A8} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A8} is $–CH_3$. In certain embodiments, at least one instance of R^{A8} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00117] In certain embodiments, u is 0. In certain embodiments, u is 1. In certain embodiments, u is 2. In certain embodiments, u is 3. In certain embodiments, u is 4.

[00118] In certain embodiments, v is 1. In certain embodiments, v is 2. In certain embodiments, v is 3. In certain embodiments, v is 4.

[00119] In certain embodiments, w is 1. In certain embodiments, w is 2. In certain embodiments, w is 3.

[00120] In certain embodiments, v is 2; and w is 1. In certain embodiments, v is 3; and w is 1. In certain embodiments, v is 4; and w is 1.

[00121] In certain embodiments, all instances of R^{A9} are the same. In certain embodiments, two instances of R^{A9} are different from each other. In certain embodiments, at least one instance of R^{A9} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{A9} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{A9} is $–CH_3$. In certain embodiments, at least one instance of R^{A9} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00122] In certain embodiments, n is 0. In certain embodiments, n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13.

[00123] In certain embodiments, R^{A10} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted carbocyclyl, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^a)_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{A10} is H. In certain embodiments, R^{A10} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of oxo; halogen; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted cyclopropyl; substituted or unsubstituted, 4- to 7-membered monocyclic carbocyclyl comprising 1 or 2 double bonds in the carbocyclic ring system; substituted or unsubstituted oxiranyl; substituted or unsubstituted, 5- to 10-membered, monocyclic or bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur; –CN; $–(C=O)R^a$; $–N(R^a)(C=O)R^a$; $–O(C=O)R^a$; $–OR^a$; and $–N(R^a)_2$). In certain embodiments, R^{A10} is substituted or unsubstituted C_{2-6} alkenyl (*e.g.*, substituted or

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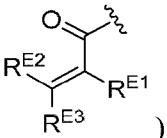
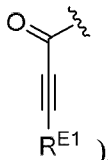
unsubstituted vinyl). In certain embodiments, R^{A10} is substituted or unsubstituted C_{2-6} alkynyl (*e.g.*, substituted or unsubstituted ethynyl). In certain embodiments, R^{A10} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{A10} is –C(=O)R^a. In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted alkyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{1-6} alkyl), such as –C(=O)Et). In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted alkenyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{2-6} alkenyl), such as –C(=O)–CH=CH_2). In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted carbocyclyl). In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted heterocyclyl). In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted phenyl). In certain embodiments, R^{A10} is –C(=O)(substituted or unsubstituted heteroaryl). In certain embodiments, R^{A10} is –C(=O)OR^a (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)) or –C(=O)N(R^a)$_2$ (*e.g.*, –C(=O)NH_2, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{A10} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{A10} is of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{A10} is of any one of Formulae (**ii-24**) to (**ii-42**). In certain embodiments, R^{A10} is of Formula (**ii-1**) (*e.g.*, of the formula: 

). In certain embodiments, R^{A10} is of Formula (**ii-3**) (*e.g.*, of the formula: 

). In certain embodiments, R^{A10} is of any one of the formulae shown in *Table 1A*.

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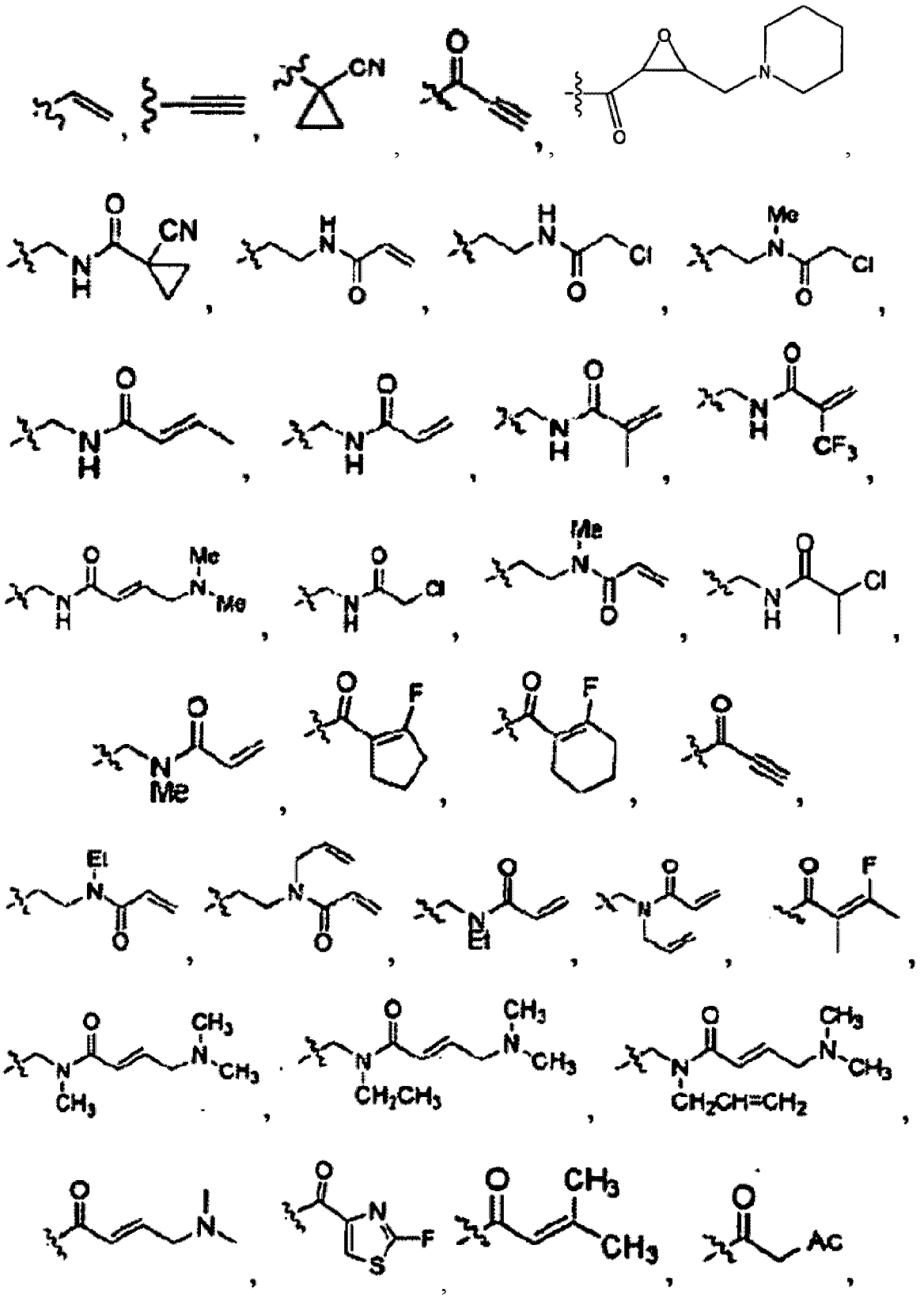
[00124] *Table 1A*. Exemplary moieties.



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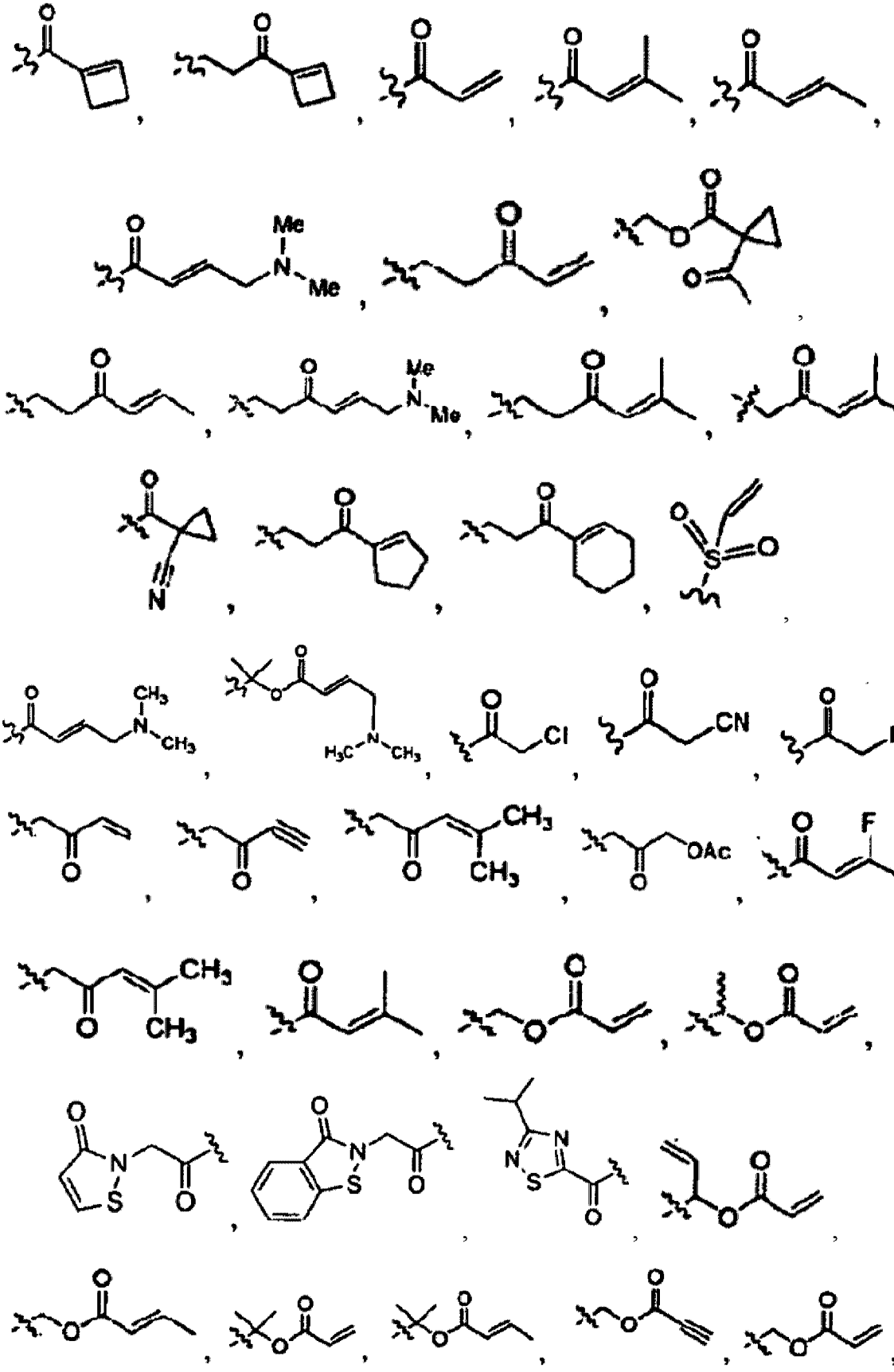

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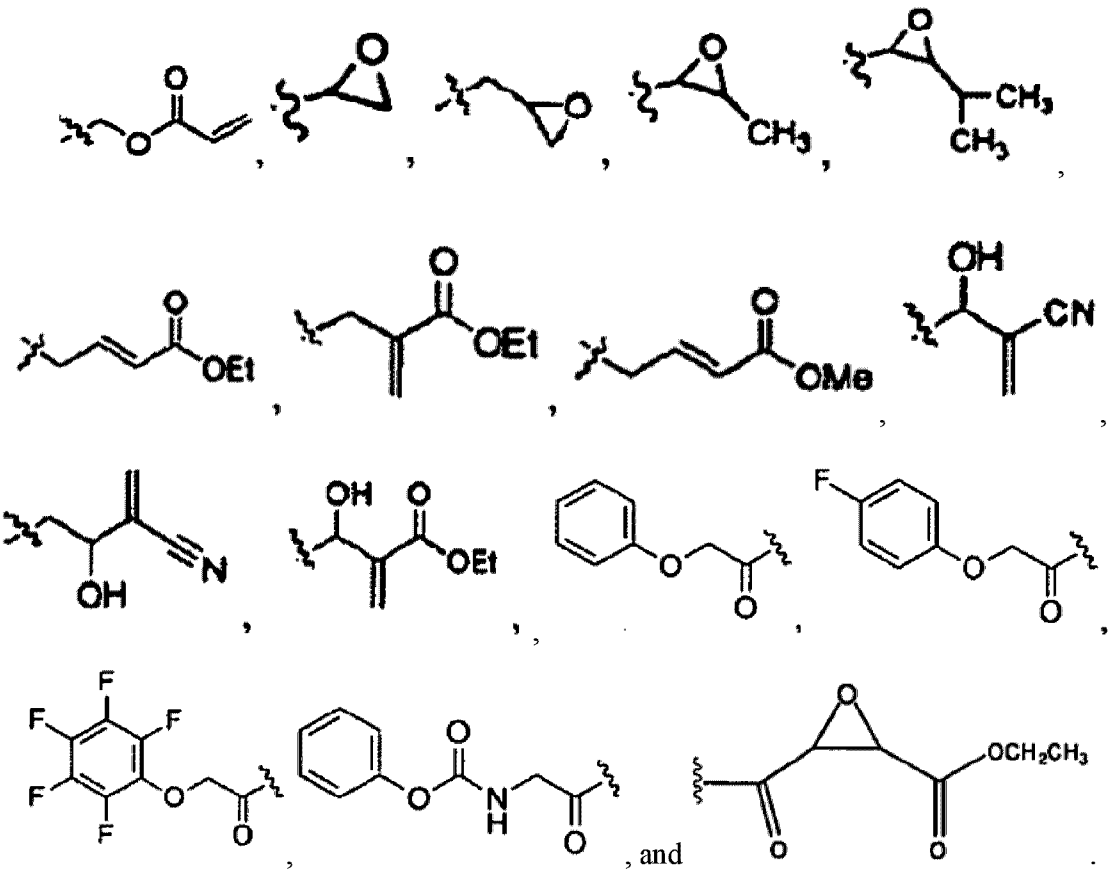

[00125] In certain embodiments, L^3 is a bond. In certain embodiments, L^3 is an optionally substituted C_{1-4} hydrocarbon chain. In certain embodiments, L^3 is an optionally substituted C_{1-4} hydrocarbon chain, wherein one or more carbon units of the hydrocarbon chain are independently replaced with –O–, –S–, $–NR^{L3a}–$, $–NR^{L3a}C(=O)–$, $–C(=O)NR^{L3a}–$, $–SC(=O)–$, $–C(=O)S–$, $–OC(=O)–$, $–C(=O)O–$, $–NR^{L3a}C(=S)–$, $–C(=S)NR^{L3a}–$, *trans*–$CR^{L3b}=CR^{L3b}–$, *cis*–$CR^{L3b}=CR^{L3b}–$, –C≡C–, –S(=O)–, –S(=O)O–, –OS(=O)–, $–S(=O)NR^{L3a}–$, $–NR^{L3a}S(=O)–$, $–S(=O)_2–$, $–S(=O)_2O–$, $–OS(=O)_2–$, $–S(=O)_2NR^{L3a}–$, or $–NR^{L3a}S(=O)_2–$. In certain embodiments, L^3 is an optionally substituted C_{1-4} hydrocarbon chain, wherein one carbon unit of the hydrocarbon chain is replaced with $–NR^{L3a}–$ (*e.g.*, –NH–). In certain embodiments, L^3 is of the formula: $–(CH_2)_{1-4}–NR^{L3a}–$ (*e.g.*, $–(CH_2)_{1-4}–NH–$) or $–NR^{L3a}–CH_2)_{1-4}–$ (*e.g.*, $–NH–CH_2)_{1-4}–$).

[00126] In certain embodiments, R^{L3a} is hydrogen.

[00127] In certain embodiments, at least one instance of R^{L3b} is hydrogen. In certain embodiments, each instance of R^{L3b} is hydrogen. In certain embodiments, at least one instance of R^{L3b} is halogen (*e.g.*, F or Cl). In certain embodiments, each instance of R^{L3b} is

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halogen (*e.g.*, F or Cl). In certain embodiments, at least one instance of R^{L3b} is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, two R^{L3b} groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring.

[00128] In certain embodiments, L^4 is a bond. In certain embodiments, L^4 is an optionally substituted C_{1-4} hydrocarbon chain.

[00129] In certain embodiments, R^{E1} is hydrogen. In certain embodiments, R^{E1} is halogen. In certain embodiments, R^{E1} is optionally substituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{E1} is optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E1a}$, $–CH_2N(R^{E1a})_2$, $–CH_2SR^{E1a}$, $–OR^{E1a}$, $–N(R^{E1a})_2$, $–Si(R^{E1a})_3$, or $–SR^{E1a}$.

[00130] In certain embodiments, R^{E2} is hydrogen. In certain embodiments, R^{E2} is halogen. In certain embodiments, R^{E2} is optionally substituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{E2} is optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, or $–SR^{E2a}$.

[00131] In certain embodiments, R^{E3} is hydrogen. In certain embodiments, R^{E3} is halogen. In certain embodiments, R^{E3} is optionally substituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{E3} is optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, or $–SR^{E3a}$.

[00132] In certain embodiments, R^{E1} and R^{E3} are joined to form an optionally substituted carbocyclic ring. In certain embodiments, R^{E1} and R^{E3} are joined to form an optionally substituted heterocyclic ring. In certain embodiments, R^{E2} and R^{E3} are joined to form an optionally substituted carbocyclic ring. In certain embodiments, R^{E2} and R^{E3} are joined to form an optionally substituted heterocyclic ring. In certain embodiments, R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic ring. In certain embodiments, R^{E1} and R^{E2} are joined to form an optionally substituted heterocyclic ring.

[00133] In certain embodiments, R^{E4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{E4} is $–OS(=O)R^{E4a}$ or $–OS(=O)_2R^{E4a}$, wherein R^{E4a} is substituted or

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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. In certain embodiments, R^{E4} is –OMs, –OTf, –OTs, –OBs, or 2-nitrobenzenesulfonyloxy. In certain embodiments, R^{E4} is –OR^{E4a}. In certain embodiments, R^{E4} is –OMe, –OCF_3, or –OPh. In certain embodiments, R^{E4} is –$OC(=O)R^{E4a}$. In certain embodiments, R^{E4} is –OC(=O)Me, –$OC(=O)CF_3$, –OC(=O)Ph, or –OC(=O)Cl. In certain embodiments, R^{E4} is –$OC(=O)OR^{E4a}$. In certain embodiments, R^{E4} is –OC(=O)OMe or –OC(=O)O(*t*-Bu).

[00134] In certain embodiments, R^{E5} is F, Cl, Br, or I.

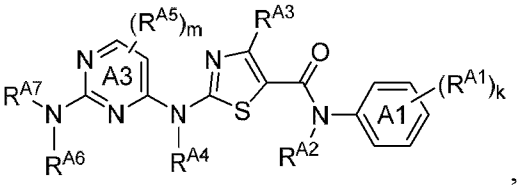
[00135] In certain embodiments, Y is O. In certain embodiments, Y is S. In certain embodiments, Y is NR^{E6} (*e.g.*, NH).

[00136] In certain embodiments, R^{E6} is H.

[00137] In certain embodiments, a is 1. In certain embodiments, a is 2.

[00138] In certain embodiments, at least one instance of z is 0. In certain embodiments, at least one instance of z is 1. In certain embodiments, at least one instance of z is 2, 3, 4, 5, or 6. In certain embodiments, two instacnes of z are the same. In certain embodiments, two instacnes of z are different from each other.

[00139] In certain embodiments, a compound of Formula (**I**) is of the formula:



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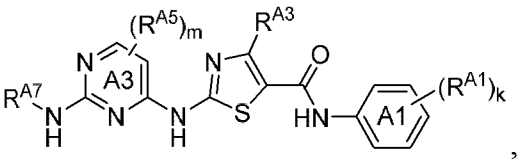
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00140] In certain embodiments, a 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.

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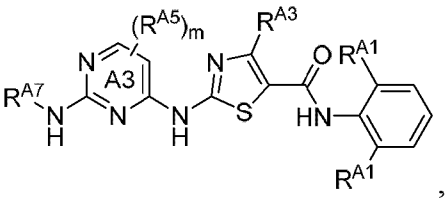
[00141] In certain embodiments, a compound of Formula (**I**) is of the formula:



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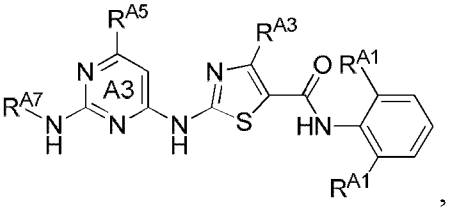
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

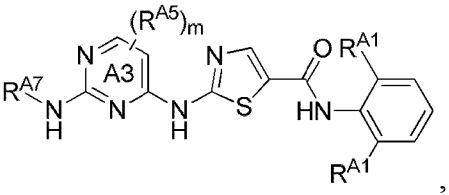
[00142] In certain embodiments, a compound of Formula (**I**) is of the formula:



,

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

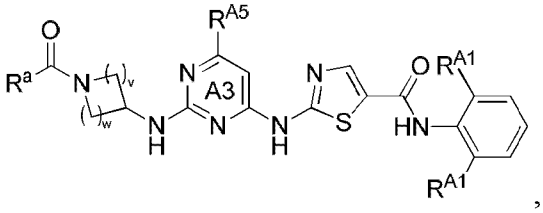
[00143] In certain embodiments, a compound of Formula (**I**) is of the formula:



,

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

[00144] In certain embodiments, a 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, wherein R^a is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{2-6} alkenyl.

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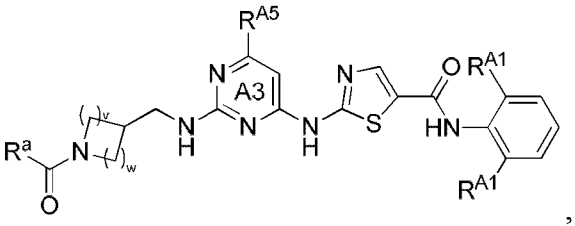
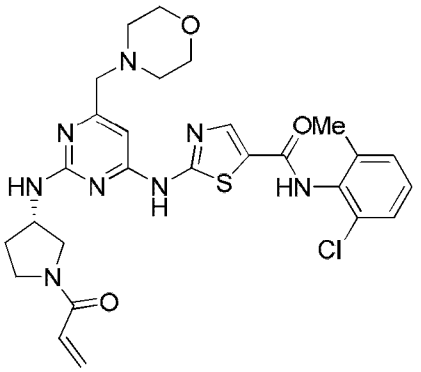
[00145] In certain embodiments, a compound of Formula (**I**) is of the formula:



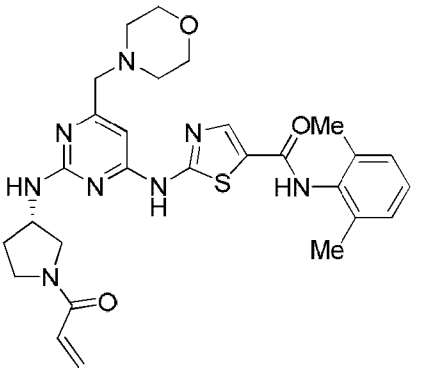
,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^a is substituted or unsubstituted C_{1-6} alkyl or substituted or unsubstituted C_{2-6} alkenyl.

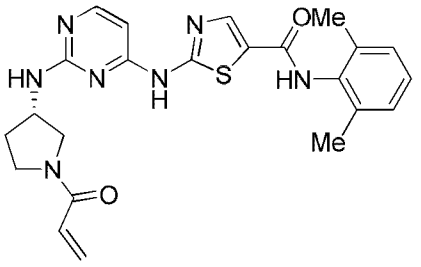
[00146] Exemplary compounds of Formula (**I**) include, but are not limited to:



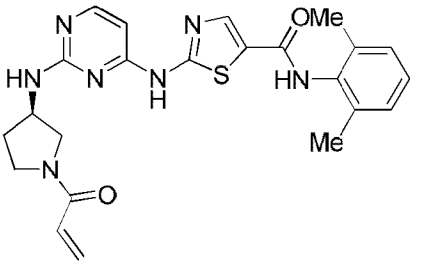
(**I-1**),



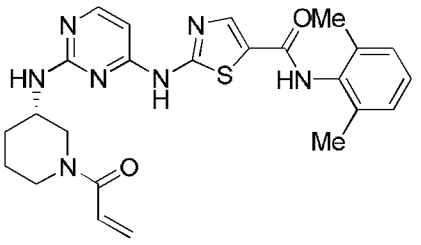
(**I-2**),



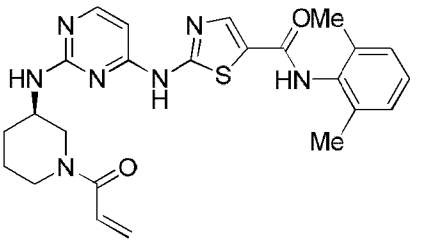
(**I-3**),



(**I-4**),



(**I-5**),



(**I-6**),

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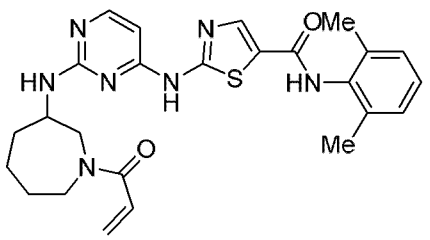
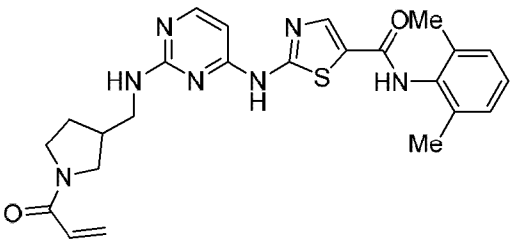
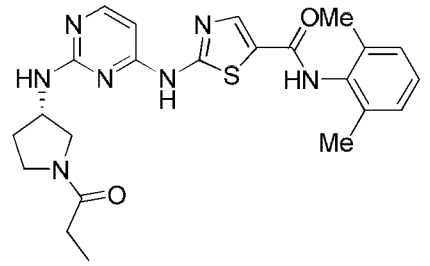


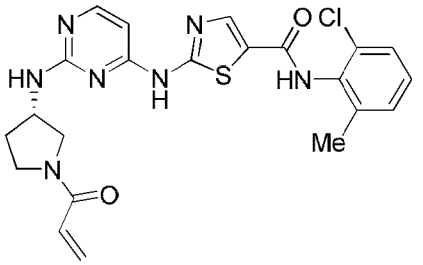
(**I-7**),



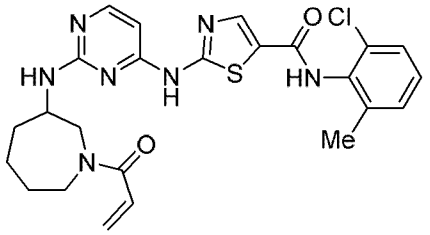
(**I-8**),



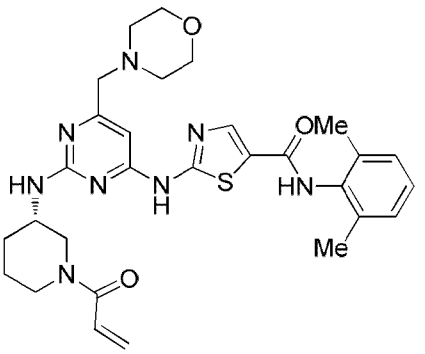
(**I-9**),



(**I-10**),



(**I-11**),

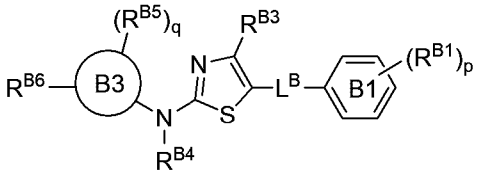


(**I-12**),

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

Compounds of Formula (II)

[00147] In certain embodiments, a compound described herein is of Formula (**II**):



(**II**),

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

each instance of R^{B1} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or

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unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $–OR^b$, $–N(R^b)_2$, $–SR^b$, –CN, –SCN, $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^b$, $–C(=O)OR^b$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$;

each instance of R^b 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^b are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring;

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

L^B is $–C(=O)–NR^{B2}–$ or $–NR^{B2}–C(=O)–$, wherein R^{B2} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

R^{B3} 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, $–OR^b$, $–N(R^b)_2$, $–SR^b$, –CN, –SCN, $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^b$, $–C(=O)OR^b$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$;

R^{B4} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

Ring B3 is a substituted or unsubstituted pyrazolyl ring;

each instance of R^{B5} 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, $–OR^b$, $–N(R^b)_2$, $–SR^b$, –CN, –SCN, $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, $–C(=NR^b)N(R^b)_2$, $–C(=O)R^b$, $–C(=O)OR^b$, $–C(=O)N(R^b)_2$, $–NO_2$, $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, $–NR^bC(=O)N(R^b)_2$, $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$;

q is 0, 1, or 2;

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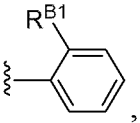
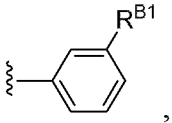
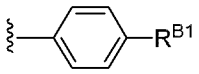
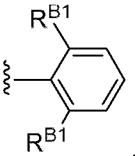
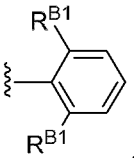
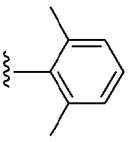
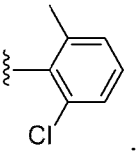
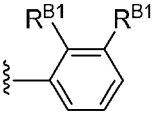
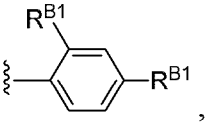
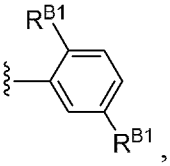
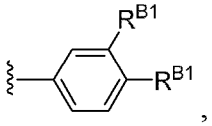
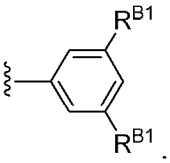
R^{B6} is substituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, $–C(=O)R^b$, $–C(=O)OR^b$, or $–C(=O)N(R^b)_2$.

[00148] Formula (**II**) includes as Ring B1 a phenyl ring that is unsubstituted (*e.g.*, when p is 0) or substituted (*e.g.*, when p is 1, 2, 3, 4, or 5) with one or more substituents R^{B1}. In certain embodiments, Ring B1 is of the formula:  ,  , or  . In certain embodiments, Ring B1 is of the formula:  . In certain embodiments, Ring B1 is of the formula:  , wherein each instance of R^{B1} is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, Ring B1 is of the formula:  or  . In certain embodiments, Ring B1 is of the formula:  ,  ,  ,  , or  .

[00149] In Formula (**II**), Ring B1 may include one or more substituents R^{B1}. In certain embodiments, all instances of R^{B1} are the same. In certain embodiments, two instances of R^{B1} are different from each other. In certain embodiments, at least one instance of R^{B1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B1} is substituted or

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unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B1} is $–CH_3$. In certain embodiments, at least one instance of R^{B1} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{B1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B1} is $–OR^b$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{B1} is $–SR^b$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{B1} is $–N(R^b)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{B1} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{B1} is $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, or $–C(=NR^b)N(R^b)_2$. In certain embodiments, at least one instance of R^{B1} is $–C(=O)R^b$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^b$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^b)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or

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unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{B1} is $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, or $–NR^bC(=O)N(R^b)_2$. In certain embodiments, at least one instance of R^{B1} is $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$.

[00150] When Formula (**II**) includes two or more instances of substituent R^b, any two instances of R^b may be the same or different from each other. In certain embodiments, at least one instance of R^b is H. In certain embodiments, each instance of R^b is H. In certain embodiments, at least one instance of R^b is substituted or unsubstituted acyl (*e.g.*, acetyl). In certain embodiments, at least one instance of R^b is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^b is $–CH_3$. In certain embodiments, at least one instance of R^b is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^b is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^b is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^b is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^b is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^b is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^b is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^b is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^b is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts) when attached to a nitrogen atom. In certain embodiments, R^b is an oxygen protecting group (*e.g.*, 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^b is a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom. In certain

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embodiments, two instances of R^b are joined to form a substituted or unsubstituted, heterocyclic ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heterocyclic ring comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^b are joined to form a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00151] In certain embodiments, 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. In certain embodiments, p is 5.

[00152] In certain embodiments, p is 1; and R^{B1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, p is 2; and each of the two instances of R^{B1} is independently substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl, such as $–CH_3$, $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl) or halogen (*e.g.*, F, Cl, Br, or I).

[00153] Formula (**II**) includes divalent linker L^B connecting Ring B1 to the thiazolyl ring. In certain embodiments, L^B is $–C(=O)–N(R^{B2})–$ (*e.g.*, –C(=O)–NH–). In certain embodiments, L^B is $–N(R^{B2})–C(=O)–$ (*e.g.*, –NH–C(=O)–).

[00154] In certain embodiments, R^{B2} is H. In certain embodiments, R^{B2} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $–CH_3$, Bn, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{B2} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00155] The thiazolyl ring of Formula (**II**) includes substituent R^{B3}. In certain embodiments, R^{B3} is H. In certain embodiments, R^{B3} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{B3} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{B3} is $–CH_3$. In certain embodiments, R^{B3} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{B3} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, R^{B3} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In

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certain embodiments, R^{B3} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{B3} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{B3} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{B3} is substituted or unsubstituted phenyl. In certain embodiments, R^{B3} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{B3} is $–OR^b$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, R^{B3} is $–SR^b$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, R^{B3} is $–N(R^b)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, R^{B3} is –CN, –SCN, or $–NO_2$. In certain embodiments, R^{B3} is $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, or $–C(=NR^b)N(R^b)_2$. In certain embodiments, R^{B3} is $–C(=O)R^b$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^b$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^b)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{B3} is $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, or $–NR^bC(=O)N(R^b)_2$. In certain embodiments, R^{B3} is $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$.

[00156] Formula (**II**) includes substituent R^{B4} on a nitrogen atom attached to the thiazolyl ring. In certain embodiments, R^{B4} is H. In certain embodiments, R^{B4} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $–CH_3$, Bn, $–CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{B4} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

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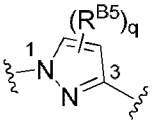
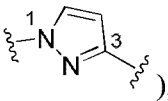
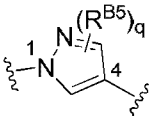
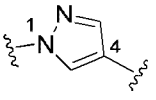
[00157] Formula (**II**) includes as Ring B3 a pyrazolyl ring that is unsubstituted (*e.g.*, when q is 0) or substituted (*e.g.*, when q is 1 or 2) with one or more substituents R^{B5}. In certain embodiments, Ring B3 is of the formula:  (*e.g.*, ), wherein the nitrogen atom labeled with "1" is attached to R^{B6}, and the carbon atom labeled with "3" is attached to the nitrogen atom to which R^{B4} is attached. In certain embodiments, Ring B3 is of the formula:  (*e.g.*, ), wherein the nitrogen atom labeled with "1" is attached to R^{B6}, and the carbon atom labeled with "4" is attached to the nitrogen atom to which R^{B4} is attached.

[00158] In Formula (**II**), Ring B3 may include one or two substituents R^{B5}. In certain embodiments, two instances of R^{B5} are the same. In certain embodiments, two instances of R^{B5} are different from each other. In certain embodiments, at least one instance of R^{B5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B5} is $-CH_3$. In certain embodiments, at least one instance of R^{B5} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{B5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one,

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two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{B5} is $–OR^b$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{B5} is $–SR^b$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{B5} is $–N(R^b)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{B5} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{B5} is $–C(=NR^b)R^b$, $–C(=NR^b)OR^b$, or $–C(=NR^b)N(R^b)_2$. In certain embodiments, at least one instance of R^{B5} is $–C(=O)R^b$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^b$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^b)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{B5} is $–NR^bC(=O)R^b$, $–NR^bC(=O)OR^b$, or $–NR^bC(=O)N(R^b)_2$. In certain embodiments, at least one instance of R^{B5} is $–OC(=O)R^b$, $–OC(=O)OR^b$, or $–OC(=O)N(R^b)_2$.

[00159] In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

[00160] Formula (**II**) includes substituent R^{B6} on a nitrogen atom attached to Ring B3. In certain embodiments, R^{B6} is substituted alkyl (*e.g.*, substituted C_{1-6} alkyl). In certain embodiments, R^{B6} is $–CF_3$, Bn, perfluoroethyl, perfluoropropyl, or perfluorobutyl. In certain embodiments, R^{B6} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, R^{B6} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{B6} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{B6} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain

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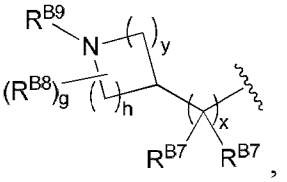
embodiments, R^{B6} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{B6} is substituted or unsubstituted phenyl. In certain embodiments, R^{B6} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{B6} is $–C(=O)R^b$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^b$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^b)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{B6} is of the formula:



,

wherein:

each instance of R^{B7} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

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

y is 1, 2, 3, or 4;

h is 1, 2, or 3;

each instance of R^{B8} is independently halogen, or substituted or unsubstituted C_{1-6} alkyl;

g is an integer between 0 and 13, inclusive; and

R^{B9} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted carbocyclyl, $–C(=O)R^a$, $–C(=O)OR^a$, $–C(=O)N(R^a)_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-42**):

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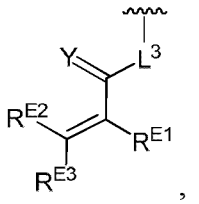

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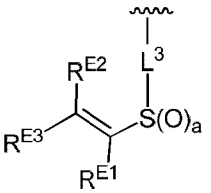

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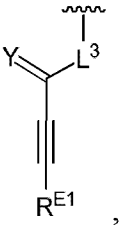

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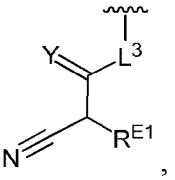
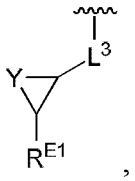


(ii-4),

(ii-5),



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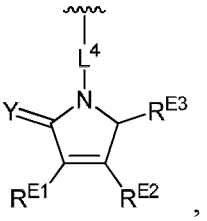

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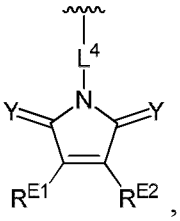

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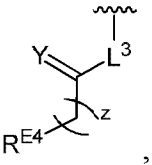

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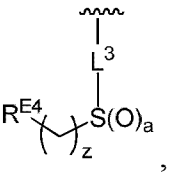

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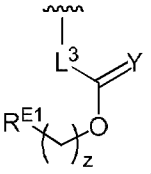

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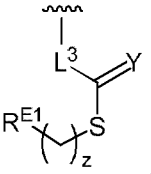

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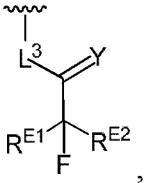

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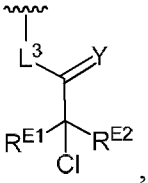

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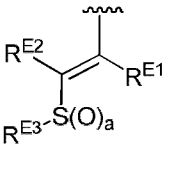

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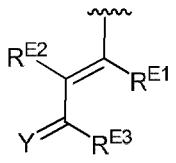

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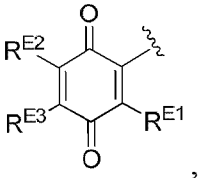

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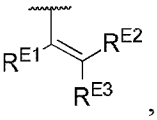

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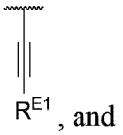

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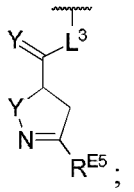

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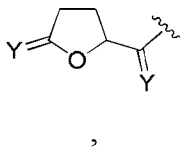

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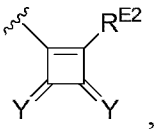

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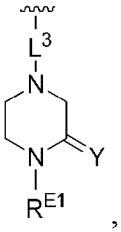

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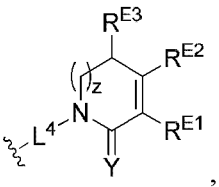

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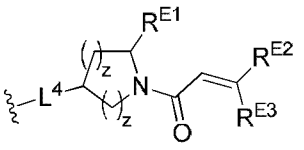

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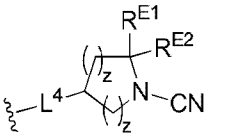
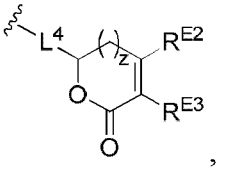
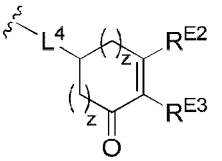


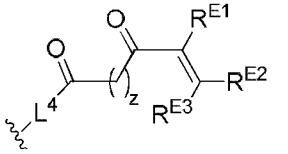
(ii–26)



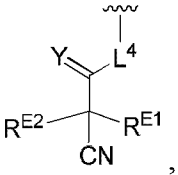
(ii–27)



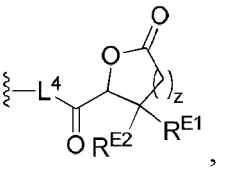
(ii–28)



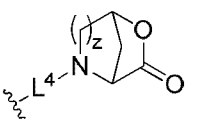
(ii–29)



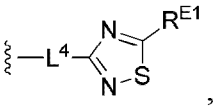
(ii–30)



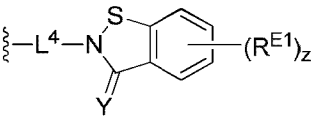
(ii–31)



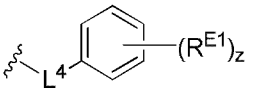
(ii–32)



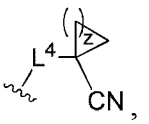
(ii–33)



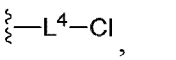
(ii–34)



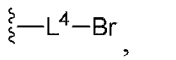
(ii–35)



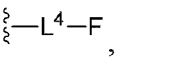
(ii–36)



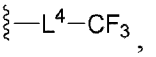
(ii–37)



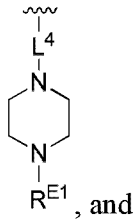
(ii–38)



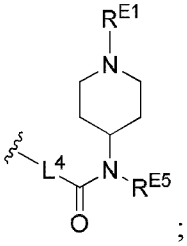
(ii–39)



(ii-40)



(ii-41), and



(ii-42);

wherein:

L^3 is a bond or an optionally substituted C_{1-4} hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with –O–, –S–, –NR^{L3a}–, –$NR^{L3a}C(=O)$–, –$C(=O)NR^{L3a}$–, –$SC(=O)$–, –$C(=O)S$–, –$OC(=O)$–, –$C(=O)O$–, –$NR^{L3a}C(=S)$–, –$C(=S)NR^{L3a}$–, *trans*–$CR^{L3b}=CR^{L3b}$–, *cis*–$CR^{L3b}=CR^{L3b}$–, –C≡C–, –$S(=O)$–, –$S(=O)O$–, –$OS(=O)$–, –$S(=O)NR^{L3a}$–, –$NR^{L3a}S(=O)$–, –$S(=O)_2$–, –$S(=O)_2O$–, –$OS(=O)_2$–, –$S(=O)_2NR^{L3a}$–, or –$NR^{L3a}S(=O)_2$–, wherein R^{L3a} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group, and wherein each occurrence of R^{L3b} is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted

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carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{L3b} groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

L^4 is a bond or an optionally substituted C_{1-4} hydrocarbon chain;

R^{E1} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E1a}$, $–CH_2N(R^{E1a})_2$, $–CH_2SR^{E1a}$, $–OR^{E1a}$, $–N(R^{E1a})_2$, $–Si(R^{E1a})_3$, and $–SR^{E1a}$, wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E2} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, and $–SR^{E2a}$, wherein each occurrence of R^{E2a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E3} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, and $–SR^{E3a}$, wherein each occurrence of R^{E3a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E3a} groups are joined to form an optionally substituted heterocyclic ring; or R^{E1} and R^{E3}, or R^{E2} and R^{E3}, or R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{E4} is a leaving group;

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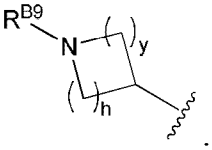
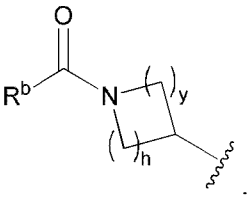
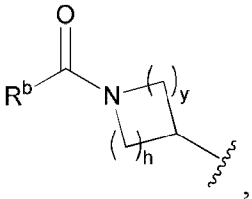
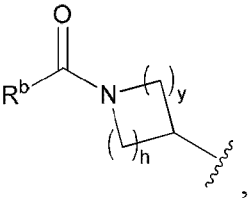
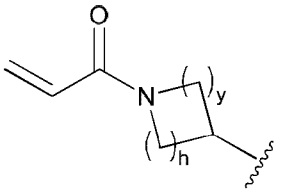
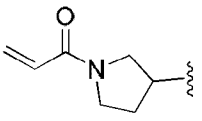
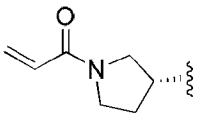
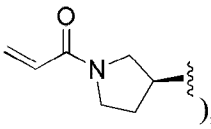
R^{E5} is halogen;

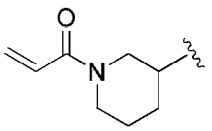
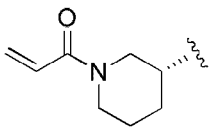
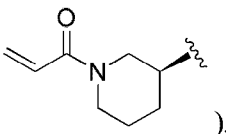
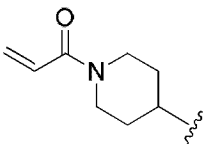
Y is O, S, or NR^{E6}, wherein R^{E6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

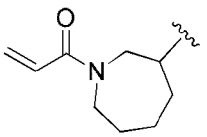
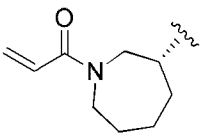
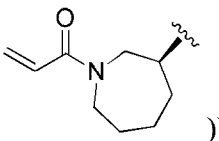
a is 1 or 2; and

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

[00161] In certain embodiments, R^{B6} is of the formula:  . In certain embodiments, R^{B6} is of the formula:  . In certain embodiments, R^{B6} is of the formula:  , wherein R^b is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{B6} is of the formula:  , wherein R^b is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{B6} is of the formula:

 (*e.g.*,  (*e.g.*,  or ),

 (*e.g.*,  or ),  , or

 (*e.g.*,  or )). In certain embodiments, R^{B6}

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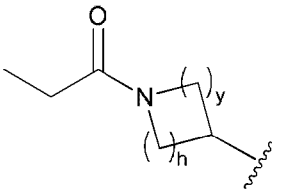
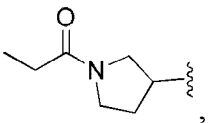
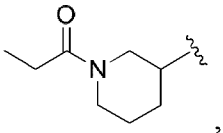
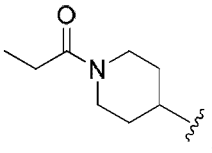
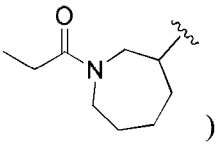
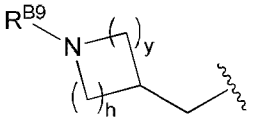
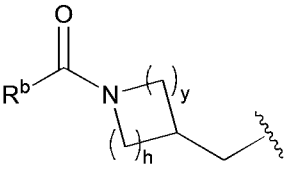
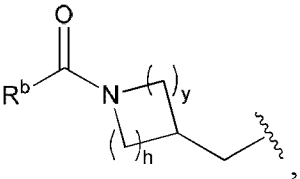
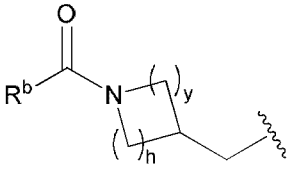
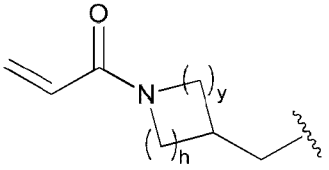
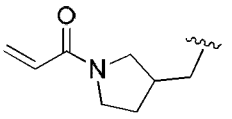
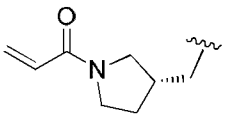
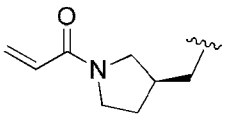
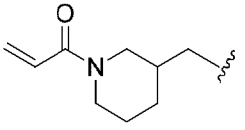
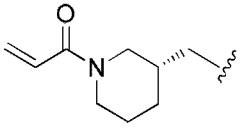
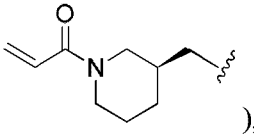
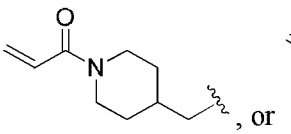
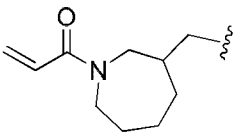
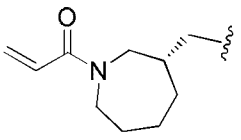
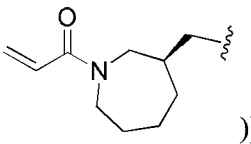
is of the formula:  (*e.g.*,  ,  ,  , or ). In certain embodiments, R^{B6} is of the formula:  . In certain embodiments, R^{B6} is of the formula:  . In certain embodiments, R^{B6} is of the formula:  , wherein R^b is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{B6} is of the formula:  , wherein R^b is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{B6} is of the formula:  (*e.g.*,  ,  , or ),  (*e.g.*,  , or ),  , or  (*e.g.*,  or )). In certain embodiments, R^{B6} is of the

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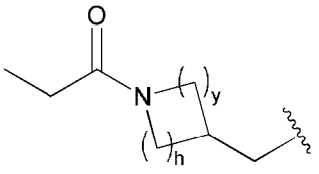
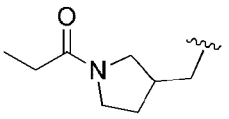
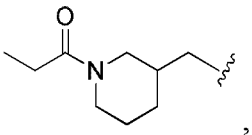
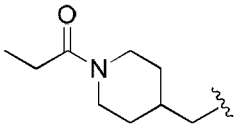
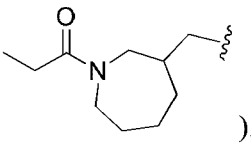
formula:  (*e.g.*,  ,  ,  , or ).

[00162] In certain embodiments, all instances of R^{B7} are the same. In certain embodiments, two instances of R^{B7} are different from each other. In certain embodiments, at least one instance of R^{B7} is H. In certain embodiments, each instance of R^{B7} is H. In certain embodiments, at least one instance of R^{B7} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B7} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B7} is $-CH_3$. In certain embodiments, at least one instance of R^{B7} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00163] In certain embodiments, x is 0. In certain embodiments, x is 1. In certain embodiments, x is 2. In certain embodiments, x is 3. In certain embodiments, x is 4.

[00164] In certain embodiments, y is 1. In certain embodiments, y is 2. In certain embodiments, y is 3. In certain embodiments, y is 4.

[00165] In certain embodiments, h is 1. In certain embodiments, h is 2. In certain embodiments, h is 3.

[00166] In certain embodiments, y is 2; and h is 1. In certain embodiments, y is 3; and h is 1. In certain embodiments, y is 4; and h is 1.

[00167] In certain embodiments, all instances of R^{B8} are the same. In certain embodiments, two instances of R^{B8} are different from each other. In certain embodiments, at least one instance of R^{B8} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{B8} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{B8} is $-CH_3$. In certain embodiments, at least one instance of R^{B8} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00168] In certain embodiments, g is 0. In certain embodiments, g is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13.

[00169] In certain embodiments, R^{B9} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl,

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substituted or unsubstituted carbocyclyl, –C(=O)R^a, –C(=O)OR^a, –C(=O)N(R^a)$_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{B9} is H. In certain embodiments, R^{B9} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of oxo; halogen; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted cyclopropyl; substituted or unsubstituted, 4- to 7-membered monocyclic carbocyclyl comprising 1 or 2 double bonds in the carbocyclic ring system; substituted or unsubstituted oxiranyl; substituted or unsubstituted, 5- to 10-membered, monocyclic or bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur; –CN; –(C=O)R^a; –N(R^a)(C=O)R^a; –O(C=O)R^a; –OR^a; and –N(R^a)$_2$). In certain embodiments, R^{B9} is substituted or unsubstituted C_{2-6} alkenyl (*e.g.*, substituted or unsubstituted vinyl). In certain embodiments, R^{B9} is substituted or unsubstituted C_{2-6} alkynyl (*e.g.*, substituted or unsubstituted ethynyl). In certain embodiments, R^{B9} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{B9} is –C(=O)R^a. In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted alkyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{1-6} alkyl), such as –C(=O)Et). In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted alkenyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{2-6} alkenyl), such as –C(=O)–CH=CH_2). In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted carbocyclyl). In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted heterocyclyl). In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted phenyl). In certain embodiments, R^{B9} is –C(=O)(substituted or unsubstituted heteroaryl). In certain embodiments, R^{B9} is –C(=O)OR^a (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)) or –C(=O)N(R^a)$_2$ (*e.g.*, –C(=O)NH_2, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{B9} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{B9} is of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{B9} is of any one of Formulae (**ii-24**) to (**ii-42**). In certain embodiments, R^{B9} is

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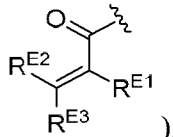
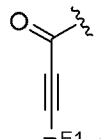
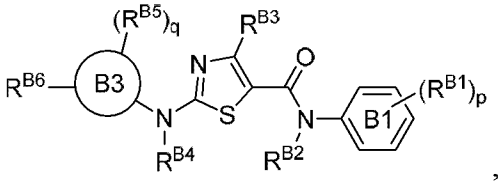
of Formula (**ii-1**) (*e.g.*, of the formula: ). In certain embodiments, R^{B9} is of Formula (**ii-3**) (*e.g.*, of the formula: ). In certain embodiments, R^{B9} is of any one of the formulae shown in *Table 1A*. The moieties included in R^{B9} are as described herein.

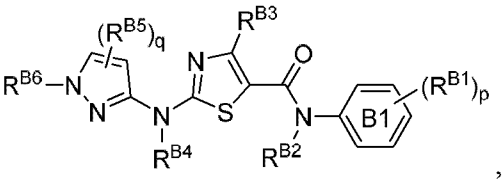
[00170] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

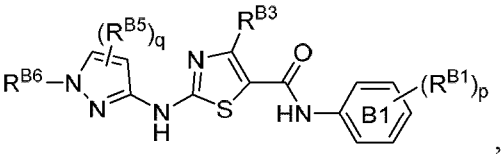
[00171] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

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



,

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

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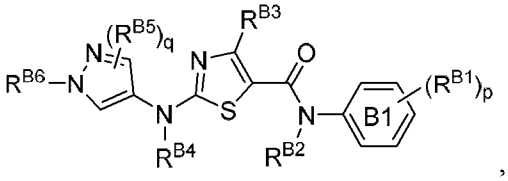
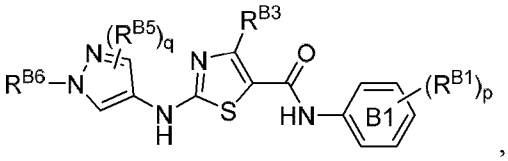
[00173] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

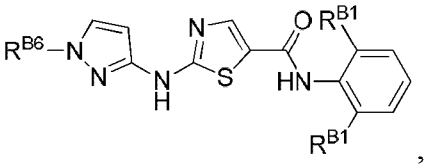
[00174] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

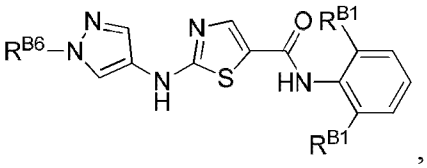
[00175] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

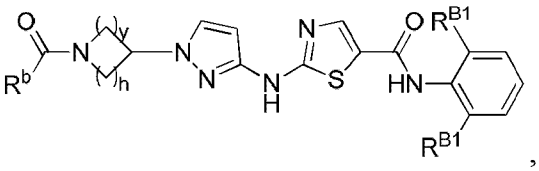
[00176] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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

[00177] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

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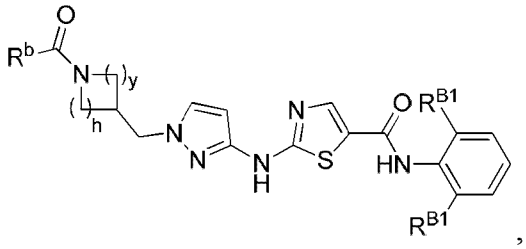
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^b is substituted or unsubstituted C_{2-6} alkenyl.

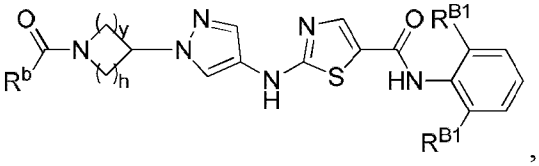
[00178] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^b is substituted or unsubstituted C_{2-6} alkenyl.

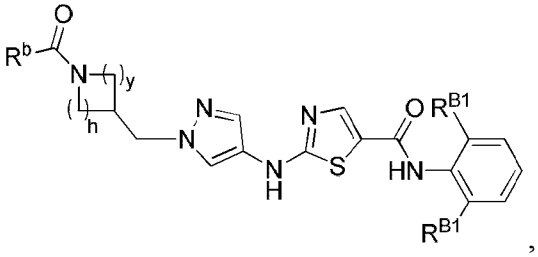
[00179] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^b is substituted or unsubstituted C_{2-6} alkenyl.

[00180] In certain embodiments, a compound of Formula (**II**) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^b is substituted or unsubstituted C_{2-6} alkenyl.

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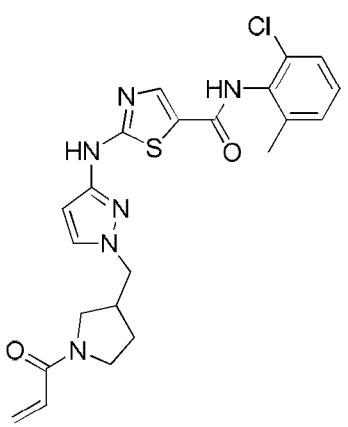
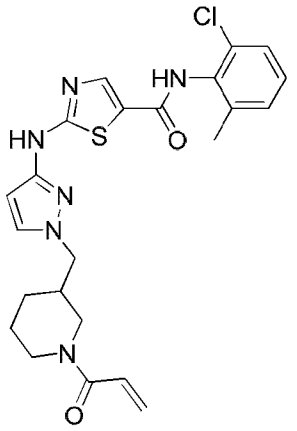
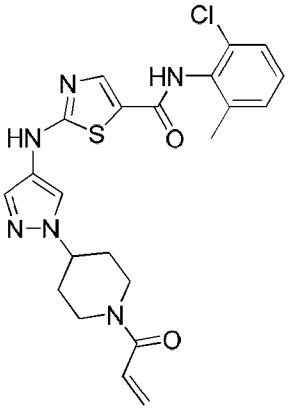
[00181] Exemplary compounds of Formula (**II**) include, but are not limited to:



(**II-1**),



(**II-2**),

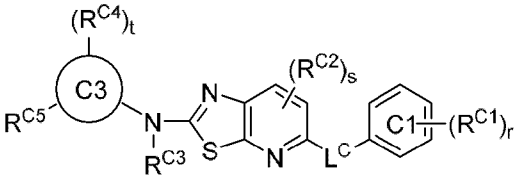


(**II-3**),

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

Compounds of Formula (III)

[00182] In certain embodiments, a compound described herein is of Formula (**III**):



(**III**),

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

each instance of R^{C1} 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, $–OR^c$, $–N(R^c)_2$, $–SR^c$, –CN, –SCN, $–C(=NR^c)R^c$, $–C(=NR^c)OR^c$, $–C(=NR^c)N(R^c)_2$, $–C(=O)R^c$, $–C(=O)OR^c$, $–C(=O)N(R^c)_2$, $–NO_2$, $–NR^cC(=O)R^c$, $–NR^cC(=O)OR^c$, $–NR^cC(=O)N(R^c)_2$, $–OC(=O)R^c$, $–OC(=O)OR^c$, or $–OC(=O)N(R^c)_2$;

each instance of R^c 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

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when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two instances of R^c are joined to form a substituted or unsubstituted, heterocyclic ring, or substituted or unsubstituted, heteroaryl ring;

r is 0, 1, 2, 3, 4, or 5;

L^C is –O– or –S–;

each instance of R^{C2} 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, $–OR^c$, $–N(R^c)_2$, $–SR^c$, –CN, –SCN, $–C(=NR^c)R^c$, $–C(=NR^c)OR^c$, $–C(=NR^c)N(R^c)_2$, $–C(=O)R^c$, $–C(=O)OR^c$, $–C(=O)N(R^c)_2$, $–NO_2$, $–NR^cC(=O)R^c$, $–NR^cC(=O)OR^c$, $–NR^cC(=O)N(R^c)_2$, $–OC(=O)R^c$, $–OC(=O)OR^c$, or $–OC(=O)N(R^c)_2$;

s is 0, 1, or 2;

R^{C3} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

Ring C3 is a substituted or unsubstituted, pyrimidinyl ring or substituted or unsubstituted, pyrazolyl ring;

each instance of R^{C4} 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, $–OR^c$, $–N(R^c)_2$, $–SR^c$, –CN, –SCN, $–C(=NR^c)R^c$, $–C(=NR^c)OR^c$, $–C(=NR^c)N(R^c)_2$, $–C(=O)R^c$, $–C(=O)OR^c$, $–C(=O)N(R^c)_2$, $–NO_2$, $–NR^cC(=O)R^c$, $–NR^cC(=O)OR^c$, $–NR^cC(=O)N(R^c)_2$, $–OC(=O)R^c$, $–OC(=O)OR^c$, or $–OC(=O)N(R^c)_2$;

t is 0, 1, or 2; and

R^{C5} 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, $–OR^c$, $–N(R^c)_2$, $–SR^c$, –CN, –SCN, $–C(=NR^c)R^c$, $–C(=NR^c)OR^c$, $–C(=NR^c)N(R^c)_2$, $–C(=O)R^c$, $–C(=O)OR^c$, $–C(=O)N(R^c)_2$, $–NO_2$, $–NR^cC(=O)R^c$, $–NR^cC(=O)OR^c$, $–NR^cC(=O)N(R^c)_2$, $–OC(=O)R^c$, $–OC(=O)OR^c$, or $–OC(=O)N(R^c)_2$.

[00183] Formula (**III**) includes as Ring C1 a phenyl ring that is unsubstituted (*e.g.*, when r is 0) or substituted (*e.g.*, when r is 1, 2, 3, 4, or 5) with one or more substituents R^{C1}. In certain embodiments, Ring C1 is unsubstituted phenyl. In certain embodiments, Ring C1 is

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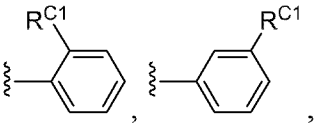
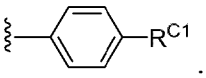
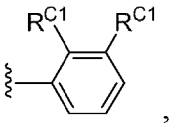
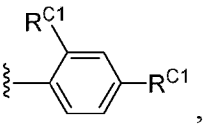
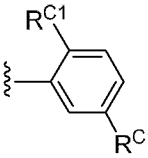
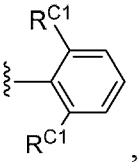
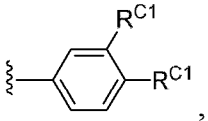
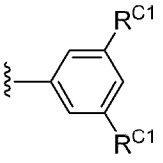
of the formula:  , , or  . In certain embodiments, Ring C1 is of the formula:  ,  ,  ,  ,  , or  .

[00184] In Formula (**III**), Ring C1 may include one or more substituents R^{C1}. In certain embodiments, all instances of R^{C1} are the same. In certain embodiments, two instances of R^{C1} are different from each other. In certain embodiments, at least one instance of R^{C1} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C1} is $–CH_3$. In certain embodiments, at least one instance of R^{C1} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{C1} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C1} is $–OR^c$ (*e.g.*, –OH, –

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O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{C1} is $–SR^c$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{C1} is $–N(R^c)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{C1} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{C1} is $–C(=NR^c)R^c$, $–C(=NR^c)OR^c$, or $–C(=NR^c)N(R^c)_2$. In certain embodiments, at least one instance of R^{C1} is $–C(=O)R^c$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^c$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^c)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{C1} is $–NR^cC(=O)R^c$, $–NR^cC(=O)OR^c$, or $–NR^cC(=O)N(R^c)_2$. In certain embodiments, at least one instance of R^{C1} is $–OC(=O)R^c$, $–OC(=O)OR^c$, or $–OC(=O)N(R^c)_2$.

[00185] When Formula (**III**) includes two or more instances of substituent R^c, any two instances of R^c may be the same or different from each other. In certain embodiments, at least one instance of R^c is H. In certain embodiments, each instance of R^c is H. In certain embodiments, at least one instance of R^c is substituted or unsubstituted acyl (*e.g.*, acetyl). In certain embodiments, at least one instance of R^c is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^c is $–CH_3$. In certain embodiments, at least one instance of R^c is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^c is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^c is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^c is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^c is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two

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double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^c is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^c is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^c is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^c is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts) when attached to a nitrogen atom. In certain embodiments, R^c is an oxygen protecting group (*e.g.*, 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^c is a sulfur protecting group (*e.g.*, acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl) when attached to a sulfur atom. In certain embodiments, two instances of R^c are joined to form a substituted or unsubstituted, heterocyclic ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heterocyclic ring comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, two instances of R^c are joined to form a substituted or unsubstituted heteroaryl ring (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[00186] In certain embodiments, r is 0. In certain embodiments, r is 1. In certain embodiments, r is 2. In certain embodiments, r is 3. In certain embodiments, r is 4. In certain embodiments, r is 5.

[00187] Formula (**III**) includes divalent linker L^C connecting Ring C1 to the 7-azabenzothiazolyl ring. In certain embodiments, L^C is –O–. In certain embodiments, L^C is –S–.

[00188] In Formula (**III**), the 7-azabenzothiazolyl ring may include one or two substituents R^{C2}. In certain embodiments, two instances of R^{C2} are the same. In certain embodiments, two instances of R^{C2} are different from each other. In certain embodiments, at least one instance of R^{C2} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C2} is $–CH_3$. In certain embodiments,

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at least one instance of R^{C2} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{C2} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C2} is $–OR^e$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{C2} is $–SR^e$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{C2} is $–N(R^e)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{C2} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{C2} is $–C(=NR^e)R^e$, $–C(=NR^e)OR^e$, or $–C(=NR^e)N(R^e)_2$. In certain embodiments, at least one instance of R^{C2} is $–C(=O)R^e$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^e$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^e)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least

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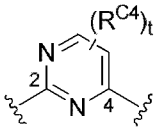
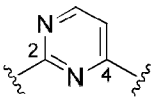
one instance of R^{C2} is $-NR^cC(=O)R^c$, $-NR^cC(=O)OR^c$, or $-NR^cC(=O)N(R^c)_2$. In certain embodiments, at least one instance of R^{C2} is $-OC(=O)R^c$, $-OC(=O)OR^c$, or $-OC(=O)N(R^c)_2$.

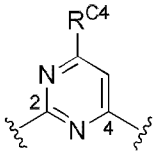
[00189] In certain embodiments, s is 0. In certain embodiments, s is 1. In certain embodiments, s is 2.

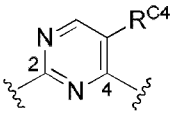
[00190] Formula (**III**) includes substituent R^{C3} on a nitrogen atom attached to the 7-azabenzothiazolyl ring. In certain embodiments, R^{C3} is H. In certain embodiments, R^{C3} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, Bn, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{C3} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

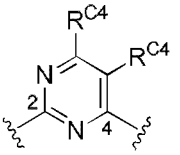
[00191] Formula (**III**) includes Ring C3. In certain embodiments, Ring C3 is a pyrimidinyl ring that is unsubstituted (*e.g.*, when t is 0) or substituted (*e.g.*, when t is 1 or 2) with one or more substituents R^{C4}. In certain embodiments, Ring C3 is of the formula:

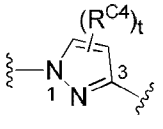


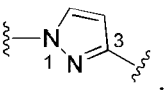
. In certain embodiments, in Formula (**III**), when Ring C3 is a substituted or unsubstituted pyrimidinyl ring, the carbon atom labeled with "2" is attached to R^{C5}, and the carbon atom labeled with "4" is attached to the nitrogen atom to which R^{C3} is attached. In certain embodiments, Ring C3 is of the formula: 

. In certain embodiments, Ring C3 is of the formula: 

, 

, or 

. In certain embodiments, Ring C3 is a pyrazolyl ring that is unsubstituted (*e.g.*, when t is 0) or substituted (*e.g.*, when t is 1 or 2) with one or more substituents R^{C4}. In certain embodiments, Ring C3 is of the formula: 

. In certain embodiments, in Formula (**III**), when Ring C3 is a substituted or unsubstituted pyrazolyl ring, the nitrogen atom labeled with "1" is attached to R^{C5}, and the carbon atom labeled with "3" is attached to the nitrogen atom to which R^{C3} is attached. In certain embodiments, Ring C3 is of the formula: 

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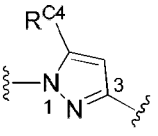
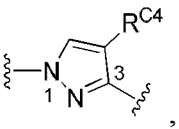
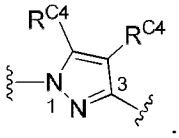
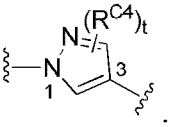
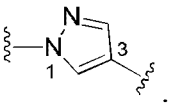
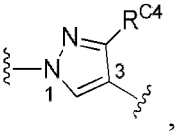
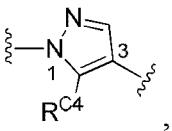
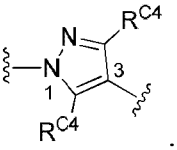
certain embodiments, Ring C3 is of the formula:  ,  , or  . In certain embodiments, Ring C3 is of the formula:  . In certain embodiments, Ring C3 is of the formula:  . In certain embodiments, Ring C3 is of the formula:  ,  , or  .

[00192] In Formula (**III**), Ring C3 may include one or two substituents R^{C4}. In certain embodiments, two instances of R^{C4} are the same. In certain embodiments, two instances of R^{C4} are different from each other. In certain embodiments, at least one instance of R^{C4} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C4} is $-CH_3$. In certain embodiments, at least one instance of R^{C4} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted phenyl. In certain embodiments, at least one instance of R^{C4} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one,

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two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, at least one instance of R^{C4} is $–OR^e$ (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, at least one instance of R^{C4} is $–SR^e$ (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, at least one instance of R^{C4} is $–N(R^e)_2$ (*e.g.*, $–NH_2$, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, $–NMe_2$)). In certain embodiments, at least one instance of R^{C4} is –CN, –SCN, or $–NO_2$. In certain embodiments, at least one instance of R^{C4} is $–C(=NR^e)R^e$, $–C(=NR^e)OR^e$, or $–C(=NR^e)N(R^e)_2$. In certain embodiments, at least one instance of R^{C4} is $–C(=O)R^e$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), $–C(=O)OR^e$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or $–C(=O)N(R^e)_2$ (*e.g.*, $–C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, at least one instance of R^{C4} is $–NR^eC(=O)R^e$, $–NR^eC(=O)OR^e$, or $–NR^eC(=O)N(R^e)_2$. In certain embodiments, at least one instance of R^{C4} is $–OC(=O)R^e$, $–OC(=O)OR^e$, or $–OC(=O)N(R^e)_2$.

[00193] In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2.

[00194] Formula (**III**) includes substituent R^{C5} on a nitrogen atom attached to Ring C3. In certain embodiments, R^{C5} is H. In certain embodiments, R^{C5} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{C5} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{C5} is $–CH_3$. In certain embodiments, R^{C5} is $–CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl. In certain embodiments, R^{C5} is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C_{2-6} alkenyl). In certain embodiments, R^{C5} is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C_{1-6} alkynyl). In certain embodiments, R^{C5} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{C5} is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 9-membered, monocyclic

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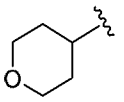
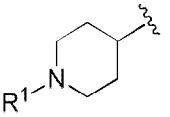
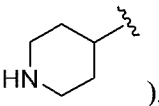
heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{C5} is substituted or unsubstituted tetrahydropyranyl or substituted or unsubstituted piperidinyl. In certain embodiments, R^{C5} is of the formula:  or  (*e.g.*, ), wherein R^1 is H, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{C5} is substituted or unsubstituted oxetanyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted morpholinyl, or substituted or unsubstituted piperazinyl. In certain embodiments, R^{C5} is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R^{C5} is substituted or unsubstituted phenyl. In certain embodiments, R^{C5} is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R^{C5} is –OR^a (*e.g.*, –OH, –O(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –OMe, –OEt, –OPr, –OBu, or –OBn), or –O(substituted or unsubstituted phenyl) (*e.g.*, –OPh)). In certain embodiments, R^{C5} is –SR^a (*e.g.*, –SH, –S(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –SMe, –SEt, –SPr, –SBu, or –SBn), or –S(substituted or unsubstituted phenyl) (*e.g.*, –SPh)). In certain embodiments, R^{C5} is –$N(R^a)_2$ (*e.g.*, –NH_2, –NH(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NHMe), or –N(substituted or unsubstituted C_{1-6} alkyl)–(substituted or unsubstituted C_{1-6} alkyl) (*e.g.*, –NMe_2)). In certain embodiments, R^{C5} is –CN, –SCN, or –NO_2. In certain embodiments, R^{C5} is –$C(=NR^a)R^a$, –$C(=NR^a)OR^a$, or –$C(=NR^a)N(R^a)_2$. In certain embodiments, R^{C5} is –$C(=O)R^a$ (*e.g.*, –C(=O)(substituted or unsubstituted alkyl) or –C(=O)(substituted or unsubstituted phenyl)), –$C(=O)OR^a$ (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)), or –$C(=O)N(R^a)_2$ (*e.g.*, –$C(=O)NH_2$, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{C5} is –$NR^aC(=O)R^a$, –$NR^aC(=O)OR^a$, or –$NR^aC(=O)N(R^a)_2$. In certain embodiments, R^{C5} is –$OC(=O)R^a$, –$OC(=O)OR^a$, or –$OC(=O)N(R^a)_2$. In certain embodiments, R^{C5} is of the formula:

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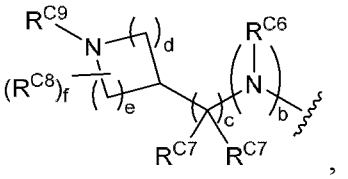


wherein:

R^{C6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

b is 0 or 1;

each instance of R^{C6} is independently hydrogen, halogen, or substituted or unsubstituted C_{1-6} alkyl;

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

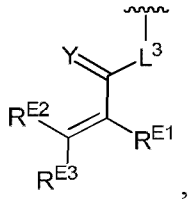
d is 1, 2, 3, or 4;

e is 1, 2, or 3;

each instance of R^{C8} is independently halogen, or substituted or unsubstituted C_{1-6} alkyl;

f is an integer between 0 and 13, inclusive; and

R^{C9} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted carbocyclyl, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-42**):



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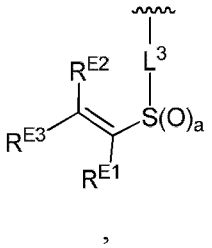

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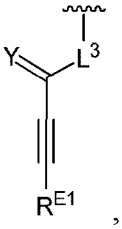

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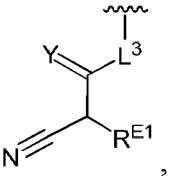
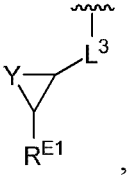


(ii-4)

(ii-5)



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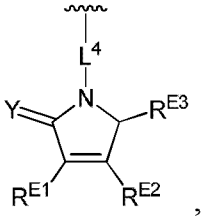

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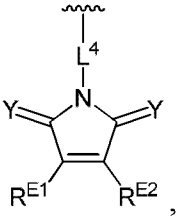

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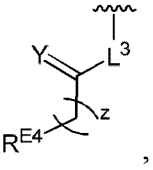

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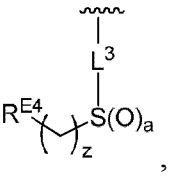

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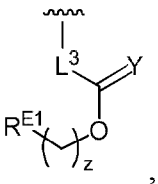

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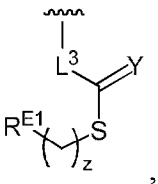

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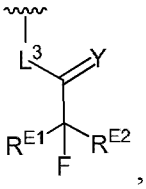

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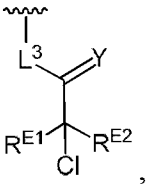

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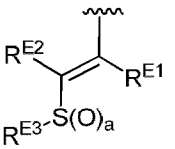

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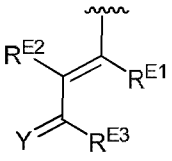

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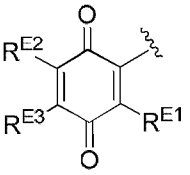

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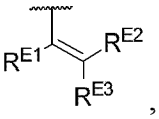

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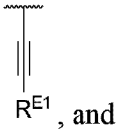

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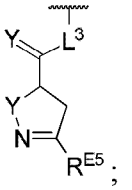
(ii-19)



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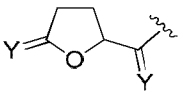

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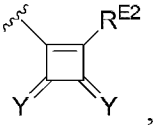

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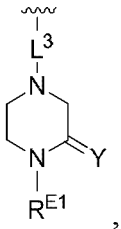
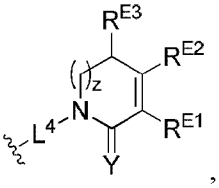


(ii-23)



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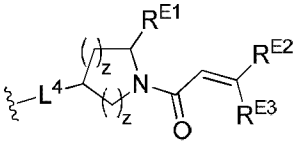

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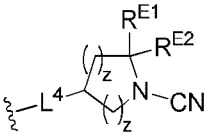
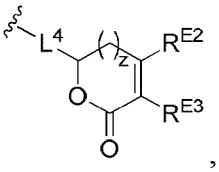
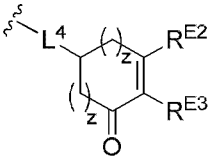


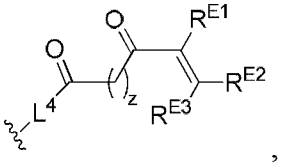
(ii–26)



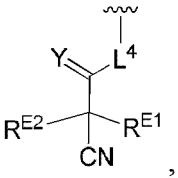
(ii–27)



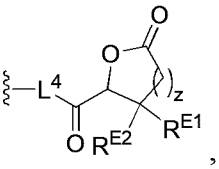
(ii–28)



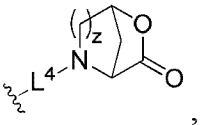
(ii–29)



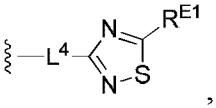
(ii–30)



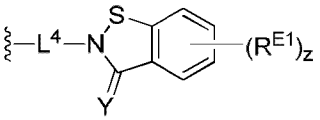
(ii–31)



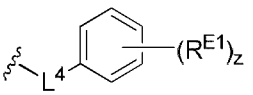
(ii–32)



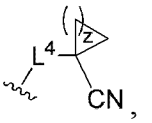
(ii–33)



(ii–34)



(ii–35)



(ii–36)

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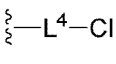
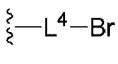
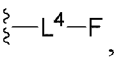


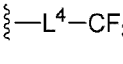
(ii–37)



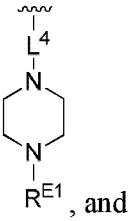
(ii–38)



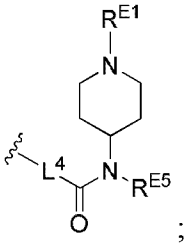
(ii–39)



(ii-40)



(ii-41)



(ii-42)

wherein:

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

L^4 is a bond or an optionally substituted C_{1-4} hydrocarbon chain;

R^{E1} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E1a}$, $–CH_2N(R^{E1a})_2$, $–CH_2SR^{E1a}$, $–OR^{E1a}$, $–N(R^{E1a})_2$, $–Si(R^{E1a})_3$, and $–SR^{E1a}$, wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E1a} groups are joined to form an optionally substituted heterocyclic ring;

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R^{E2} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, and $–SR^{E2a}$, wherein each occurrence of R^{E2a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E3} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, and $–SR^{E3a}$, wherein each occurrence of R^{E3a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E3a} groups are joined to form an optionally substituted heterocyclic ring;

or R^{E1} and R^{E3}, or R^{E2} and R^{E3}, or R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{E4} is a leaving group;

R^{E5} is halogen;

Y is O, S, or NR^{E6}, wherein R^{E6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

a is 1 or 2; and

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

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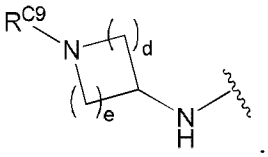
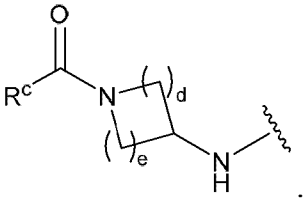
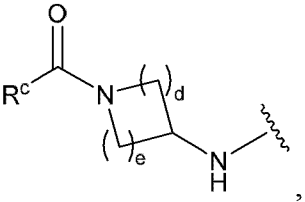
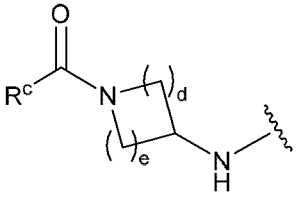
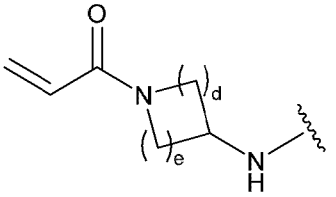
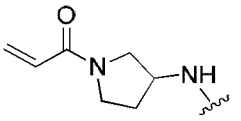
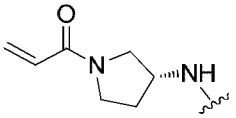
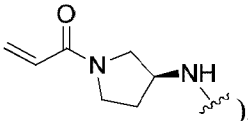
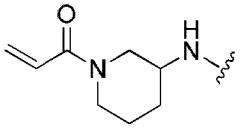
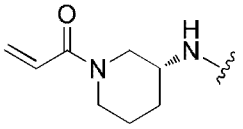
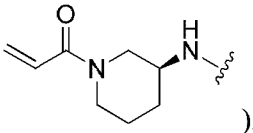
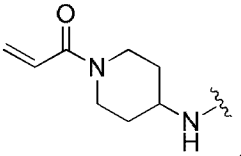
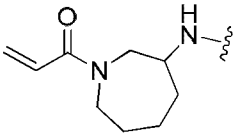
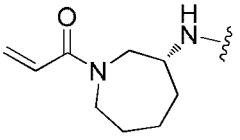
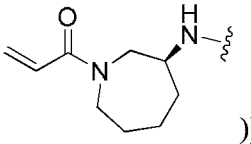
[00195] In certain embodiments, R^{C5} is of the formula:  . In certain embodiments, R^{C5} is of the formula:  . In certain embodiments, R^{C5} is of the formula:  , wherein R^c is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{C5} is of the formula:  , wherein R^c is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{C5} is of the formula:  (*e.g.*,  ,  or ),  (*e.g.*,  or ),  , or  (*e.g.*,  or )). In certain embodiments, R^{C5} is of the

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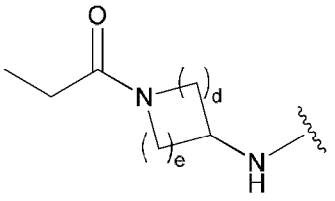
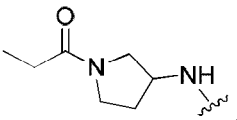
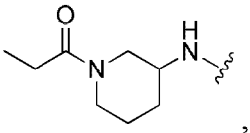
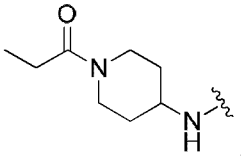
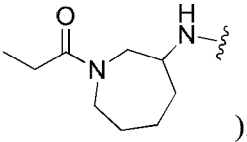
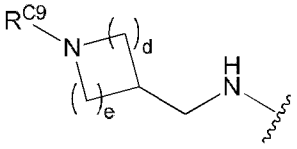
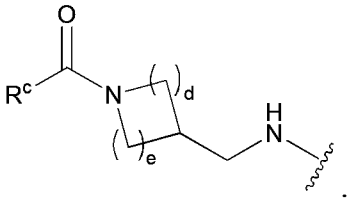
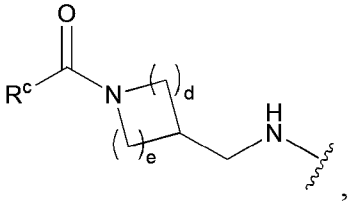
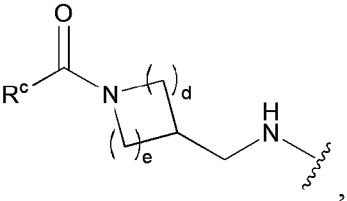
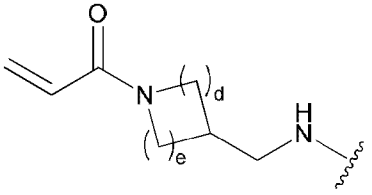
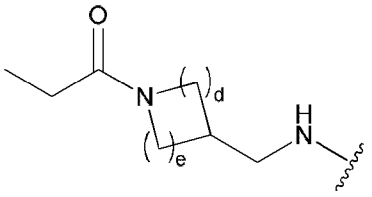
formula:  (*e.g.*,  ,  ,  , or ). In certain embodiments, R^{C5} is of the formula:  . In certain embodiments, R^{C5} is of the formula:  . In certain embodiments, R^{C5} is of the formula:  , wherein R^e is substituted or unsubstituted C_{2-6} alkenyl. In certain embodiments, R^{C5} is of the formula:  , wherein R^e is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^{C5} is of the formula:  . In certain embodiments, R^{C5} is of the formula:  .

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[00196] In certain embodiments, R^{C6} is H. In certain embodiments, R^{C6} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, $-CH_3$, Bn, $-CF_3$, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl). In certain embodiments, R^{C6} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[00197] In certain embodiments, b is 0. In certain embodiments, b is 1.

[00198] In certain embodiments, b is 1; and R^{C6} is H.

[00199] In certain embodiments, all instances of R^{C7} are the same. In certain embodiments, two instances of R^{C7} are different from each other. In certain embodiments, at least one instance of R^{C7} is H. In certain embodiments, each instance of R^{C7} is H. In certain embodiments, at least one instance of R^{C7} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C7} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C7} is $-CH_3$. In certain embodiments, at least one instance of R^{C7} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00200] In certain embodiments, c is 0. In certain embodiments, c is 1. In certain embodiments, c is 2. In certain embodiments, c is 3. In certain embodiments, c is 4.

[00201] In certain embodiments, d is 1. In certain embodiments, d is 2. In certain embodiments, d is 3. In certain embodiments, d is 4.

[00202] In certain embodiments, e is 1. In certain embodiments, e is 2. In certain embodiments, e is 3.

[00203] In certain embodiments, d is 2; and e is 1. In certain embodiments, d is 3; and e is 1. In certain embodiments, d is 4; and e is 1.

[00204] In certain embodiments, all instances of R^{C8} are the same. In certain embodiments, two instances of R^{C8} are different from each other. In certain embodiments, at least one instance of R^{C8} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^{C8} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, at least one instance of R^{C8} is $-CH_3$. In certain embodiments, at least one instance of R^{C8} is $-CF_3$, Bn, unsubstituted ethyl, perfluoroethyl, unsubstituted propyl, perfluoropropyl, unsubstituted butyl, or perfluorobutyl.

[00205] In certain embodiments, f is 0. In certain embodiments, f is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13.

[00206] In certain embodiments, R^{C9} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl,

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substituted or unsubstituted carbocyclyl, –C(=O)R^a, –C(=O)OR^a, –C(=O)N(R^a)$_2$, a nitrogen protecting group, or of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{C9} is H. In certain embodiments, R^{C9} is substituted or unsubstituted C_{1-6} alkyl (*e.g.*, C_{1-6} alkyl substituted with one or more substituents independently selected from the group consisting of oxo; halogen; substituted or unsubstituted C_{2-6} alkenyl; substituted or unsubstituted cyclopropyl; substituted or unsubstituted, 4- to 7-membered monocyclic carbocyclyl comprising 1 or 2 double bonds in the carbocyclic ring system; substituted or unsubstituted oxiranyl; substituted or unsubstituted, 5- to 10-membered, monocyclic or bicyclic heteroaryl, wherein 1, 2, 3, or 4 atoms in the heteroaryl ring system are independently oxygen, nitrogen, or sulfur; –CN; –(C=O)R^a; –N(R^a)(C=O)R^a; –O(C=O)R^a; –OR^a; and –N(R^a)$_2$). In certain embodiments, R^{C9} is substituted or unsubstituted C_{2-6} alkenyl (*e.g.*, substituted or unsubstituted vinyl). In certain embodiments, R^{C9} is substituted or unsubstituted C_{2-6} alkynyl (*e.g.*, substituted or unsubstituted ethynyl). In certain embodiments, R^{C9} is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R^{C9} is –C(=O)R^a. In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted alkyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{1-6} alkyl), such as –C(=O)Et). In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted alkenyl) (*e.g.*, –C(=O)(substituted or unsubstituted C_{2-6} alkenyl), such as –C(=O)–CH=CH_2). In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted carbocyclyl). In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted heterocyclyl). In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted phenyl). In certain embodiments, R^{C9} is –C(=O)(substituted or unsubstituted heteroaryl). In certain embodiments, R^{C9} is –C(=O)OR^a (*e.g.*, –C(=O)O(substituted or unsubstituted alkyl) or –C(=O)O(substituted or unsubstituted phenyl)) or –C(=O)N(R^a)$_2$ (*e.g.*, –C(=O)NH_2, –C(=O)NH(substituted or unsubstituted alkyl), –C(=O)NH(substituted or unsubstituted phenyl), –C(=O)N(substituted or unsubstituted alkyl)–(substituted or unsubstituted alkyl), or –C(=O)N(substituted or unsubstituted phenyl)–(substituted or unsubstituted alkyl)). In certain embodiments, R^{C9} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts). In certain embodiments, R^{C9} is of any one of Formulae (**ii-1**) to (**ii-23**). In certain embodiments, R^{C9} is of any one of Formulae (**ii-24**) to (**ii-42**). In certain embodiments, R^{C9} is

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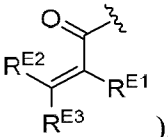
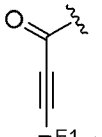
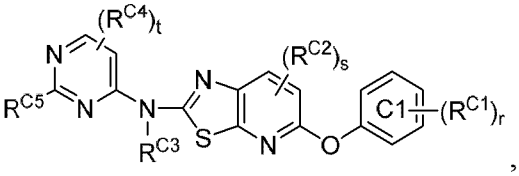
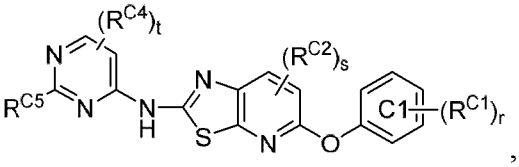
of Formula (**ii-1**) (*e.g.*, of the formula: ). In certain embodiments, R^{C9} is of Formula (**ii-3**) (*e.g.*, of the formula: ). In certain embodiments, R^{C9} is of any one of the formulae shown in *Table 1A*. The moieties included in R^{C9} are as described herein.

[00207] In certain embodiments, a compound of Formula (**III**) is of the formula:



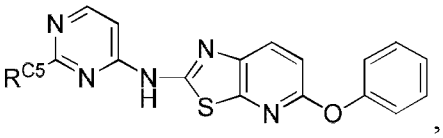
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00208] In certain embodiments, a compound of Formula (**III**) is of the formula:



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

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



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

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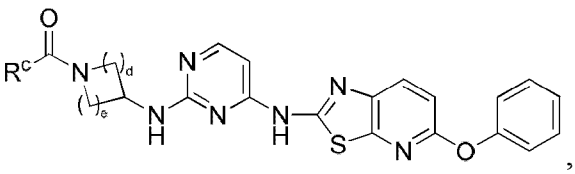
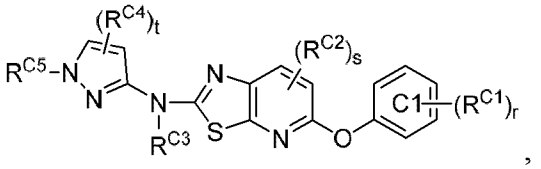
[00210] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^c is substituted or unsubstituted C_{2-6} alkenyl.

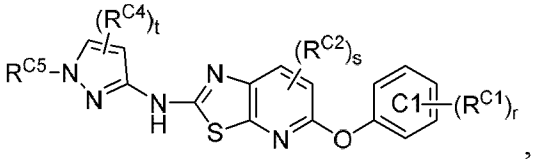
[00211] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

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

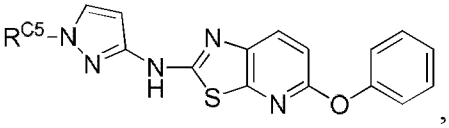
[00212] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

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

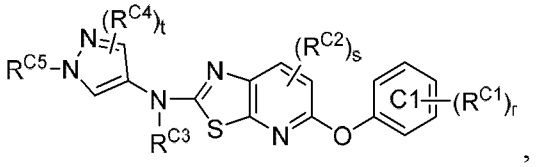
[00213] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

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

[00214] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

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

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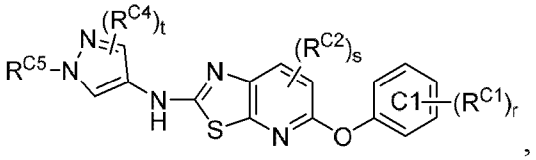
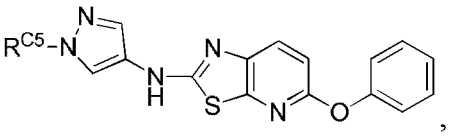
[00215] In certain embodiments, a compound of Formula (**III**) is of the formula:



,

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

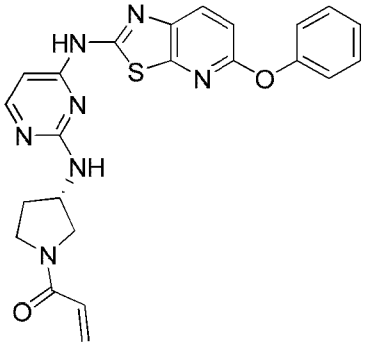
[00216] In certain embodiments, a compound of Formula (**III**) is of the formula:



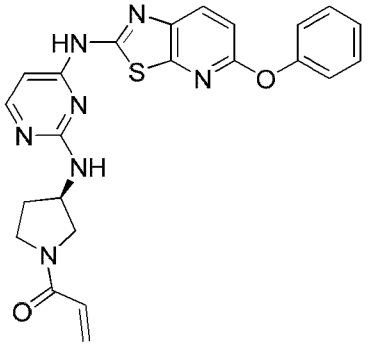
,

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

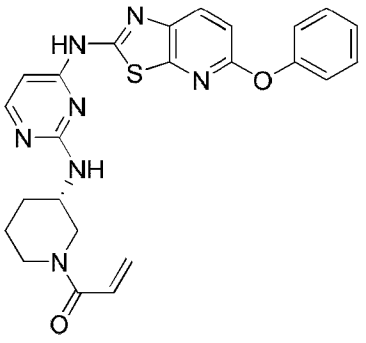
[00217] Exemplary compounds of Formula (**III**) include, but are not limited to:



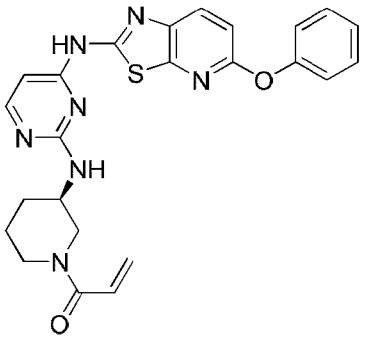
(**III-1**),



(**III-2**),



(**III-3**),



(**III-4**),

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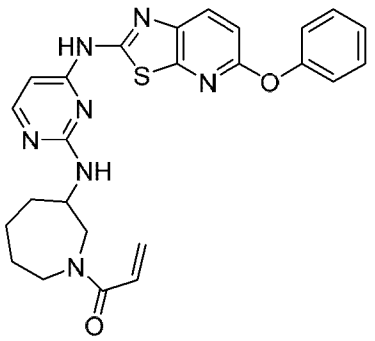
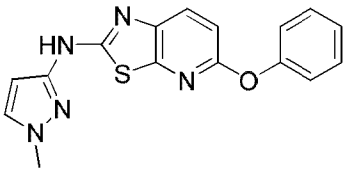
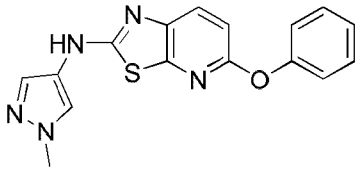


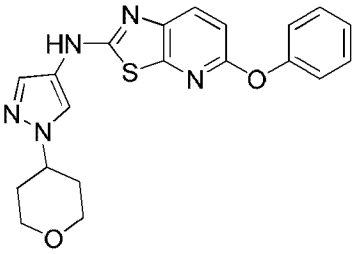
(III-5),



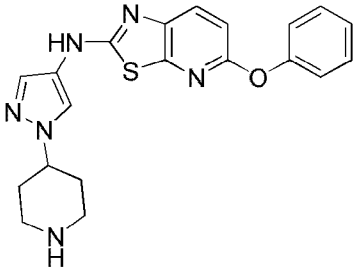
(III-6),



(III-7),



(III-8),



(III-9),

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

Pharmaceutical Compositions, Kits, and Administration

[00218] The present disclosure provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, a pharmaceutical composition described herein comprises a compound described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. The pharmaceutical compositions described herein may be useful in treating and/or preventing proliferative diseases (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)) in a subject, inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell.

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[00219] In certain embodiments, a subject described herein is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, a subject described herein described herein is a human. In certain embodiments, a subject described herein is a non-human animal. In certain embodiments, a subject described herein is a mammal (*e.g.*, non-human mammal). In certain embodiments, a subject described herein is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, a subject described herein is a companion animal such as a dog or cat. In certain embodiments, a subject described herein is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, a subject described herein is a zoo animal. In another embodiment, a subject described herein is a research animal such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal (*e.g.*, transgenic mice and transgenic pigs). In certain embodiments, a subject described herein is a fish or reptile.

[00220] In certain embodiments, a biological sample described herein is bone marrow, lymph node, spleen, or blood.

[00221] In certain embodiments, a tissue described herein is blood. In certain embodiments, a tissue described herein is bone marrow. In certain embodiments, a tissue described herein is a central nervous system (CNS) tissue (*e.g.*, brain, spinal cord, meninges). In certain embodiments, a tissue described herein is an immune privileged tissue. In certain embodiments, a tissue described herein is the placenta or testicle. In certain embodiments, a tissue described herein is a fetus. In certain embodiments, a tissue described herein is the eye. In certain embodiments, a tissue described herein is the spleen. In certain embodiments, a tissue described herein is the marginal zone.

[00222] In certain embodiments, a cell described herein is *in vitro*. In certain embodiments, a cell described herein is *ex vivo*. In certain embodiments, a cell described herein is *in vivo*. In certain embodiments, a cell described herein is a malignant cell (*e.g.*, malignant blood cell). In certain embodiments, a cell described herein is a malignant hematopoietic stem cell (*e.g.*, malignant myeloid cell or malignant lymphoid cell). In certain embodiments, a cell described herein is a malignant lymphocyte (*e.g.*, malignant T-cell or malignant B-cell). In certain embodiments, a cell described herein is a malignant red blood cell, malignant white blood cell, or malignant platelet. In certain embodiments, a cell described herein is a malignant neutrophil, malignant macrophage, or malignant plasma cell.

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[00223] In certain embodiments, the compound described herein is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount (*e.g.*, amount effective for treating a proliferative disease in a subject in need thereof). In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject in need thereof. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a cell. In certain embodiments, the effective amount is an amount effective for inducing apoptosis in a cell. In certain embodiments, the effective amount is a prophylactically effective amount (*e.g.*, amount effective for preventing a proliferative disease in a subject in need thereof and/or for keeping a subject in need thereof in remission of a proliferative disease).

[00224] In certain embodiments, a protein kinase described herein is HCK. In certain embodiments, a protein kinase described herein is BTK. In certain embodiments, a protein kinase described herein is IRAK1 or IRAK4. In certain embodiments, a protein kinase described herein is BMX. In certain embodiments, a protein kinase described herein is a PI3K. In certain embodiments, a protein kinase described herein is ABL, ACK, ARG, BLK, CSK, EphB1, EphB2, FGR, FRK, FYN, SRC, YES, LCK, LYN, MAP2K5, NLK, PIP4K2C, p38a, SNRK, SRC, or TEC. In certain embodiments, a protein kinase described herein is 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, or EGFR(E746-A750del). In certain embodiments, a protein kinase described herein is 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,

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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), or CSF1R.

[00225] In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) by not more than 10%, not more than 20%, not more than 30%, not more than 40%, not more than 50%, not more than 60%, not more than 70%, not more than 80%, not more than 90%, not more than 95%, or not more than 98%. In certain embodiments, the effective amount is an amount effective for inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) by a range between a percentage described in this paragraph and another percentage described in this paragraph, inclusive.

[00226] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include bringing the compound described herein (*i.e.*, the "active ingredient") into association with a carrier or excipient, and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping, and/or packaging the product into a desired single- or multi-dose unit.

[00227] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as one-half or one-third of such a dosage.

[00228] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition described herein will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. The composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00229] 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,

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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.

[00230] 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.

[00231] 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.

[00232] 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

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

[00233] 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.

[00234] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, antiprotozoan preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[00235] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00236] 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.

[00237] 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.

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[00238] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00239] 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.

[00240] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant® Plus, Phenonip®, methylparaben, Germall® 115, Germaben® II, Neolone®, Kathon®, and Euxyl®.

[00241] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00242] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00243] 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, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary

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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.

[00244] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates described herein are mixed with solubilizing agents such as Cremophor®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00245] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00246] 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.

[00247] 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

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

[00248] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00249] 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.

[00250] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the art of pharmacology. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00251] 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

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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 a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of encapsulating agents which can be used include polymeric substances and waxes.

[00252] Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier or excipient and/or any needed preservatives and/or buffers as can be required. Additionally, the present disclosure contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00253] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration. Jet injection devices which deliver liquid formulations to the dermis *via* a liquid jet injector and/or *via* a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable.

[00254] 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.

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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.

[00255] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration *via* the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers, or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00256] 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).

[00257] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate.

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

[00258] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00259] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00260] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1-1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier or excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are also contemplated as being within the scope of this disclosure.

[00261] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order

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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.

[00262] The compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions described herein will be decided by a physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex, and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00263] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration *via* blood and/or lymph supply, and/or direct administration to an affected site. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration). In certain embodiments, the compound or pharmaceutical composition described herein is suitable for topical administration to the eye of a subject.

[00264] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. An effective amount may be included in a single dose (*e.g.*, single oral dose) or multiple doses (*e.g.*, multiple oral doses). In certain embodiments, when multiple doses are administered to a subject or applied to a biological sample, tissue, or cell,

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

[00265] Dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for

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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.

[00266] A compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents (*e.g.*, therapeutically and/or prophylactically active agents) useful in treating and/or preventing a proliferative disease. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their activity (*e.g.*, activity (*e.g.*, potency and/or efficacy) in treating a proliferative disease in a subject in need thereof, in preventing a proliferative disease in a subject in need thereof, and/or in inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell), improve bioavailability, improve safety, reduce drug resistance, reduce and/or modify metabolism, inhibit excretion, and/or modify distribution in a subject, biological sample, tissue, or cell. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects. In certain embodiments, a pharmaceutical composition described herein including a compound described herein and an additional pharmaceutical agent shows a synergistic effect that is absent in a pharmaceutical composition including one of the compound and the additional pharmaceutical agent, but not both.

[00267] 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 in treating and/or preventing a proliferative disease. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved for human or veterinary use by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful in treating a proliferative disease. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful in preventing a proliferative disease. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful in inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent useful in

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inducing apoptosis in a cell. In certain embodiments, the additional pharmaceutical agent is a pharmaceutical agent approved by a regulatory agency (*e.g.*, the US FDA) for treating and/or preventing a proliferative disease. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional pharmaceutical agent(s) and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agent(s) in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00268] In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent (*e.g.*, anti-cancer agent). In certain embodiments, the additional pharmaceutical agent is an anti-leukemia agent. In certain embodiments, the additional pharmaceutical agent is ABITREXATE™ (methotrexate), ADE ™, Adriamycin RDF® (doxorubicin hydrochloride), Ambochlorin ™ (chlorambucil), ARRANON® (nelarabine), ARZERRA® (ofatumumab), BOSULIF® (bosutinib), BUSULFEX™ (busulfan), CAMPATH® (alemtuzumab), CERUBIDINE® (daunorubicin hydrochloride), CLAFEN™ (cyclophosphamide), CLOFAREX™ (clofarabine), CLOLAR® (clofarabine), CVP, CYTOSAR-U® (cytarabine), CYTOXAN® (cyclophosphamide), ERWINAZE® (Asparaginase Erwinia Chrysanthemi), FLUDARA™ (fludarabine phosphate), FOLEX® (methotrexate), FOLEX PFS™ (methotrexate), GAZYVA® (obinutuzumab), GLEEVEC™ (imatinib mesylate), Hyper-CVAD, ICLUSIG® (ponatinib hydrochloride), IMBRUVICA® (ibrutinib), LEUKERAN® (chlorambucil), LINFOLIZIN™ (chlorambucil), MARQIBO® (vincristine sulfate liposome), METHOTREXATE LPF™ (methorexate), 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), SYNRIBO™ (omacetaxine mepesuccinate), TARABINE PFS™ (cytarabine), TASIGNA® (nilotinib), TREANDA® (bendamustine hydrochloride), TRISENOX® (arsenic trioxide), VINCASAR PFS™ (vincristine sulfate), ZYDELIG® (idelalisib), or a combination thereof. In certain embodiments, the additional pharmaceutical agent is an anti-lymphoma

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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),

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AREDIA® (pamidronate disodium), ARIMIDEX® (anastrozole), AROMASIN® (exemestane), AVASTIN® (bevacizumab), BECENUM™ (carmustine), BEP, BICNU® (carmustine), BLENOXANE® (bleomycin), CAF™, CAMPTOSAR® (irinotecan hydrochloride), CAPOX™, CAPRELSA® (vandetanib), CARBOPLATIN-TAXO®L, 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),

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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), SYLATRO™ (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 protein kinase inhibitor (*e.g.*, tyrosine protein kinase inhibitor). In certain embodiments, the additional pharmaceutical agent is an inhibitor of a Src family kinase. In certain embodiments, the additional pharmaceutical agent is an HCK inhibitor or BTK inhibitor. 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 ABL, ACK, ARG, BLK, CSK, EphB1, EphB2, FGR, FRK, FYN, SRC, YES, LCK, LYN, MAP2K5, NLK, PIP4K2C, p38a, SNRK, SRC, 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,

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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.

[00269] Also encompassed by the disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a pharmaceutical composition or compound described herein and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a pharmaceutical composition or compound described herein. In some embodiments, the

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pharmaceutical composition or compound described herein provided in the first container and the second container are combined to form one unit dosage form.

[00270] In certain embodiments, a kit described herein includes a first container comprising a compound or pharmaceutical composition described herein. In certain embodiments, a kit described herein is useful in treating a proliferative disease (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)) in a subject in need thereof, preventing a proliferative disease in a subject in need thereof, inhibiting the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell, and/or inducing apoptosis in a cell.

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

Methods of Treatment

[00272] The compounds described herein may:

- exhibit kinase inhibitory activity,
- exhibit the ability to inhibit transforming growth factor b-activated kinase-1 (TAK1), hemopoietic cell kinase (HCK) or both TAK1 and HCK,
- exhibit the ability to inhibit Bruton's tyrosine kinase (BTK), v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC) family of kinases or both BTK and SRC,
- exhibit cytotoxic or growth inhibitory effect on Waldenström's macroglobulinemia (WM) cell lines maintained *in vitro* or in animal studies using a scientifically acceptable cancer cell xenograft model; and/or
- exhibit a therapeutic profile (*e.g.,* optimum safety and curative effect) that is superior to existing chemotherapeutic agents.

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[00273] Without wishing to be bound by any particular theory, the compounds described herein may be able to attach (*e.g.*, covalently attach) to a protein kinase described herein. In certain embodiments, the R^{A10}, R^{B9}, or R^{C9} group of a compound described herein is able to attach (*e.g.*, covalently attach) to the protein kinase.

[00274] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a subject, the methods comprising administering to the subject an effective amount (*e.g.*, therapeutically effective amount) of a compound or pharmaceutical composition described herein.

[00275] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a biological sample, the methods comprising contacting the biological sample with an effective amount of a compound or pharmaceutical composition described herein.

[00276] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a tissue, the methods comprising contacting the tissue with an effective amount of a compound or pharmaceutical composition described herein.

[00277] In another aspect, the present disclosure provides methods of inhibiting the activity of a protein kinase in a cell, the methods comprising contacting the cell with an effective amount of a compound or pharmaceutical composition described herein.

[00278] In some embodiments, the protein kinase is involved in the myeloid differentiation primary response gene (88) (MYD88) signaling pathway. In certain embodiments, the protein kinase is a Src family kinase, such as hemopoietic cell kinase (HCK). In certain embodiments, the protein kinase is Bruton's tyrosine kinase (BTK). In certain embodiments, the protein kinase is IRAK1, IRAK4, BMX, or a PI3K.

[00279] MYD88 is an adaptor molecule for Toll-like receptors (TLR) with the exception of TLR-3 and interleukin-1 receptor (IL-1R) signaling. Following TLR or IL-1R stimulation, MYD88 is recruited to the activated receptor complex as a homodimer which then complexes with interleukin-1 receptor-associated kinase 4 (IRAK4) and activates IRAK1 and IRAK2. Tumor necrosis factor receptor associated factor 6 (TRAF6) is then activated by IRAK1 leading to NFκB activation via IκBα phosphorylation.

[00280] Transforming growth factor b-activated kinase-1 (TAK1; also known as MAP3K7), is a member of the serine/threonine protein kinase family. This kinase mediates the signaling transduction induced by TGF beta and morphogenetic protein (BMP), and controls a variety of cell functions including transcription regulation and apoptosis. TAK1 knockout is embryonic lethal to mice. Conditional knock-down of TAK1 in adult mice results

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in systemic inflammation, spenomegaly, degeneration in heart, kidneys and liver and increased proliferation and differentiation of myeloid progenitor cells. TAK1 is located downstream of Myd88, Bruton's tyrosine kinase (BTK) and interleukin-1 receptor-associated kinase (IRAK), and is being investigated for its role in innate immunity, inflammatory response and Ras dependent cancers.

[00281] HCK is a non-receptor tyrosine-protein kinase found in hematopoietic cells and is known to interact with Bruton's tyrosine kinase (BTK) upon activation by B cell receptors (Proc Natl Acad Sci U S A. 1994 August 16; 91(17): 8152–8155). HCK transmits signals from cell surface receptors and plays an important role in the regulation of innate immune responses, including neutrophil, monocyte, macrophage and mast cell functions, phagocytosis, cell survival and proliferation, cell adhesion and migration. It acts downstream of receptors that bind the Fc region of immunoglobulins, such as FCGR1A and FCGR2A, but also CSF3R, PLAUR, the receptors for IFNG, IL2, IL6 and IL8, and integrins, such as ITGB1 and ITGB2. During the phagocytic process, it mediates mobilization of secretory lysosomes, degranulation, and activation of NADPH oxidase to bring about the respiratory burst. It also plays a role in the release of inflammatory molecules, promotes reorganization of the actin cytoskeleton and actin polymerization, and formation of podosomes and cell protrusions.

[00282] BTK is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. BTK plays an essential role in the B cell signaling pathway linking cell surface B cell receptor BCR stimulation to downstream intracellular responses. BTK is a key regulator of B cell development activation signaling and survival (Kurosaki, *Curr. Op. Imm.*, **2000**, 276-281; Schaeffer and Schwartzberg, *Curr. Op. Imm.*, **2000**, 282-288). In addition BTK plays a role in a number of other hematopoietic cell signaling pathways, *e.g.*, Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen stimulated platelet aggregation. See *e.g.*, C.A. Jeffries, *et al.*, *J. Biol. Chem.*, **2003**, *278*, 26258-26264; N.J. Horwood, *et al.*, *J. Exp. Med.*, **2003**, *197*, 1603-1611; Iwaki *et al.*, *J. Biol. Chem.*, **2005**, *280*(48), 40261-40270; Vassilev *et al.*, *J. Biol. Chem.*, **1999**, *274*(3),1646-1656; and Quek *et al.*, *Curr. Biol.*, **1998**, *8*(20),1137-1140. Activated Btk interacts with MyD88 and TRIF, promoting the activation of MyD88-dependent and TRIF-dependent pathways (*Nature Immunology*, **2011**, *12*, 416–424). BTK inhibitors are well-known in the art, and include, for example, ibrutinib and benzonaphthyridinones (see U.S. provisional patent application

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U.S.S.N. 61/716,273, filed October 19, 2012). Additional non-limiting examples of BTK inhibitors are disclosed in WO 1999/054286, WO 2013/010380, WO 2009/137596, WO 2011/029043, WO 2010/056875, WO 2000/056737, and WO 2013/067277.

[00283] IRAK1 and IRAK4 are serine/threonine-protein kinases that play a critical role in initiating innate immune response against foreign pathogens. They are involved in Toll-like receptor (TLR) and IL-1R signaling pathways, and are rapidly recruited by MYD88 to the receptor-signaling complex upon TLR activation. Association with MYD88 leads to IRAK1 phosphorylation by IRAK4 and subsequent autophosphorylation and kinase activation of IRAK1 (*Immunity*, **1997**, *7*(6), 837-47). IRAK4-/- mice have abolished cellular responses to various IL-1 and TLR ligands and are severely impaired in their response to viral and bacterial challenges. IRAK1-/- mice show a similar but partial response. IRAK1 and IRAK4 inhibitors are well-known in the art, and include, for example, those disclosed in WO 2003/030902, WO 2012/007375, GM Buckely et al. *Biorg. Med. Chem. Lett.* **2008** *18* 3211-3214, and GM Buckely et al. *Biorg. Med. Chem. Lett.* **2008** *18* 3656-3660, WO2013/074986, and U.S. 61/727,640.

[00284] "Bone Marrow on X chromosome" kinase (BMX, also termed ETK) is a non-receptor tyrosine kinase and is activated downstream of phosphatidylinositol-3 kinase (PI-3K) and v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (SRC), but its substrates are unknown. Positional scanning peptide library screening revealed a marked preference for a priming phosphotyrosine (pY) in the -1 position. Potential substrates include multiple tyrosine kinases with kinase domain pYpY sites required for full activity. BMX has been found to phosphorylate residue Y577 of focal adhesion kinase (FAK) subsequent to Y576 phosphorylation by SRC. In addition, BMX loss by RNA interference and mouse embryonic fibroblasts (MEFs) from *Bmx* negative (Bmx^-) mice displayed impaired FAK signaling. Insulin receptor (IR) phosphorylation similarly was decreased by BMX loss, as was hepatic IR phosphorylation in Bmx^- mice. However, glucose tolerance was increased, reflecting a marked compensatory decrease in the activity of the AKT phosphatase PHLPP. These findings reveal a mechanism through which BMX functions as a central regulator of multiple kinase pathways. BMX inhibitors are well-known in the art, and include, for example, those disclosed in U.S.S.N. 61/716,273 and 61/717,345.

[00285] Phosphatidylinositol 3-kinases (PI3-kinases or PI3Ks) are a family of enzymes involved in cellular functions such as cell growth, proliferation, differentiation, motility, survival and intracellular trafficking, which in turn are involved in cancer. PI3Ks are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position

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hydroxyl group of the inositol ring of phosphatidylinositol (Ptdlns). Phosphatidylinositol 3-kinase is composed of an 85 kDa regulatory subunit and a 110 kDa catalytic subunit. The protein encoded by PI3KCA gene represents the catalytic subunit, which uses ATP to phosphorylate phosphatidylinositols (Ptdlns), Ptdlns4P and Ptdlns(4,5)P2. PI3K inhibitors are well-known in the art, and include, for example, those disclosed in WO 2013/088404, WO 2012/068096, and WO 2013/052699.In certain embodiments, the activity of the protein kinase is inhibited by the compounds or pharmaceutical compositions described herein by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. In certain embodiments, the activity of the protein kinase is inhibited by the compounds or pharmaceutical compositions described herein by not more than 90%, not more than 80%, not more than 70%, not more than 60%, not more than 50%, not more than 40%, not more than 30%, not more than 20%, or not more than 10%. Combinations of the above-referenced ranges (*e.g.*, at least 10% and not more than 50%) are also within the scope of the disclosure.

[00286] In some embodiments, the activity of a protein kinase described herein is selectively inhibited by the compounds or pharmaceutical compositions described herein, compared to the activity of a different protein (*e.g.*, a different protein kinase). In certain embodiments, the activity of a Src family kinase (*e.g.*, HCK) is selectively inhibited by a compound or pharmaceutical composition described herein, compared to the activity of a different protein. In certain embodiments, the activity of BTK is selectively inhibited by a compound or pharmaceutical composition described herein, compared to the activity of a different protein.

[00287] The selectivity of a compound or pharmaceutical composition described herein in inhibiting the activity of a protein kinase over a different protein (*e.g.*, a different protein kinase) may be measured by the quotient of the IC_{50} value of the compound or pharmaceutical composition in inhibiting the activity of the different protein over the IC_{50} value of the compound or pharmaceutical composition in inhibiting the activity of the protein kinase. The selectivity of a compound or pharmaceutical composition described herein for a protein kinase over a different protein may also be measured by the quotient of the K_d value of an adduct of the compound or pharmaceutical composition and the different protein over the K_d value of an adduct of the compound or pharmaceutical composition and the protein kinase. In certain embodiments, the selectivity is at least 2-fold, at least 3-fold, at least 5-fold, at least 10-fold, at least 30-fold, at least 100-fold, at least 300-fold, at least 1,000-fold, at least 3,000-fold, at least 10,000-fold, at least 30,000-fold, or at least 100,000-fold. In certain

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embodiments, the selectivity is not more than 100,000-fold, not more than 10,000-fold, not more than 1,000-fold, not more than 100-fold, not more than 10-fold, or not more than 2-fold. Combinations of the above-referenced ranges (*e.g.*, at least 2-fold and not more than 10,000-fold) are also within the scope of the disclosure.

[00288] In some embodiments, the activity of a protein kinase is non-selectively inhibited by the compounds or pharmaceutical compositions described herein.

[00289] In certain embodiments, the activity of a protein kinase described herein is aberrant. In certain embodiments, the activity of a protein kinase described herein is increased. In certain embodiments, the activity of a protein kinase described herein is increased compared to normal (*i.e.*, non-cancerous) cells.

[00290] In some proliferative diseases, such as MYD88 L265P driven Waldenström's macroglobulinemia, certain protein kinase (*e.g.*, a Src family kinase (*e.g.*, HCK), BTK) is activated. Thus the compounds and pharmaceutical compositions may be useful in treating and/or preventing proliferative diseases by, *e.g.*, inhibiting the activity of protein kinases.

[00291] Another aspect of the present disclosure relates to methods of treating a proliferative disease in a subject in need thereof, the methods comprising administering to the subject an effective amount (*e.g.*, therapeutically effective amount) of a compound or pharmaceutical composition described herein.

[00292] Another aspect of the present disclosure relates to methods of preventing proliferative disease in a subject in need thereof, the methods comprising administering to the subject an effective amount (*e.g.*, prophylactically effective amount) of a compound or pharmaceutical composition described herein.

[00293] In certain embodiments, the compounds and pharmaceutical compositions are useful in treating and/or preventing proliferative diseases, such as proliferative diseases associated with MYD88. MYD88 gene has been implicated in many proliferative diseases. Activated B cell type diffuse large B cell lymphoma (ABC-DLBCL), a particularly aggressive subtype of DLBCL whose pathogenesis relies on constitutively active NFκB, is frequently associated with MYD88 mutations. 39% of tumor samples contain mutations in MYD88, and 29% of those mutations result in a single nucleotide change from leucine into proline at position 265 (L265P) (Ngo *et al.*, *Nature*. 2011 Feb 3; 470(7332):115-9). shRNA knockdown of MYD88 in lymphoma cell lines demonstrated that MYD88 mutations are critical for their survival and high NFκB transcription factor activity (Ngo *et al.*, *Nature*. 2011 Feb 3; 470(7332):115-9). A hyperphosphorylated isoform of IRAK1 was strongly associated with the L265P mutant form of MYD88, suggesting that this mutation is a gain-of-

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function mutation that leads to the constitutive activation of downstream IRAKs (Ngo *et al.*, *Nature*. 2011 Feb 3; 470(7332):115-9). The effects of the L265P mutation include increased NFκB activity as well as increased JAK-STAT3 signaling and the production of pro-inflammatory cytokines such as IL-6, IL-10, and IFN-β (Ngo *et al.*, *Nature*. 2011 Feb 3; 470(7332):115-9). The production of these cytokines further activates JAK-STAT3 signaling as part of an autocrine loop that enhances the survival of the lymphoma cells (Lam *et al.*, *Blood*. 2008 Apr 1; 111(7):3701-13; Ding *et al.*, *Blood*. 2008 Feb 1; 111(3):1515-23).

[00294] MYD88 mutations have since been seen in a number of other human malignancies, with the L265P mutation found in almost 100% of Waldenström's macroglobulinemia (WM), 2-10% of chronic lymphocytic leukemia (CLL), 69% of cutaneous diffuse large B cell lymphoma (CBCL), and 38% of primary central nervous system lymphoma (PCNSL) (Wang *et al.*, *Blood Lymphat Cancer* (2013) 2013:53–6110). However, the effect of single MYD88 L265P mutation on tumor growth is confounded by the accumulation of other potential damaging mutations in the same malignant clones. Recently, a retroviral gene transfer strategy to study the effects of single MYD88 mutation in otherwise normal mature B cells found that the MYD88 L265P mutation alone was able to drive limited rounds of mitogen independent B cell proliferation both *in vitro* and *in vivo* (Wang *et al.*, *J Exp Med*. 2014 Mar 10; 211(3):413-26). Nevertheless, the drive for B cell proliferation was dependent on intact nucleic acid sensing toll-like receptor (TLR) activity since Unc93b13d mutation or Tlr9 deficiency inhibited the proliferation of MYD88 L265P B cells *in vitro* (Wang *et al.*, *J Exp Med* (2014) 211:413–2610). Other studies have also shown that oncogenic MYD88 depends on TLRs by using the depletion of UNC91B1, PRAT4A, and CD14 in ABC-DLBCL lines as well as by using pharmacological inhibitors to TLR7 and TLR9 (Lim *et al.* In: Proceedings of the 104th Annual Meeting of the American Association for Cancer Research; 2013 Apr 6-10; Washington, DC. Philadelphia: AACR; Cancer Res; (2013) 73(8 Suppl):Abst 2332.10.1158/1538-7445.AM2013-2332). Given that intact TLR activity is critical for lymphoma cells carrying MYD88 mutations, targeting this pathway appears to be attractive for treating these malignancies. Indeed, blocking endosome acidification using chloroquine selectively inhibits MYD88 L265P mutation driven B cell proliferation *in vitro* (Wang *et al.*, *J Exp Med* (2014) 211:413–2610).

[00295] In certain embodiments, a subject described herein is diagnosed as having WM. The subject may present one or more signs, symptoms, or clinical features of WM including anemia, hyper-viscosity, neuropathy, coagulopathies, splenomegaly, hepatomegaly, adenopathy, and an IgM serum paraprotein. In certain embodiments, the subject is diagnosed

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as having WM on the basis that the subject has a mutation at position 38182641 of chromosome 3p22.2. In some embodiments, the mutation results in a single nucleotide change from T to C in the MYD88 gene. In some embodiments, the mutation results in an amino acid change from leucine to proline at position 265 in the MYD88 gene. The mutation may be detected in a biological sample obtained from the subject using any suitable method known in the art, including but not limited to, direct sequencing of nucleic acid molecules, HPLC analysis, DNA chip technologies, and mass spectroscopy.

[00296] In certain embodiments, a proliferative disease that is treated and/or prevented by a method described herein is a proliferative disease associated with an MYD88 mutation (*e.g.*, MYD88 L265P mutation). In certain embodiments, the proliferative disease is cancer. In certain embodiments, the proliferative disease is a hematological malignancy. In certain embodiments, the proliferative disease is myelodysplasia. 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 lymphoma. In certain embodiments, the proliferative disease is Waldenström's macroglobulinemia. In certain embodiments, the proliferative disease is activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), central nervous system (CNS) lymphoma (*e.g.*, primary CNS lymphoma, secondary CNS lymphoma), lymphoma of an immune privileged site, testicular lymphoma, or marginal zone lymphoma. In certain embodiments, the proliferative disease is cerebral lymphoma, ocular lymphoma, lymphoma of the placenta, or lymphoma of the fetus. In certain embodiments, the proliferative disease is a benign neoplasm. In certain embodiments, the proliferative disease is pathological angiogenesis. In certain embodiments, the proliferative disease is an inflammatory disease. In certain embodiments, the proliferative disease is an autoimmune disease.

[00297] In certain embodiments, a method described herein further includes administering to the subject an additional pharmaceutical agent. In certain embodiments, a method described herein further includes contacting the biological sample with an additional pharmaceutical agent. In certain embodiments, a method described herein further includes contacting the tissue with an additional pharmaceutical agent. In certain embodiments, a method described herein further includes contacting the cell with an additional pharmaceutical agent. In certain embodiments, a method described herein further includes radiotherapy, immunotherapy, and/or transplantation (*e.g.*, bone marrow transplantation).

[00298] Another aspect of the present disclosure relates to methods of inducing apoptosis in a cell, the methods comprising contacting the cell with an effective amount of a

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compound or pharmaceutical composition described herein. Without wishing to be bound by any particular theory, the compounds and pharmaceutical compositions described herein may be able to inhibit the proliferation of and/or to kill cells, such as malignant cells (*e.g.*, malignant cells whose proliferation and/or survival are driven by MYD88 L265P expression). In certain embodiments, a compound or pharmaceutical composition described herein inhibits the proliferation of a cell by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, or at least 90%. In certain embodiments, a compound or pharmaceutical composition described herein inhibits the proliferation of a cell by not more than 10%, not more than 20%, not more than 30%, not more than 40%, not more than 50%, not more than 70%, or not more than 90%. In certain embodiments, a compound or pharmaceutical composition described herein kills at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 70%, or at least 90% cells. In certain embodiments, a compound or pharmaceutical composition described herein kills not more than 10%, not more than 20%, not more than 30%, not more than 40%, not more than 50%, not more than 70%, or not more than 90% cells. Combinations of the above-referenced ranges (*e.g.*, at least 10% and not more than 50%) are also within the scope of the disclosure.

Methods of Screening a Library of Compounds

[00299] Another aspect of the disclosure relates to methods of screening a library of compounds, and pharmaceutical acceptable salts thereof, to identify a compound, or a pharmaceutical acceptable salt thereof, that is useful in the methods of the disclosure. In certain embodiments, the methods of screening a library include obtaining at least two different compounds described herein; and performing at least one assay using the different compounds described herein. In certain embodiments, at least one assay is useful in identifying a compound that is useful in the described methods.

[00300] Typically, the methods of screening a library of compounds involve at least one assay. In certain embodiments, the assay is performed to detect one or more characteristics associated with the treatment of a proliferative disease (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)) in a subject in need thereof, with the prevention of a proliferative disease (*e.g.*, myelodysplasia, leukemia, lymphoma (*e.g.*, Waldenström's macroglobulinemia)) in a subject in need thereof, with the inhibition of the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell, and/or with the induction of apoptosis in a cell. The characteristics may be desired characteristics (*e.g.*, a proliferative disease in a subject having been treated, a subject having

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been prevented from having a proliferative disease, the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell having been inhibited, and/or the apoptosis in a cell having been induced). The characteristics may be undesired characteristics (*e.g.*, a proliferative disease in a subject having not been treated, a subject having not been prevented from having not a proliferative disease, the activity of a protein kinase (*e.g.*, HCK, BTK) in a subject, biological sample, tissue, or cell having not been inhibited, and/or the apoptosis in a cell having not been induced). The assay may be an immunoassay, such as a sandwich-type assay, competitive binding assay, one-step direct test, two-step test, or blot assay. The step of performing at least one assay may be performed robotically or manually. In certain embodiments, the assay comprises (a) contacting a library of compounds with a protein kinase; and (b) detecting the binding of the library of compounds to the protein kinase. In certain embodiments, the assay comprises detecting the specific binding of the library of compounds to the protein kinase. In certain embodiments, the detected binding of the library of compounds to the protein kinase is useful in identifying the compound that is useful in the methods of the disclosure. In certain embodiments, the step of detecting the binding comprises using differential scanning fluorimetry (DSF), isothermal titration calorimetry (ITC), and/or an amplified luminescence proximity homogeneous assay (ALPHA). The step of performing at least one assay may be performed in a cell *in vitro*, *ex vivo*, or *in vivo*. In certain embodiments, the step of performing at least one assay is performed in a cell *in vitro*. In certain embodiments, the assay comprises (a) contacting a library of compounds with a cell; and (b) detecting a decrease in cell proliferation, an increase in cell death, and/or an increase in cell differentiation.

Uses

[00301] In another aspect, the present disclosure provides the compounds described herein for use in a method of the disclosure.

[00302] In still another aspect, the present disclosure provides the pharmaceutical compositions described herein for use in a method of the disclosure.

[00303] In still another aspect, the present disclosure provides uses of the compounds described herein in a method of the disclosure.

[00304] In further another aspect, the present disclosure provides uses of the pharmaceutical compositions described herein in a method of the disclosure.

EXAMPLES

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[00305] In order that the present disclosure 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.

Preparation of the Compounds

[00306] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures (*e.g.*, Examples 1 to 21). 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.

General methods and materials for preparing exemplary compounds described herein

[00307] The following general methods and materials may be independently applicable to any one of Examples 1 to 21. Commercially available reagents and solvents were used without further purification. All reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F254) and/or Waters LCMS system (Waters 2489 UV/Visible Detector, Waters 3100 Mass, Waters 515 HPLC pump, Waters 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFire™ C18 column (4.6 × 50 mm, 5 μm particle size): Method A; solvent gradient = 97% A at 0 min, 0% A at 5 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate : 2.5 mL/min. Purification of reaction products was carried out by flash chromatography using CombiFlash® Rf with Teledyne Isco RediSep® Rf High Performance Gold or Silicycle SiliaSep™ High Performance columns (4 g, 12 g, or 24 g) and Waters LCMS system using SunFire™ Prep C18 column (19 × 50 mm, 5 μm particle size): solvent gradient = 100% A at 0 min, 20% A at 6 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate : 25 mL/min. The purity of all compounds was over 95% and was analyzed with Waters LCMS system. ^{1}H NMR spectra were obtained using a Varian Inova-500 or 600 (500 or 600 MHz for ^{1}H NMR) spectrometer. Chemical shifts are reported relative to chloroform (δ =7.26) or dimethyl sulfoxide (δ = 2.50) for ^{1}H NMR. Data are reported as (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

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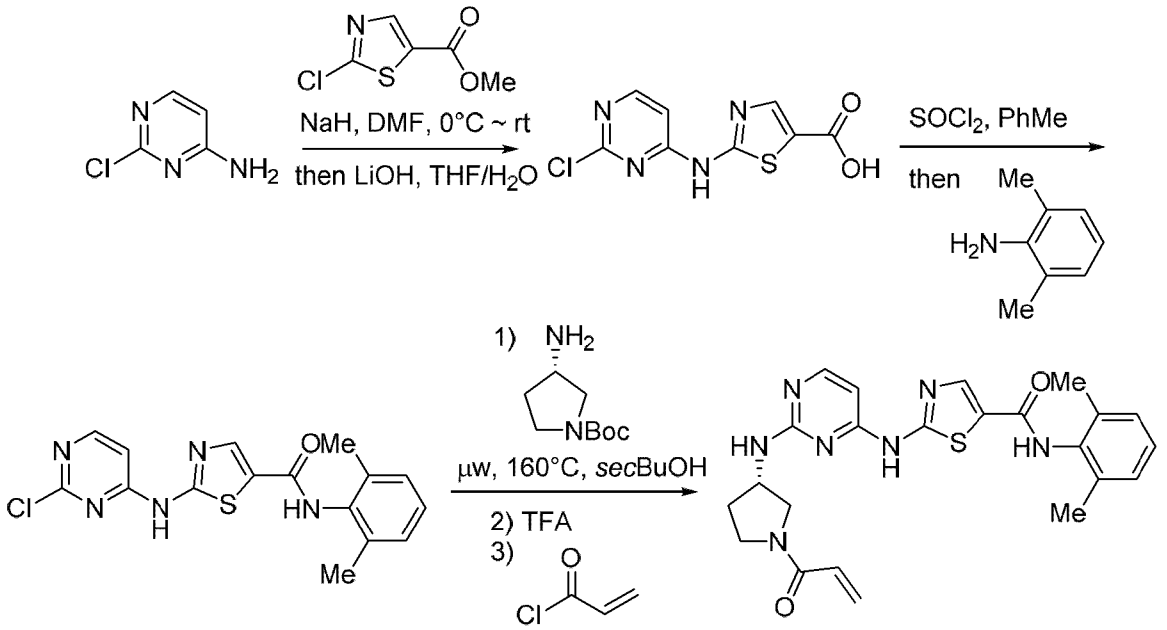
General procedure I for the aromatic nucleophilic displacement reaction

[00308] The following General procedure I may be independently applicable to any one of Examples 1 to 21. A microwave vial was charged with 2-((2-chloropyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide (1 eq), the amine analogue (2 eq) and anhydrous *sec*-butanol (0.05 M). The vial was sealed and was heated in the Biotage Initiator microwave at 160 °C until the reaction had reached completion. The solvent was removed under reduced pressure and the residue redissolved in DCM, and TFA was added and the reaction mixture was stirred at ambient temperature for 2h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC.

General procedure II for the acrylamide formation

[00309] The following General procedure II may be independently applicable to any one of Examples 1 to 21. The amine intermediate (1 eq) was dissolved in a 1:1 mixture of THF and saturated $NaHCO_3$ aqueous solution, and cooled to 0 °C. To the stirring mixture was added a dilute solution of acryloyl chloride (3 eq) in THF, the reaction was stirred at 0 °C and gradually warmed to ambient temperature. After 30min, the reaction was extracted with ethyl acetate twice, the organic extracts were combined and concentrated under reduced pressure. The residue was directly purified by preparative HPLC.

Example 1. Preparation of (S)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



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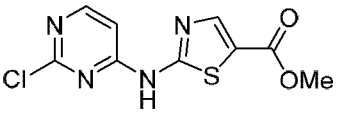
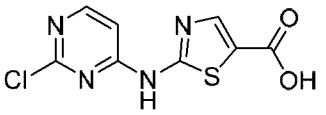
Methyl 2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxylate



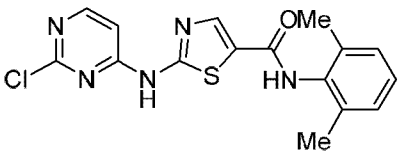
[00310] A solution of a mixture of 2-chloropyrimidin-4-amine (5.0 g, 38.5 mmol) and methyl 2-chlorothiazole-5-carboxylate (6.85 g, 38.5 mmol, 1 equivalent (eq)) in dry *N,N*-dimethylformamide (75 ml) was cooled to 0 °C and was treated portionwise over 5 min with sodium hydride (60% w/w in mineral oil, 3.1 g, 76.9 mmol, 2 eq). The reaction mixture was stirred at 0 °C for 1 h and warmed to ambient temperature for a further 1 h. The mixture was treated with saturated ammonium chloride, followed by saturated aqueous Na_2CO_3 solution to reach pH 9, and the resulting mixture was extracted with 1:1 mixture of dichloromethane and ethyl acetate. The organic extracts were combined, dried using a hydrophobic frit, and evaporated under reduced pressure. The residue was purified by chromatography on silica to afford the title compound as an off-white solid. **LCMS** retention time (RT): 2.70 (Method A), Mass *m/z*: 270.99 (M+1).

2-((2-Chloropyrimidin-4-yl)amino)thiazole-5-carboxylic acid



[00311] To a solution of methyl 2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxylate (1 g, 3.7 mmol) in 1:1 mixture of THF/H_2O (15 mL) was added LiOH monohydrate (2.6 g, 29.6 mmol, 8 eq), and the reaction mixture was stirred at ambient temperature for 12 h. After 12 h, the reaction mixture was concentrated under reduced pressure and cooled to 0 °C, and concentrated HCl was added dropwise to reach pH 6. The precipitate was filtered, washed with cold water, and dried using a hydrophobic frit to afford the titled compound as a white solid. **LCMS** RT: 2.13 (Method A), Mass *m/z*: 257.05 (M+1).

2-((2-Chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00312] To a solution of 2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxylic acid (50 mg, 0.195 mmol) in toluene (1 mL) was added thionyl chloride (2.26 mL, 1.95 mmol, 10

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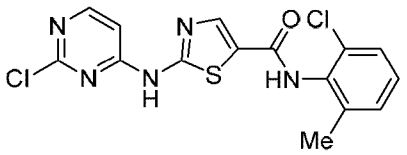
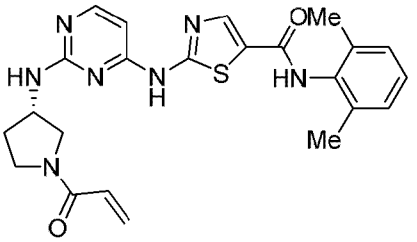
eq). The reaction mixture was stirred at 90 °C for 3 h, cooled to room temperature (rt), and concentrated under reduced pressure. The crude was dissolved in 1,2-dichloroethane (DCE, 1 mL), and 2,6-dimethylaniline (48 µL, 0.390 mmol, 2 eq) and DIPEA (*N*,*N*-diisopropylethylamine, 68 µL, 0.390 mmol, 2 eq) was added. The reaction mixture was stirred at 80 °C for 12 h and cooled to ambient temperature, and water was added. The mixture was extracted with isopropanol/chloroform (1:4) three times, the organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford the title compound as a yellowish solid. **LCMS** RT: 2.95 (Method A), Mass *m/z*: 360.22 (M+1).

N-(2-Chloro-6-methylphenyl)-2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxamide



[00313] *N*-(2-chloro-6-methylphenyl)-2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxylic acid and 2-chloro-6-methylaniline using the same procedure. **LCMS** RT: 2.98 (Method A), Mass *m/z*: 380.26 (M+1).

(*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00314] (*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate using general procedures I and II. **LCMS** RT: 2.23 (Method A), Mass *m/z*: 464.48 (M+1).

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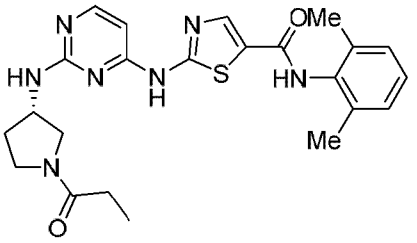
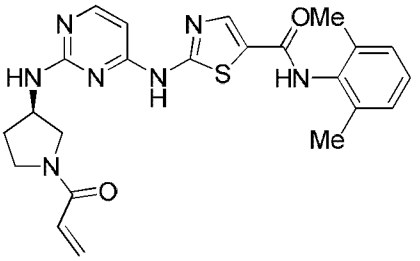
Example 2. Preparation of (S)-N-(2,6-dimethylphenyl)-2-((2-((1-propionylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)thiazole-5-carboxamide



[00315] (*S*)-*N*-(2,6-dimethylphenyl)-2-((2-((1-propionylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)thiazole-5-carboxamidewas prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide, *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate and propionyl chloride using general procedures I and II. **LCMS** RT: 2.28 (Method A), Mass *m/z*: 466.62 (M+1). 1H NMR (400 MHz,) δ 12.47 (s, 1H), 9.77 (s, 1H), 8.53 (s, 1H), 8.38 – 8.28 (m, 1H), 8.08 (dd, J = 6.4, 3.1 Hz, 1H), 7.13 (d, J = 1.8 Hz, 3H), 6.44 (t, J = 5.5 Hz, 1H), 4.51 (d, J = 98.4 Hz, 1H), 3.97 – 2.94 (m, 3H), 2.28 – 2.21 (m, 1H), 2.19 (d, J = 2.0 Hz, 6H), 2.08 (t, J = 7.5 Hz, 1H), 1.97 (d, J = 8.8 Hz, 1H), 1.01 – 0.91 (m, 3H), 0.91 – 0.78 (m, 2H).

Example 3. Preparation of (R)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00316] (*R*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl (*R*)-3-aminopyrrolidine-1-carboxylate using general procedures I and II. **LCMS** RT: 2.23 (Method A), Mass *m/z*: 464.54 (M+1). 1H NMR (400 MHz,) δ 12.47 (s, 1H), 9.77 (s, 1H), 8.46 (s, 1H), 8.33 (d, J = 5.3 Hz, 1H), 8.08 (d, J = 6.6 Hz, 1H), 7.12 (s, 3H), 6.66 – 6.40 (m, 2H), 6.12 (ddd, J = 17.3, 5.8, 2.5 Hz, 1H), 5.71 – 5.59 (m, 1H), 4.57 (d, J = 69.4 Hz, 1H), 4.04 – 2.75 (m, 3H), 2.19 (s, 6H), 2.35 – 1.93 (m, 1H), 1.33 – 0.66 (m, 2H).

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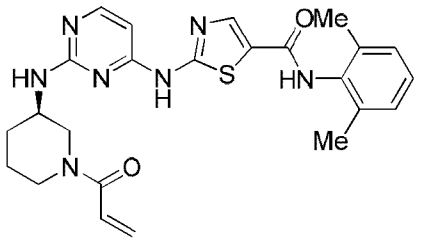
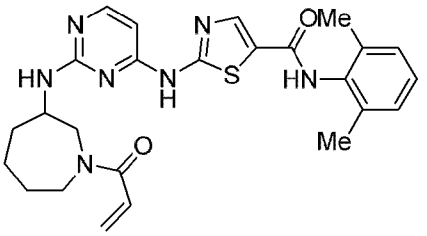
Example 4. Preparation of (R)-2-((2-((1-acryloylpiperidin-3-yl)amino)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00317] (*R*)-2-((2-((1-acryloylpiperidin-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate using general procedures I and II. **LCMS** RT: 2.10 (Method A), Mass *m/z*: 478.53 (M+1).

Example 5. Preparation of 2-((2-((1-acryloylazepan-3-yl)amino)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00318] 2-((2-((1-acryloylazepan-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl 3-aminoazepane-1-carboxylate using general procedures I and II. **LCMS** RT: 2.50 (Method A), Mass *m/z*: 492.59 (M+1). 1H NMR (400 MHz, DMSO-d6) δ 9.80 (s, 1H), 8.34 (s, 1H), 8.23 (s, 1H), 8.09 (d, J = 6.5 Hz, 1H), 7.13 (s, 3H), 6.78 (dd, J = 16.6, 10.5 Hz, 1H), 6.45 (d, J = 6.7 Hz, 1H), 6.06 (d, J = 16.6 Hz, 1H), 5.64 (d, J = 10.6 Hz, 1H), 4.48 (s, 1H), 3.42 (s, 5H), 2.19 (s, 6H), 1.80-1.50 (m, 4H), 1.23 (m, 1H), 0.84 (m, 1H).

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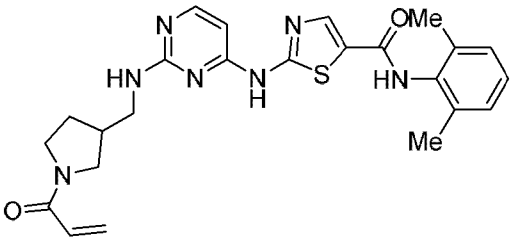
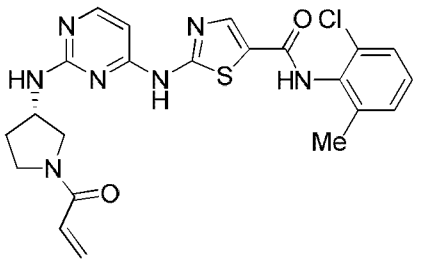
Example 6. Preparation of 2-((2-(((1-acryloylpyrrolidin-3-yl)methyl)amino)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00319] 2-((2-(((1-acryloylpyrrolidin-3-yl)methyl)amino)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate using general procedures I and II. **LCMS** RT: 2.25 (Method A), Mass *m/z*: 478.60 (M+1). 1H NMR (400 MHz, DMSO-d6) δ 12.56 (s, 1H), 9.83 (d, J = 8.8 Hz, 1H), 8.48 (s, 1H), 8.35 (s, 1H), 8.06 (d, J = 6.5 Hz, 1H), 7.14 (s, 3H), 6.52 (dd, J = 16.8, 9.2 Hz, 1H), 6.42 (t, J = 5.6 Hz, 1H), 6.11 – 5.99 (m, 1H), 5.60 – 5.40 (m, 1H), 4.00 – 2.97 (m, 4H), 2.82 – 2.54 (m, 1H), 2.20 (s, 6H, overlap), 2.17 – 1.97 (m, 1H), 1.87 – 1.55 (m, 1H), 1.24 (m, 1H), 0.85 (d, J = 7.2 Hz, 1H).

Example 7. Preparation of (S)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00320] (*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from *N*-(2-chloro-6-methylphenyl)-2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxamide and *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate using general procedures I and II. **LCMS** RT: 2.25 (Method A), Mass *m/z*: 484.52 (M+1). 1H NMR (400 MHz, DMSO-d6) δ 9.99 (s, 1H), 8.43 (d, J = 6.7 Hz, 1H), 8.30 (s, 1H), 8.06 (s, 1H), 7.44 – 7.31 (m, 1H), 7.31 – 7.17 (m, 2H), 6.34 (d, J = 6.2 Hz, 1H), 6.23 – 6.02 (m, 2H), 5.58 (d, J = 9.9 Hz, 1H), 3.43 (s, 4H), 2.21 (s, 4H), 1.95 (s, 1H), 1.36 – 1.02 (m, 1H), 0.82 (s, 1H).

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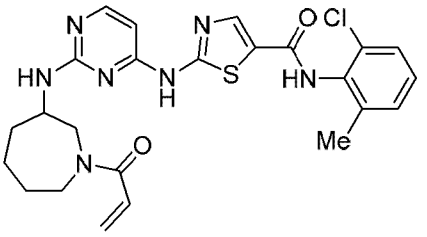
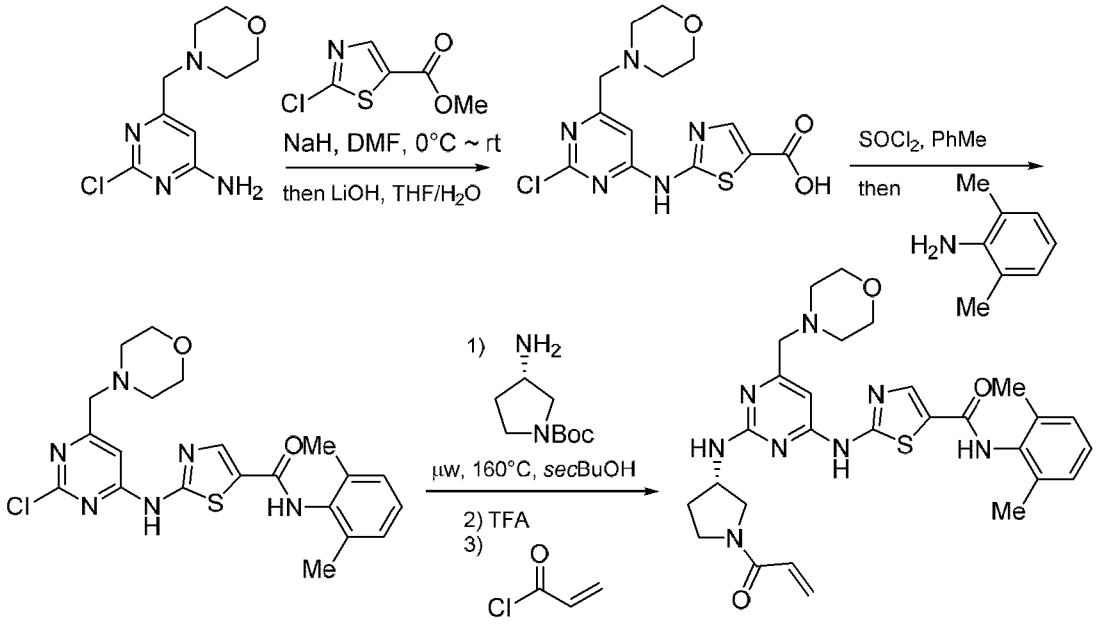
Example 8. Preparation of 2-((2-((1-acryloylazepan-3-yl)amino)pyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00321] 2-((2-((1-acryloylazepan-3-yl)amino)pyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from N-(2-chloro-6-methylphenyl)-2-((2-chloropyrimidin-4-yl)amino)thiazole-5-carboxamide and tert-butyl 3-aminoazepane-1-carboxylate using general procedures I and II. **LCMS** RT: 2.50 (Method A), Mass m/z: 512.69 (M+1).

Example 9. Preparation of (S)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)-6-(morpholinomethyl)pyrimidin-4-yl)amino)-N-(2,6-dimethylphenyl)thiazole-5-carboxamide



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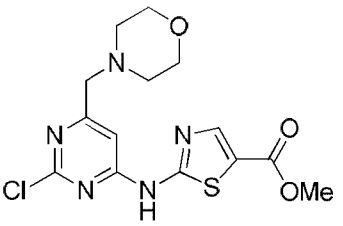
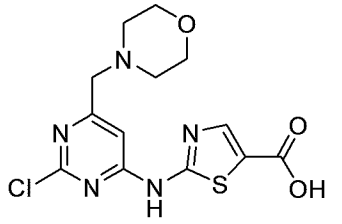
Methyl 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)thiazole-5-carboxylate



[00322] A solution of a mixture of 2-chloropyrimidin-4-amine (730 mg, 3.2 mmol) and methyl 2-chlorothiazole-5-carboxylate (626 mg, 3.5 mmol, 1.1 eq) in dry *N,N*-dimethylformamide (15 ml) was cooled to 0 °C and was treated portionwise over 5 min with sodium hydride (60% w/w in mineral oil, 256 mg, 6.4 mmol, 2 eq). The reaction mixture was stirred at 0 °C for 1 h and warmed to ambient temperature for a further 1 h. The mixture was treated with saturated ammonium chloride, followed by saturated aqueous Na_2CO_3 solution to reach pH 9 and the product was extracted with 1:1 mixture of dichloromethane and ethyl acetate. The organic extracts were combined, dried using a hydrophobic frit and evaporated under reduced pressure. The residue was purified by chromatography on silica to afford the title compound as an off-white solid. **LCMS** RT: 2.07 (Method A), Mass *m/z*: 370.37 (M+1).

2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)thiazole-5-carboxylic acid



[00323] To a solution of methyl 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)thiazole-5-carboxylate (190 mg, 0.51 mmol) in THF/H_2O (1:2 mixture, 6 mL) , was added LiOH monohydrate (32 mg, 0.77 mmol, 1.5 eq) in one portion and the reaction mixture was stirred at ambient temperature for 12h. After 12h, the reaction mixture was concentrated under reduced pressure and cooled to 0 °C and concentrated HCl was added dropwise to reach pH 6. The precipitate was filtered, washed with cold water, dried using a hydrophobic frit to afford the titled compound as a white solid. LCMS RT: 1.67 (Method A), Mass *m/z*: 356.24 (M+1).

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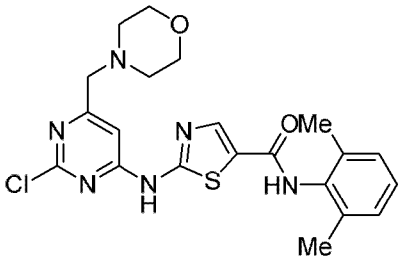
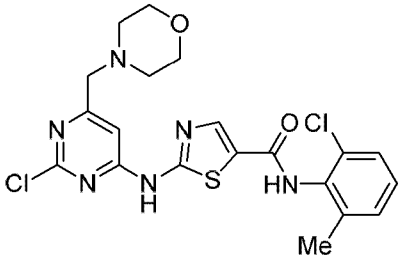
2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00324] To a solution of 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)thiazole-5-carboxylic acid (175 mg, 0.49 mmol) in toluene (3 mL) was added thionyl chloride (5.68 mL, 4.9 mmol, 10 eq). The reaction mixture was stirred at 90 °C for 3h before cooled to room temperature and concentrated under reduced pressure. The crude was dissolved in DCE and 2,6-dimethylaniline and DIPEA was added. The reaction mixture was stirred at 80 °C for 12h before cooled to ambient temperature and water was added. The mixture was extracted with isopropanol/chloroform (1:4) three times, the organic extracts were combined, washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica to afford the title compound as a yellowish solid. **LCMS** RT: 2.23 (Method A), Mass *m/z*: 479.48 (M+1).

2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00325] 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)thiazole-5-carboxylic acid and 2-chloro-6-methylaniline using the same procedure.

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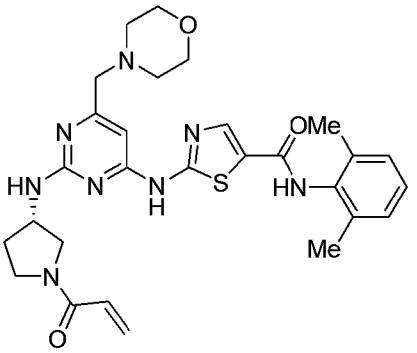
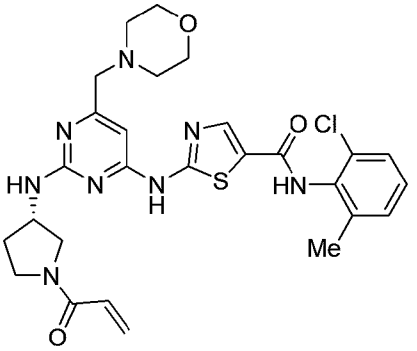
(*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide



[00326] (*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2,6-dimethylphenyl)thiazole-5-carboxamide and *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.10 (Method A), Mass *m/z*: 563.55 (M+1).

Example 10. Preparation of (S)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)-6-(morpholinomethyl)pyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00327] (*S*)-2-((2-((1-acryloylpyrrolidin-3-yl)amino)-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from 2-((2-chloro-6-(morpholinomethyl)pyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide and *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.17 (Method A), Mass *m/z*: 583.52 (M+1).

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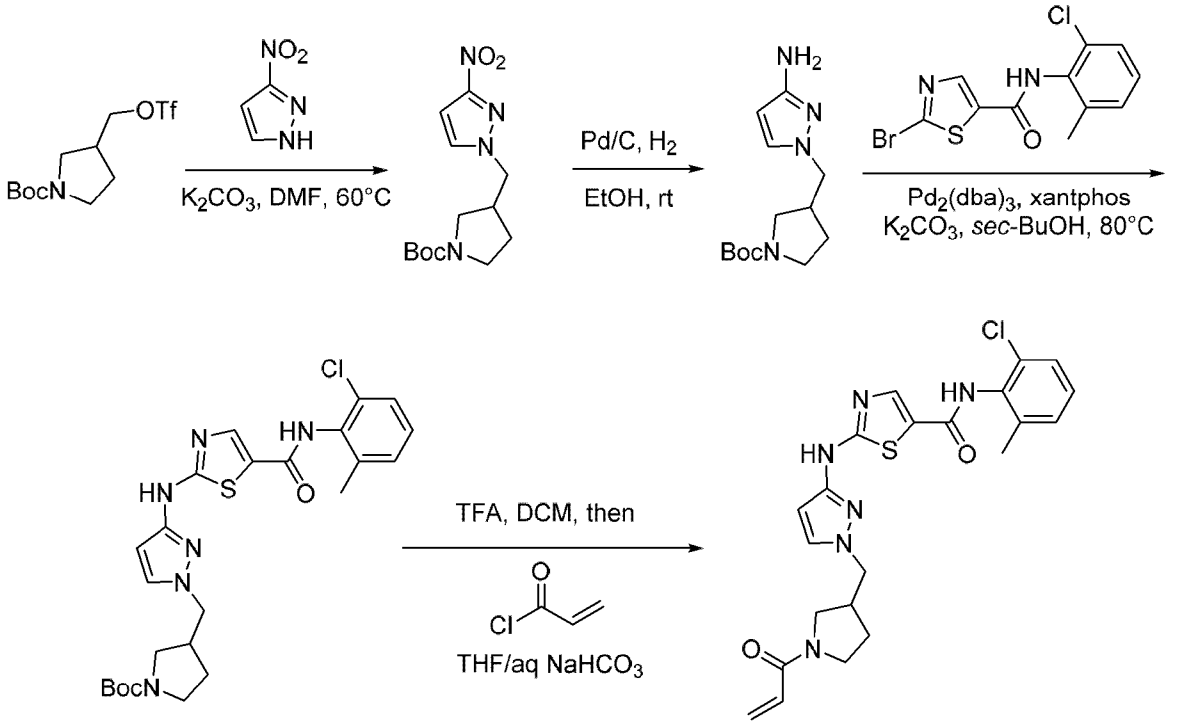
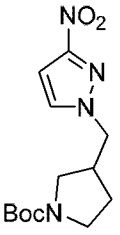
Example 11. Preparation of 2-((1-((1-acryloylpyrrolidin-3-yl)methyl)-1H-pyrazol-3-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



***tert*-butyl 3-((3-nitro-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate**



[00328] To a solution of *tert*-butyl 3-((((trifluoromethyl)sulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (1.47 g, 4.98 mmol) and 3-nitro-1*H*-pyrazole (619 mg, 5.48 mmol, 1.1 eq) in DMF (25 mL) was added K_2CO_3 (2.06 g, 14.94 mmol, 3 eq) in one portion, the reaction mixture was stirred at 60 °C for 12h. The mixture was cooled to ambient temperature and extracted with ethyl acetate, the combined extracts were washed with water, 1N HCl and brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound, as a crude and used directly in the next step. **LCMS** RT: 3.78 (Method A), Mass *m/z*: 300.06 (M+1).

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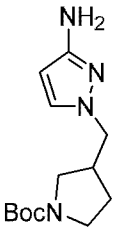
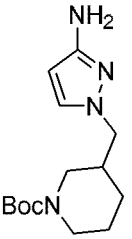
***tert*-butyl 3-((3-amino-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate**



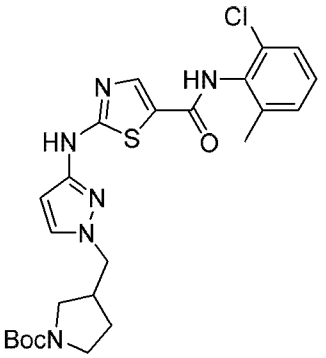
[00329] *tert*-butyl 3-((3-nitro-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate was dissolved in ethanol, 10 wt% Pd/C was added to the solution and the reaction mixture was stirred under H_2 atmosphere at ambient temperature for 3h. The suspension was filtered through a pad of celite™ and the filtrate concentrated under reduced pressure to afford the title compound. **LCMS** RT: 1.97 (Method A), Mass *m/z*: 267.33 (M+1).

***tert*-butyl 3-((3-amino-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate**



[00330] *tert*-butyl 3-((3-amino-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate was prepared using *tert*-butyl 3-((((trifluoromethyl)sulfonyl)oxy)methyl)piperidine-1-carboxylate and 3-nitro-1*H*-pyrazole following the same procedure. **LCMS** RT: 2.18 (Method A), Mass *m/z*: 281.21 (M+1).

***tert*-butyl 3-((3-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate**



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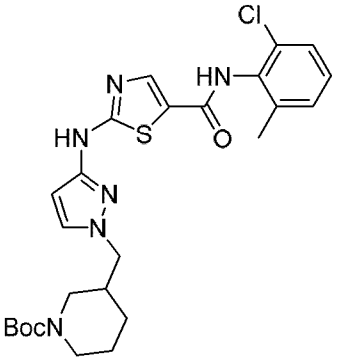
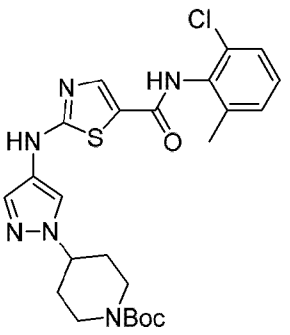
[00331] To a solution of 2-bromo-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (75 mg, 0.23 mmol) and *tert*-butyl 3-((3-amino-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate (120 mg, 0.45 mmol, 2 eq) in *sec*-butanol (1 mL) was added K_2CO_3 (94 mg, 0.68 mmol, 3 eq). The reaction mixture was degassed *via* sonication, before $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol, 0.06 eq) and xantphos (12.0 mg, 0.020 mmol, 0.09 eq) were added to the mixture. The reaction was stirred at 80 °C for 3h, filtered and dried under reduced pressure, and the residue was purified by preparative HPLC to yield the title compound. **LCMS** RT: 3.57 (Method A), Mass *m/z*: 517.61 (M+1).

***tert*-butyl 3-((3-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate**



[00332] *tert*-butyl 3-((3-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate was prepared from *tert*-butyl 3-((3-amino-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate and 2-bromo-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide following the same procedure. LCMS RT: 3.65 (Method A), Mass *m/z*: 531.66 (M+1).

***tert*-butyl 4-(4-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate**



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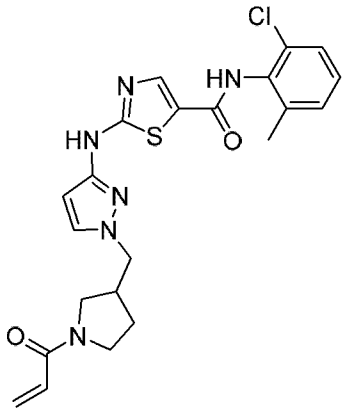
[00333] *tert*-butyl 4-(4-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate was prepared from *tert*-butyl 4-(4-amino-1*H*-pyrazol-1-yl)piperidine-1-carboxylate and 2-bromo-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide following the same procedure. **LCMS** RT: 3.28 (Method A), Mass *m/z*: 517.61 (M+1).

2-((1-((1-acryloylpyrrolidin-3-yl)methyl)-1*H*-pyrazol-3-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00334] *tert*-butyl 3-((3-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)methyl)pyrrolidine-1-carboxylate was dissolved in a 1:1 mixture of DCM and TFA. The reaction was stirred at ambient temperature for 2h and dried under reduced pressure. The residue was dissolved in a 1:1 mixture of THF and saturated $NaHCO_3$ aqueous solution and cooled to 0 °C. To the stirring mixture was added a dilute solution of acryloyl chloride in THF, the reaction was stirred at 0 °C and gradually warmed to ambient temperature. After 30min, the reaction was extracted with Ethyl acetate twice, the organic extracts combined and concentrated under reduced pressure. The residue was directly purified by preparative HPLC to yield the title compound. **LCMS** RT: 2.98 (Method A), Mass *m/z*: 485.47 (M+1). 1H NMR (400 MHz, DMSO-d6) δ 11.12 (s, 1H), 9.78 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 6.4 Hz, 1H), 7.69 (t, J = 2.6 Hz, 1H), 7.43 – 7.19 (m, 3H), 6.54 (dd, J = 16.8, 10.3 Hz, 1H), 6.07 (ddd, J = 16.9, 5.1, 2.4 Hz, 1H), 5.95 (dd, J = 9.7, 2.2 Hz, 1H), 5.61 (ddd, J = 10.2, 7.8, 2.5 Hz, 1H), 4.11 (d, J = 7.3 Hz, 1H), 3.57 – 3.40 (m, 3H), 3.25 (m, 1H), 2.80 – 2.60 (m, 1H), 2.23 (s, 3H), 1.97 (ddt, J = 41.2, 12.5, 6.3 Hz, 1H), 1.67 (ddd, J = 45.6, 12.8, 7.7 Hz, 1H).

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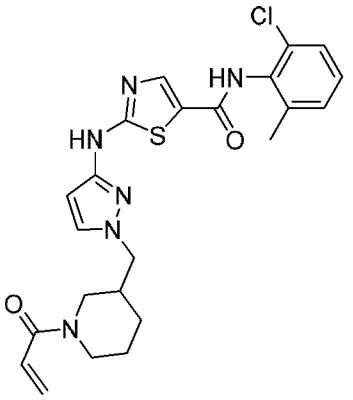
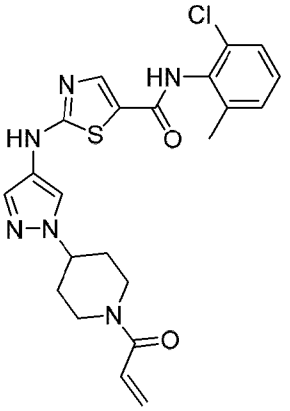
Example 12. Preparation of 2-((1-((1-acryloylpiperidin-3-yl)methyl)-1H-pyrazol-3-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00335] 2-((1-((1-acryloylpiperidin-3-yl)methyl)-1*H*-pyrazol-3-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from *tert*-butyl 3-((3-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)methyl)piperidine-1-carboxylate following the same procedure. **LCMS** RT: 2.83 (Method A), Mass *m/z*: 471.60 (M+1). 1H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 9.79 (s, 1H), 8.13 (s, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.38 (dd, J = 7.5, 2.0 Hz, 1H), 7.32 – 7.16 (m, 2H), 6.70 (ddd, J = 51.7, 16.7, 10.4 Hz, 1H), 6.02 (dd, J = 16.7, 2.4 Hz, 1H), 5.96 (d, J = 2.3 Hz, 1H), 5.59 (t, J = 12.6 Hz, 1H), 4.22 – 3.91 (m, 4H), 3.14 – 2.80 (m, 2H), 2.23 (s, 3H), 1.98 (s, 1H), 1.68 (d, J = 12.1 Hz, 2H), 1.44 – 1.16 (m, 2H).

Example 13. Preparation of 2-((1-(1-acryloylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide



[00336] 2-((1-(1-acryloylpiperidin-4-yl)-1*H*-pyrazol-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide was prepared from *tert*-butyl 4-(4-((5-((2-chloro-6-

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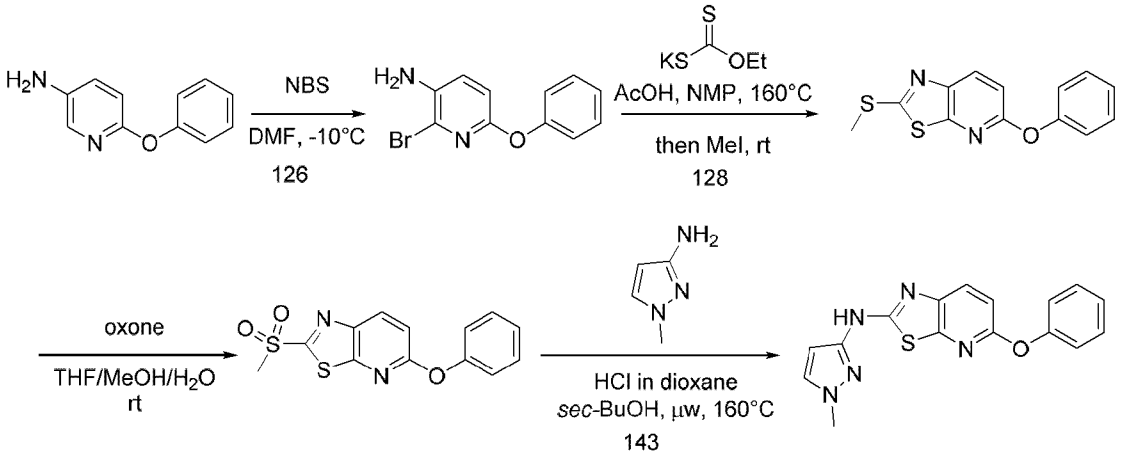
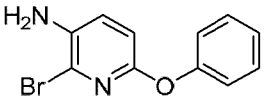
methylphenyl)carbamoyl)thiazol-2-yl)amino)-1*H*-pyrazol-1-yl)piperidine-1-carboxylate following the same procedure. **LCMS** RT: 2.67 (Method A), Mass *m/z*: 471.41 (M+1).

Example 14. Preparation of N-(1-methyl-1H-pyrazol-3-yl)-5-phenoxythiazolo[5,4-b]pyridin-2-amine

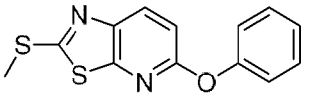


2-bromo-6-phenoxypyridin-3-amine



[00337] To a solution of 6-phenoxypyridin-3-amine (2 g, 10.8 mmol) in DMF (20 mL) was added *N*-bromosuccinimide (1.91 g, 10.8 mmol, 1 eq) at -10 °C for 5 min. The reaction mixture was quenched with saturated. $NaHCO_3$ solution at -10 °C. The mixture was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography to afford title compound as a reddish brown solid. **LCMS** RT: 3.33 (Method A), Mass *m/z*: 261.21 (M+1).

2-(methylthio)-5-phenoxythiazolo[5,4-*b*]pyridine



[00338] To a solution of 2-bromo-6-phenoxypyridin-3-amine (2.29 g, 8.64 mmol) in NMP (80 mL) was added potassium ethyl xanthogenate (6.9 g, 43.2 mmol, 5 eq) and acetic acid (3.1 mL, 43.2 mmol, 5 eq). The reaction mixture was heated at 150 °C for 16 hours. The

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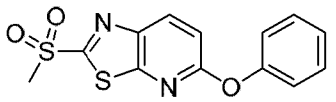
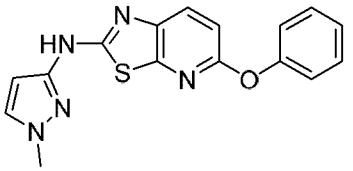
mixture was cooled to 50 °C and iodomethane (538 µL, 86.4 mmol, 10 eq) was added. The reaction mixture was further stirred for 30 minutes and partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford title compound as a bright brown solid. **LCMS** RT: 3.95 (Method A), Mass *m/z*: 275.21 (M+1).

2-(methylsulfonyl)-5-phenoxythiazolo[5,4-*b*]pyridine



[00339] To a solution of 2-(methylthio)-5-phenoxythiazolo[5,4-*b*]pyridine (3.0 g, 11 mmol) in THF (18 mL) and methanol (18 mL) was added Oxone™ (6.66 g, 44 mmol, 4 eq) in water (18 mL). The reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was filtered and concentrated under reduced pressure to give the title product as a bright brown solid. **LCMS** RT: 3.38 (Method A), Mass *m/z*: 307.19 (M+1).

N-(1-methyl-1*H*-pyrazol-3-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine



[00340] To a solution of 2-(methylsulfonyl)-5-phenoxythiazolo[5,4-*b*]pyridine and 1-methyl-1*H*-pyrazol-3-amine (30 mg, 0.1 mmol) in *sec*-butanol (1 mL) was added HCl in dioxane (0.1 mL). The reaction mixture was heated in the Biotage Initiator microwave at 160 °C until the reaction had reached completion. The solvent was removed under reduced pressure and the residue purified directly by preparative HPLC. **LCMS** RT: 3.23 (Method A), Mass *m/z*: 324.09 (M+1).

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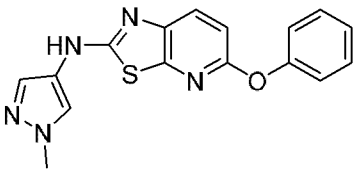
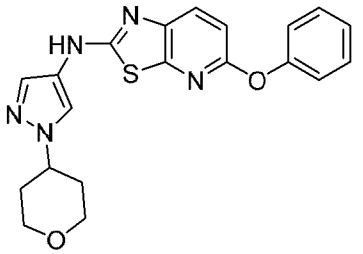
Example 15. Preparation of N-(1-methyl-1H-pyrazol-4-yl)-5-phenoxythiazolo[5,4-b]pyridin-2-amine



[00341] *N*-(1-methyl-1*H*-pyrazol-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine was prepared from 2-(methylsulfonyl)-5-phenoxythiazolo[5,4-*b*]pyridine and 1-methyl-1*H*-pyrazol-4-amine following the same procedure. **LCMS** RT: 3.18 (Method A), Mass *m/z*: 324.15 (M+1).

Example 16. Preparation of 5-phenoxy-N-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)thiazolo[5,4-b]pyridin-2-amine



[00342] 5-phenoxy-*N*-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)thiazolo[5,4-*b*]pyridin-2-amine was prepared from 2-(methylsulfonyl)-5-phenoxythiazolo[5,4-*b*]pyridine and 1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-amine following the same procedure. **LCMS** RT: 3.22 (Method A), Mass *m/z*: 394.45 (M+1).

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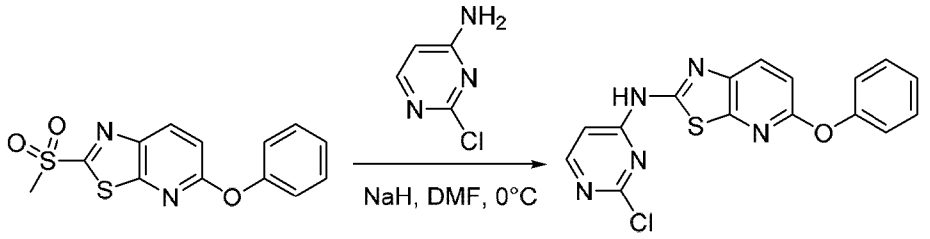
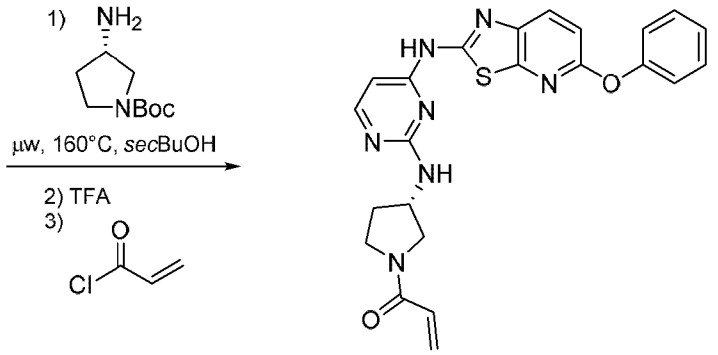
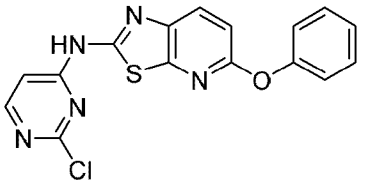
Example 17. Preparation of (S)-1-(3-((4-((5-phenoxythiazolo[5,4-b]pyridin-2-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one





N-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine



[00343] A solution of 2-(methylsulfonyl)-5-phenoxythiazolo[5,4-*b*]pyridine and 2-chloropyrimidin-4-amine (192 mg, 1.49 mmol) in DMF (9 mL) was cooled to 0 °C and NaH (184 mg, 4.47 mmol, 3 eq, 60% in mineral) was added to the stirring mixture. The reaction was warmed to ambient temperature and stirred for a further 2h. The mixture was treated with saturated ammonium chloride. Saturated aqueous Na_2CO_3 was added to reach pH 9 and the product was extracted with 1:1 mixture of dichloromethane and ethyl acetate. The organic extracts were combined, dried using a hydrophobic frit and evaporated to dryness. The residue was purified by chromatography on silica to afford the title compound as an off-white solid. **LCMS** RT: 3.62 (Method A), Mass *m/z*: 356.24 (M+1).

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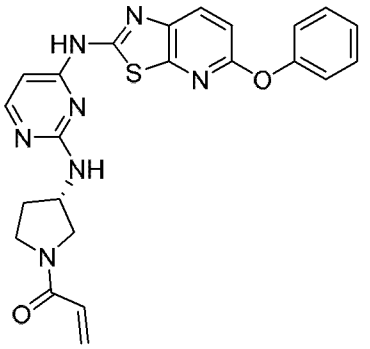
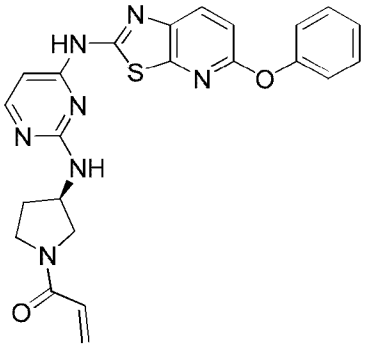
(*S*)-1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one



[00344] (*S*)-1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one was prepared from *N*-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine and *tert*-butyl (*S*)-3-aminopyrrolidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.62 (Method A), Mass *m/z*: 460.51 (M+1).

Example 18. Preparation of (R)-1-(3-((4-((5-phenoxythiazolo[5,4-b]pyridin-2-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one



[00345] (*R*)-1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)pyrrolidin-1-yl)prop-2-en-1-one was prepared from *N*-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine and *tert*-butyl (*R*)-3-aminopyrrolidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.47 (Method A), Mass *m/z*: 460.51 (M+1).

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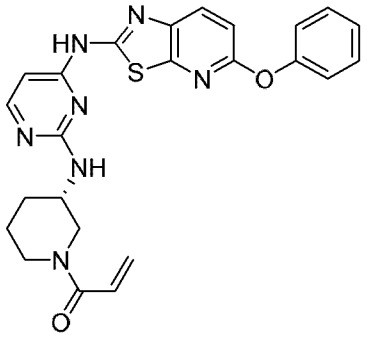
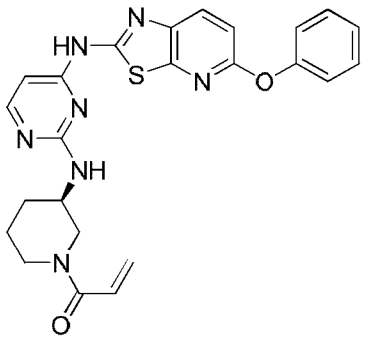
Example 19. Preparation of (S)-1-(3-((4-((5-phenoxythiazolo[5,4-b]pyridin-2-yl)amino)pyrimidin-2-yl)amino)piperidin-1-yl)prop-2-en-1-one



[00346] (*S*)-1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)piperidin-1-yl)prop-2-en-1-one was prepared from *N*-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine and *tert*-butyl (*S*)-3-aminopiperidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.57 (Method A), Mass *m/z*: 474.56 (M+1).

Example 20. Preparation of (R)-1-(3-((4-((5-phenoxythiazolo[5,4-b]pyridin-2-yl)amino)pyrimidin-2-yl)amino)piperidin-1-yl)prop-2-en-1-one



[00347] (*R*)-1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)piperidin-1-yl)prop-2-en-1-one was prepared from *N*-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine and *tert*-butyl (*R*)-3-aminopiperidine-1-carboxylate following general procedures I and II. **LCMS** RT: 2.55 (Method A), Mass *m/z*: 474.50 (M+1).

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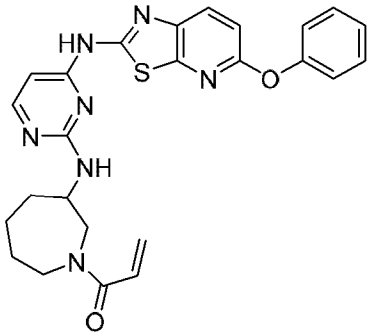
Example 21. Preparation of 1-(3-((4-((5-phenoxythiazolo[5,4-b]pyridin-2-yl)amino)pyrimidin-2-yl)amino)azepan-1-yl)prop-2-en-1-one



[00348] 1-(3-((4-((5-phenoxythiazolo[5,4-*b*]pyridin-2-yl)amino)pyrimidin-2-yl)amino)azepan-1-yl)prop-2-en-1-one was prepared from *N*-(2-chloropyrimidin-4-yl)-5-phenoxythiazolo[5,4-*b*]pyridin-2-amine and *tert*-butyl 3-aminoazepane-1-carboxylate following general procedures I and II. **LCMS** RT: 2.73 (Method A), Mass *m/z*: 488.49 (M+1).

Example 22. Inhibitory activities of exemplary compounds described herein against select protein kinases and cells

[00349] The inhibitory activities of exemplary compounds described herein against select protein kinases and cells were determined. Cell survival following treatment of exemplary compounds described herein was assessed by CellTiter-Glo® Luminescent cell viability assay (Promega). The cells were seeded into 384 well plates with the EL406 Combination Washer Dispenser (BioTek Instruments, Inc.), and a series diluted exemplary compounds (20~0.0006 μM) were injected into the culture media with the JANUS Automated Workstation (PerkinElmer Inc.). The cells were treated for 72 hours at 37 °C with 5% CO_2. Luminescent measurement is performed using the 2104 Envision® Multilabel Reader (PerkinElmer Inc.). EC_{50} values were calculated with GRAPHPAD™ PRISM™ software. Exemplary results are shown in *Table 1B.*

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[00350] *Table 1B*. Exemplary biological data of exemplary compounds described herein.

Compound	BTK IC_{50} (nM)	HCK IC_{50} (nM)	BCWM.1 EC_{50} (nM)	MWCL-1 EC_{50} (nM)	TMD-8 EC_{50} (nM)	HBL-1 EC_{50} (nM)
Dasatinib			1.20	7.41	18.70	190.00
I-1	1.61	0.59	73.40	50.00	301.00	522.00
I-3	0.60	<0.495	19.30	55.20	158.00	669.00
I-6	1.90	4.24	69.60	93.70	80.20	229.00
I-2	1.63	0.73	41.00	67.00	311.00	1670.00
I-4	1.38	0.59	53.00	85.00	315.00	449.00
I-7	<0.495	<0.495	22.00	19.00	49.00	70.00
I-8	<0.495	<0.495	75.00	103.00	301.00	522.00
I-10	1.74	2.42	170.00	191.00	1010.00	1640.00
I-11	5.52	3.99	129.00	245.00	500.00	623.00
III-1	86.60	1820.00	1830.00	4080.00	3850.00	3200.00
III-2	281.00	402.00	916.00	1350.00	2640.00	2960.00
III-3	19.40	2150.00	2710.00	5750.00	4130.00	2960.00
III-4	367	1150	808	2160	2120	2550
III-5	9.06	1910	1190	3370	1230	896
III-6	2580	4550	270	2170	467	450
III-7	> 10000	> 10000	> 20000	> 20000	> 20000	> 20000
III-8	> 10000	> 10000	7250	> 20000	14600	> 20000
III-9	2660	7200	8290	16600	18300	>20000
II-1	1.1	1.64	84	121	573	735
II-2	<0.495	1.94	196	166	929	1000
II-3	19.9	25.3	690	772	2540	3650
I-9	0.5	<0.495	9.84	25	70.9	220
I-12			75.50	317.00	453.00	1200.00

Table 1B. (continued)

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Compound	OCI-Ly3 EC_{50} (nM)	OCI-Ly19 EC_{50} (nM)	Ramos EC_{50} (nM)	OCI-Ly7 EC_{50} (nM)	RPMI-8226 EC_{50} (nM)	OPM-2 EC_{50} (nM)
Dasatinib	8060.00	3860.00	4560.00	155.00	5390.00	7110.00
I-1	NA	NA	NA			
I-3	39500.00	13000.00	> 20000	370.00		
I-6	NA	NA	NA	520.00		
I-2	> 20000	> 20000	> 20000			
I-4		4270	>20000			
I-7		399	133			
I-8		3770	7970			
I-5						
I-10		5700	12			
I-11		3680	1580			
III-1		1250	3700			
III-2		1100	2300			
III-3		2500	8460			
III-4		1170	2190			
III-5		1330	2720			
III-6		321	749			
III-7		9520	> 20000			
III-8		12600	> 20000			
III-9		7060	11800			
II-1		7880	>20000			
II-2		6540	>20000			
II-3		9970	>20000			
I-9	14500	10000	> 20000			
I-12				309.00		

NA: Not available.

*Example 23. KINATIV assay of compounds **I-3** and **I-9***

[00351] BCWM.1 cells were treated with compound **I-3** or **I-9** (1 μM) for 90 minutes. The cells were harvested and lysed. The lysates were divided into two parts: one part was directly labeled with an ATP-biotin probe (no GENEFILTERS™ (GF)), and the other part was first gel-filtered, and, 15 minutes after gel-filtering, probe labeled (GENEFILTERS (GF)). Bound kinases were identified and quantitated by ACTIVX as described in Patricelli *et al.*, *Biochemistry*, **2007**, 46(2): 350-358. The compounds were tested in duplicates against duplicate or quadruplicate control samples. Exemplary results are shown in *Table 2*, where the % changes of MS (mass spectroscopy) signals of compounds **I-3** or **I-9**, compared to the control samples, are reported. The results shown in *Table 2* were statistically significant (Student T-test score <0.04). A compound inhibited the kinase activity when a % change of the MS signal shown in *Table 2* is positive (*e.g.*, greater than 0%) or increased the kinase

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activity when a % change of the MS signal shown in *Table 2* is negative (*e.g.*, lower than 0%).

[00352] *Table 2*. Exemplary KINATIV assay results of compounds **I-3** and **I-9**.

Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 μM	I-9 1 μM	I-3 1 μM	I-9 1 μM
				no GF	GF	no GF	GF
ABL, ARG	UniRef100_P00519, UniRef100_P42684	LMTGDTYTAHAGAKFPIK	Activation Loop	75.4	46.1	93.5	75.4
ABL, ARG	UniRef100_P00519, UniRef100_P42684	YSLTVAVKTLKEDTMEVEEFLK	Lys1	86.9	40.6	93.2	71.8
ACK	UniRef100_Q07912	TVSVAVKCLKPDVLSQPEAMDDFIR	Lys1	5.8	15.6	52.7	2.4
AGK	UniRef100_Q53H12	ATVFLNPAACKGK	ATP	-0.2		-12.4	
AKT1	UniRef100_P31749	GTFGKVILVK	ATP Loop	-20.4	-25.1	-21.9	-16.8
AKT2, AKT3	UniRef100_Q9Y243, UniRef100_P31751	GTFGKVILVR	ATP Loop	-19.2	-9.7	-14.5	5.4
AMPKa1, AMPKa2	UniRef100_P54646, UniRef100_Q96E92	DLKPENVLLDAHMNAK	Lys2	-7.6	22.1	12.1	5.8
ARAF	UniRef100_P10398	DLKSNNIFLHEGLTVK	Lys2	-152.4	-56.6	-402.1	-95.1
ATM	UniRef100_Q13315	QLVKGRDDLRQDAVMQQVFQMCNTLLQR	ATP	20.7		19.5	
ATR	UniRef100_Q13535	FYIMMCKPK	ATP	-31.6	28.1	25.3	16.5
AurA	UniRef100_O14965	FILALKVLFK	Lys1	12	-14.5	-13	1.4
AurA	UniRef100_O14965	DIKPENLLLGSAGELK	Lys2	12.7	-6.6	-5.9	1.2
AurA, AurB, AurC	UniRef100_O14965, UniRef100_Q9UQB9, UniRef100_Q96GD4	GKFGNVYLAR	ATP Loop	7.7	5.5	4.7	2.8
AurB	UniRef100_Q96GD4	SHFIVALKVLFK	Lys1	-2.2	-20.6	-23.6	-21.5
BLK	UniRef100_P51451	IIDSEYTAQEGAKFPIK	Activation Loop	>96	93.7	>96	95.4
BRAF	UniRef100_P15056	DLKSNNIFLHEDLTVK	Lys2	-7.6	-18.3	-48.9	-12.9
BTK	UniRef100_Q06187	YVLDDEYTSSVGSKFPVR	Activation Loop	94.7	96.7	95.2	70.7
CaMK1d	UniRef100_Q8IU85	LFAVKCIPK	Lys1	-0.4	-7.5	-5	-4.6
CaMK2d	UniRef100_Q13557	IPTGQEYAAKIINTKK	Lys1	-1.3	-8.1	-25	-8.2

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
CaMK2g	UniRef100_Q13555	TSTQEYAAKIINTK	Lys1	13.7	-17.7	-12	-4.4
CaMK4	UniRef100_Q16566	DLKPENLLYATPAPDAPLK	Lys2	6.8	-10.3	-0.1	-13.1
CaMKK2	UniRef100_Q96RR4	DIKPSNLLVGEDGHIK	Lys2	-2.1	-4.9	1.7	0.5
CASK	UniRef100_O14936	ETGQQFAVKIVDVAK	Lys1	-1	-10.4	0.5	3.9
CDC2	UniRef100_Q5H9N4	DLKPQNLLIDDKGTIK	Protein Kinase Domain	-0.7	-2.6	-4.3	-3.2
CDC7	UniRef100_O00311	DVKPSNFLYNR	Lys2		-12.5		-2.2
CDK11, CDK8	UniRef100_P49336, UniRef100_Q9BWU1	DLKPANILVMGEGPER	Lys2	-15.2	28.6	20.4	11.8
CDK2	UniRef100_P24941	DLKPQNLLINTEGAIK	Lys2	3.6	-8.7	1.2	-4.3
CDK4	UniRef100_P11802	DLKPENILVTSGGTVK	Lys2	10.3	1.2	4.8	3.4
CDK5	UniRef100_Q00535	DLKPQNLLINR	Lys2	11.8	-1.1	-1.8	7.7
CDK6	UniRef100_Q00534	DLKPQNILVTSSGQIK	Lys2	12.4	2.7	3.6	3.5
CDK7	UniRef100_P50613	DLKPNNLLLDENGVLK	Lys2	8.9	1.3	5.1	5.1
CDK9	UniRef100_P50750	DMKAANVLITR	Lys2	-1.7	32.7	25.9	23.1
CHED	UniRef100_Q14004	DIKCSNILLNNR	Lys2		5.7		15.3
CHK1	UniRef100_B4DT73	DIKPENLLLDER	Lys2	9.7	-25.9	5.6	-2
CHK2	UniRef100_O96017	DLKPENVLLSSQEEDCLIK	Lys2	8.2	-13.1	-11.9	-2.5
CK1a	UniRef100_P48729	DIKPDNFLMGIGR	Lys2	-18.2	32.6	30.6	12.5
CK1d, CK1e	UniRef100_P49674, UniRef100_P48730	DVKPDNFLMGLGKK	Lys2	-16.5	26.3	10.8	12.8
CK1g1, CK1g2, CK1g3	UniRef100_Q9Y6M4, UniRef100_P78368, UniRef100_Q9HCP0	KIGCGNFGELR	ATP Loop		-8.2		-4.7
CK1g2	UniRef100_P78368	DVKPENFLVGRPGTK	Lys2	-3.7	-8.9	-4.5	-10.9
CK2a2	UniRef100_P19784	DVKPHNVMIDHQQK	Lys2	-8.7	7	4	-1.8
CLK1	UniRef100_P49759	LTHTDLKPENILFVQSDYTEAYNPK	Lys2		-25		-6.2
CLK2	UniRef100_P49760	LTHTDLKPENILFVNSDYELTYNLEK	Lys2		-19.3		-10.6
CLK3	UniRef100_P49761	YEIVGNLGEGTFGKVVECLDHAR	ATP Loop	17.6	-19	3.6	-10.3

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
COT	UniRef100_P41279	GAFGKVYLAQDIK	ATP Loop		-37.3		-40.3
CRK7	UniRef100_Q9NYV4	DIKCSNILLNNSGQIK	Lys2		13		27.8
CSK	UniRef100_P41240	VSDFGLTKEASSTQDTGKLPVK	Activation Loop	36	-6	60.3	1.5
DGKA	UniRef100_P23743	IDPVPNTHPLLVFVNPKSGGK	ATP	-5.2	-1.5	-24	-6.6
DGKH	UniRef100_Q86XP1	ATFSFCVSPLLVFVNSKSGDNQGVK	ATP	15.2	-21.2	-44.1	-12.5
DLK	UniRef100_Q12852	DLKSPNMLITYDDVVK	Lys2	10.2		-8	
DNAPK	UniRef100_P78527	KGGSWIQEINVAEK	ATP	-2.2	-0.3	10.5	-0.4
DNAPK	UniRef100_P78527	EHPFLVKGGEDLR	ATP	-15.1	-35.1	11	3.4
eEF2K	UniRef100_O00418	YIKYNSNSGFVR	ATP	-18.9	-51.4	-27.8	-48.7
EGFR	UniRef100_P00533	IPVAIKELR	Lys1	20		17	
EphB1	UniRef100_P54762	YLQDDTSDPTYTSSLGGKIPVR	Activation Loop	92.9	53.3	95.7	78.9
EphB2	UniRef100_P29323	FLEDDTSDPTYTSALGGKIPIR	Activation Loop	91	81.7	91.6	85.6
Erk1	UniRef100_P27361	DLKPSNLLINTTCDLK	Lys2	-0.6	-3.1	1.5	3.1
Erk2	UniRef100_P28482	DLKPSNLLLNTTCDLK	Lys2	-1.8	-3.8	1.1	4
Erk3	UniRef100_Q16659	DLKPANLFINTEDLVLK	Lys2	23.2	16.9	23.8	25.3
Erk5	UniRef100_Q13164	DLKPSNLLVNENCELK	Lys2	3	-1.8	8.3	1.1
FER	UniRef100_P16591	TSVAVKTCKEDLPQELK	Lys1	9.1	-8.4	-14	2.6
FES	UniRef100_P07332	LRADNTLVAVKSCR	Lys1	10.7	-11.2	-13.3	-3.9
FGR	UniRef100_P09769	LIKDDEYNPCQGSKFPIK	Activation Loop	95.7	84.7	95.4	72.1
FRAP	UniRef100_P42345	IQSIAPSLQVITSKQRPR	ATP	6.9	-8.1	-21.4	2.2
FRK	UniRef100_P42685	HEIKLPVK	Activation Loop	92.4	36.7	95.8	73.6
FYN	UniRef100_P06241	VAIKTLKPGTMSPESFLEEAQIMK	Lys1		>91		>91
FYN, SRC, YES	UniRef100_P12931, UniRef100_P07947, UniRef100_P06241	QGAKFPIKWTAPEAALYGR	Activation Loop	87.3	72.5	85.7	80.4
GAK	UniRef100_O14976	DLKVENLLLSNQGTIK	Lys2		-14.5		33.8
GCK	UniRef100_Q12851	DIKGANLLLTLQGDVK	Lys2	18.1	4.5	17.8	16.4
GCN2	UniRef100_Q9P2K8	DLKPVNIFLDSDDHVK	Lys2	-2.8	-18.8	-14.3	-10.7

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
GSK3A	UniRef100_P49840	DIKPQNLLVDPDTAVLK	Lys2	3.5	2.3	9	1.9
GSK3B	UniRef100_P49841	DIKPQNLLLDPDTAVLK	Lys2	9.4	-9.8	-0.5	-1.3
HPK1	UniRef100_Q92918	DIKGANILINDAGEVR	Lys2	18.8	-2.9	5.9	7.3
IKKa	UniRef100_O15111	DLKPENIVLQDVGGK	Lys2	14.6	-3.3	-4.4	-0.4
IKKb	UniRef100_O14920	DLKPENIVLQQGEQR	Lys2	3.6	0.4	-6.4	-1.4
IKKe	UniRef100_Q14164	SGELVAVKVFNTTSYLRPR	Lys1	5.5	-12.6	-21.5	-6.1
ILK	UniRef100_Q13418	WQGNDIVVKVLK	Lys1	3.2	-1.9	-9.7	1.2
ILK	UniRef100_Q13418	ISMADVKFSFQCPGR	Protein Kinase Domain	3.6	24.5	9.7	12.4
IRAK1	UniRef100_P51617	AIQFLHQDSPSLIHGDIKSSNVLLDER	Lys2	-4.8	-2.6	-19.8	-3.2
IRAK3	UniRef100_Q9Y616	VEIQNLTYAVKLFK	Lys1	-11.3	7.2	-5.5	-1.4
IRAK4	UniRef100_Q9NWZ3	DIKSANILLDEAFTAK	Lys2	16.4	-3.2	-11	6.2
IRE1	UniRef100_O75460	DLKPHNILISMPNAHGK	Lys2	-12.1	24.3	13.2	2
ITPK1	UniRef100_Q13572	ESIFFNSHNVSKPESSSVLTELDKIEGVFERPSDEVIR	ATP	8.5	-10	1.5	1.7
JAK1	UniRef100_P23458	QLASALSYLEDKDLVHGNVCTKNLLLAR	Protein Kinase Domain	12.3	-11.5	-25	-6.7
JAK1 domain2	UniRef100_P23458	IGDFGLTKAIETDKEYYTVK	Activation Loop	-2.9	-15.6	-1.6	-13.9
JAK1 domain2	UniRef100_P23458	YDPEGDNTGEQVAVKSLKPESGGNHIADLKK	Lys1	-2.1	-18.1	-29.1	-14.4
JAK3 domain2	UniRef100_P52333	IADFGLAKLLPLDKDYYVVR	Activation Loop	-1.5	-21.6	-0.6	13.5
JNK1, JNK2, JNK3	UniRef100_P45983, UniRef100_P53779, UniRef100_P45984	DLKPSNIVVK	Lys2	14.9	-7	4.7	0.5
KHS1	UniRef100_Q9Y4K4	NVHTGELAAVKIIK	Lys1		-7.5		-8.7
KHS2	UniRef100_Q8IVH8	NVNTGELAAIKVIK	Lys1		-23.6		-22.7
KSR1	UniRef100_Q8IVT5	SKNVFYDNGKVVITDFGLFGISGVVR	Activation Loop	7.1	-8.7	-41.8	-25.6
KSR1, KSR2	UniRef100_Q6VAB6, UniRef100_Q8IVT5	SKNVFYDNGK	Activation Loop	-4.3	-14.6	-24.2	-16.2
LATS1	UniRef100_O95835	ALYATKTLR	Lys1	14.6	-2.8	-5.2	5.4

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
LATS2	UniRef100_Q9NRM7	DIKPDNILIDLDGHIK	Lys2	9.4	-12.3	-17.9	-5.1
LCK	UniRef100_P06239	EGAKFPIKWTAPEAINYGTFTIK	Activation Loop	92.6	61.6	92.7	82.8
LKB1	UniRef100_Q15831	DIKPGNLLLTTGGTLK	Lys2	-11.2	-11.2	-8.7	-7.4
LOK	UniRef100_O94804	DLKAGNVLMTLEGDIR	Lys2	-8.6	26.2	8.5	15.2
LRRK2	UniRef100_Q5S007	DLKPHNVLLFTLYPNAAIIAK	Lys2	11.6	-26.4	-6.6	-21.7
LYN	UniRef100_P07948	VAVKTLKPGTMSVQAFLEEANLMK	Lys1	>98	85.2	>98	94
MAP2K1	UniRef100_Q02750	IMHRDVKPSNILVNSR	Lys2	0.1	28.5	25	3.5
MAP2K1, MAP2K2	UniRef100_P36507, UniRef100_Q02750	KLIHLEIKPAIR	Lys1	13.5	-9.2	-5.7	-1.1
MAP2K1, MAP2K2	UniRef100_P36507, UniRef100_Q02750	DVKPSNILVNSR	Lys2	20.8	-6.4	-6.9	-4.5
MAP2K2	UniRef100_P36507	HQIMHRDVKPSNILVNSR	Lys2	-3.5	34.6	16.5	12.5
MAP2K3	UniRef100_P46734	DVKPSNVLINK	Lys2	15.6	-21.3	5.8	-3.6
MAP2K4	UniRef100_P45985	DIKPSNILLDR	Lys2	-3.9	-5.4	1.1	-2.1
MAP2K5	UniRef100_Q13163	DVKPSNMLVNTR	Lys2	-2.2	16.8	44.4	16.3
MAP2K6	UniRef100_P52564	DVKPSNVLINALGQVK	Lys2	10.6	-22.1	-2	-5.9
MAP2K7	UniRef100_O14733	DVKPSNILLDER	Lys2	1.5	-2.8	-9.1	-0.3
MAP3K1	UniRef100_Q13233	DVKGANLLIDSTGQR	Lys2	22.5	11.1	18.8	9.8
MAP3K2	UniRef100_Q9Y2U5	ELAVKQVQFDPDSPETSKEVNALECEIQLLK	Lys1	-2.1	-16.2	-21.7	-8.3
MAP3K2, MAP3K3	UniRef100_Q9Y2U5, UniRef100_Q99759	DIKGANILR	Lys2	15.3	0.7	-12.6	6.8
MAP3K3	UniRef100_Q99759	ELASKQVQFDPDSPETSKEVSALECEIQLLK	Lys1	13.2	-13.7	-40.9	-19.7
MAP3K4	UniRef100_Q9Y6R4	DIKGANIFLTSSGLIK	Lys2	16.8	3.2	1.2	10.9
MAP3K5	UniRef100_Q99683	DIKGDNVLINTYSGVLK	Lys2	8.3	-9	-5.9	8.1
MAP3K6	UniRef100_O95382	DIKGDNVLINTFSGLLK	Lys2	15.9	-13.4	-15.4	-5
MARK2, MARK3	UniRef100_P27448, UniRef100_Q7KZI7	DLKAENLLLDADMNIK	Lys2	-17.6	27.8	16.2	9.5
MARK3	UniRef100_P27448	EVAIKIIDKTQLNPTSLQK	Lys1	7.9	-6.4	-12.9	-4.8

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
MARK3, MARK4	UniRef100_Q96L34, UniRef100_P27448	EVAIKIIDK	Lys1	2.5	-10.4	-4	-7.1
MARK4	UniRef100_Q96L34	DLKAENLLLDAEANIK	Lys2	-8.5	-12.2	-8.7	-10.2
MAST1, MAST2	UniRef100_Q6P0Q8, UniRef100_Q9Y2H9	DLKPDNLLITSMGHIK	Lys2	-13.4	22	26.3	-0.5
MAST3	UniRef100_O60307	DLKPDNLLITSLGHIK	Lys2	8.1	-22.1	-11.9	-11.9
MASTL	UniRef100_Q96GX5	GAFGKVYLGQK	ATP Loop	5.3	0.4	6	1.8
MASTL	UniRef100_Q96GX5	LYAVKVVK	Lys1	16.4	2.4	9.8	8
MELK	UniRef100_Q14680	DLKPENLLFDEYHK	Lys2	-12.1	-9.6	-10.6	-9.5
MER	UniRef100_Q12866	NCMLRDDMTVCVADFGLSKK	Activation Loop		6.3		-12.5
MER, TYRO3	UniRef100_Q06418, UniRef100_Q12866	KIYSGDYYR	Activation Loop	2.4	-14.7	0.4	3.1
MET	UniRef100_P08581	DMYDKEYYSVHNK	Activation Loop	-12.9		-45.2	
MLK1	UniRef100_P80192	DLKSSNILILQK	Lys2		1		9
MLK3	UniRef100_Q16584	DLKSNNILLLQPIESDDMEHK	Lys2	-7.2	24.1	6.3	3.9
MLK4	UniRef100_Q5TCX8	DLKSSNILLLEK	Lys2	-3.8	-22	-11.8	-18.5
MLKL	UniRef100_Q8NB16	APVAIKVFK	Lys1	-5.6	-4.7	-4.6	-3.9
MPSK1	UniRef100_O75716	DLKPTNILLGDEGQPVLMDLGSMNQACIHVEGSR	Lys2	-9.7	21.9	20.9	10.1
MSK1 domain1	UniRef100_O75582	DIKLENILLDSNGHVVLTDFGLSK	Lys2	-2.8	-22.8	-9	-23.9
MSK2 domain1	UniRef100_O75676	DLKLENVLLDSEGHIVLTDFGLSK	Lys2	-2	-27	-17.3	-18.7
MST1	UniRef100_Q13043	ETGQIVAIKQVPVESDLQEIIK	Lys1	-4.5	-28.8	-20.9	-11.3
MST2	UniRef100_Q13188	ESGQVVAIKQVPVESDLQEIIK	Lys1	-12.1	-24.9	-18	-11.9
MST3	UniRef100_Q9Y6E0	DIKAANVLLSEHGEVK	Lys2	-2	-1.9	-3.8	-1.4
MST4	UniRef100_Q9P289	TQQVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSSYVTK	Lys1	-6.7	-31.5	-36.1	-20
MST4, YSK1	UniRef100_O00506, UniRef100_Q9P289	DIKAANVLLSEQGDVK	Lys2	18.1	9.7	15.5	15.2
NDR1	UniRef100_Q15208	DIKPDNLLLDSK	Lys2	2.3	-4.2	-5.5	2.8

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
NDR2	UniRef100_Q9Y2H1	DIKPDNLLLDAK	Lys2	11.6	-5.6	-9.6	2.9
NEK1	UniRef100_Q96PY6	DIKSQNIFLTK	Lys2	7.4	-3.7	-7.6	4.6
NEK2	UniRef100_P51955	DLKPANVFLDGK	Lys2	20.5	-8.2	0.9	4.3
NEK3	UniRef100_P51956	SKNIFLTQNGK	Activation Loop		-21.2		-3.2
NEK4	UniRef100_P51957	DLKTQNVFLTR	Lys2	10.1	-13.1	7.3	-1.7
NEK6, NEK7	UniRef100_Q8TDX7, UniRef100_Q9HC98	DIKPANVFITATGVVK	Lys2	6.4	-3.3	-13.1	-0.8
NEK7	UniRef100_Q8TDX7	AACLLDGVPVALKK	Lys1	5.7	11.3	-14.7	8
NEK8	UniRef100_Q86SG6	DLKTQNILLDK	Lys2	5.1	-14.1	-14.5	-5.8
NEK9	UniRef100_Q8TD19	DIKTLNIFLTK	Lys2	15.4	-21.3	-9.9	-12.6
NLK	UniRef100_Q9UBE8	DIKPGNLLVNSNCVLK	Lys2	66.2	-1.2	85.9	51.8
OSR1	UniRef100_C9JIG9, UniRef100_O95747	DVKAGNILLGEDGSVQIADFGVSAFLATGGDITR	Lys2	13.8	2.7	4	13.9
p38a	UniRef100_Q16539	DLKPSNLAVNEDCELK	Lys2	43.5	-7.8	70	9.8
p38a	UniRef100_Q16539	QELNKTIWEVPER	Protein Kinase Domain	32.6	-2.9	67.9	8.7
p38d, p38g	UniRef100_O15264, UniRef100_P53778	DLKPGNLAVNEDCELK	Lys2	5.7	-8.8	-0.7	-27.1
p70S6K	UniRef100_P23443	DLKPENIMLNHQGHVK	Lys2	-77.2	15.9	-51.5	-8.6
p70S6Kb	UniRef100_Q9UBS0	DLKPENIMLSSQGHIK	Lys2	-36.7	24.3	6.8	3.1
PAN3	UniRef100_Q58A45	VMDPTKILITGK	Protein Kinase Domain	-17.5	23.2	2.5	4
PCTAIRE1	UniRef100_Q00536	SKLTDNLVALKEIR	Lys1	10	4.1	-14.7	6.5
PCTAIRE2, PCTAIRE3	UniRef100_Q00537, UniRef100_Q07002	SKLTENLVALKEIR	Lys1	-0.4	-4.7	-12	-0.8
PDK1	UniRef100_O15530	EYAIKILEK	Lys1	-8.4	-6.4	-3.5	-6.6
PEK	UniRef100_Q9NZJ5	DLKPSNIFFTMDDVVK	Lys2	-12.8	22.1	6.4	15.4
PFTAIRE1	UniRef100_O94921	LVALKVIR	Lys1	0.9	-3.9	-6.6	-3.1
PHKg1	UniRef100_Q16816	DLKPENILLDDNMNIK	Protein Kinase Domain	31.7	-51	-38.8	-26.2
PHKg2	UniRef100_P15735	ATGHEFAVKIMEVTAER	Lys1	-31.2	12.5	22.3	5.3

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
PI4K2B	UniRef100_Q8TCG2	SEEPYGQLNPKWTK	ATP		2.6		6.5
PI4KA, PI4KAP2	UniRef100_A4QPH2, UniRef100_P42356	SGTPMQSAAKAPYLAK	ATP	-3.7	20.3	12	3.6
PI4KB	UniRef100_Q9UBF8	VPHTQAVVLNSKDK	ATP	6.4	-24.3	-4.1	-3.1
PIK3C2B	UniRef100_O00750	VIFKCGDDLRQDMLTLQMIR	ATP	-1.8	28.5	39.1	12.7
PIK3C3	UniRef100_Q8NEB9	TEDGGKYPVIFKHGDDLR	ATP	2.4	-23.4	-0.8	-9.4
PIK3CB	UniRef100_P42338	VFGEDSVGVIFKNGDDLRQDMLTLQMLR	ATP	-9.1	33.6	39.9	18.5
PIK3CD	UniRef100_O00329	VNWLAHNVSKDNRQ	ATP	-3.4	-19.7	-17.2	-9.7
PIK3CG	UniRef100_P48736	KKPLWLEFK	ATP	-9.6	-15.1	-3.4	-9.6
PIP4K2A	UniRef100_P48426	AKELPTLKDNDFINEGQK	ATP	-4.9	-10.5	-15.2	-8.3
PIP4K2B	UniRef100_P78356	AKDLPTFKDNDFLNEGQK	ATP		17.6		-19
PIP4K2C	UniRef100_Q8TBX8	TLVIKEVSSEDIADMHSNLSNYHQYIVK	ATP	-14.1	10	27	-3.9
PIP5K1A	UniRef100_Q99755	EKPLPTFKDLDFLQDIPDGLFLDADMYNALCK	ATP	26.2		30.5	
PIP5K3	UniRef100_Q9Y2I7	GGKSGAAFYATEDDRFILK	ATP	6.5	-6.7	-4.6	-4.6
PITSLRE	UniRef100_P21127	DLKTSNLLLSHAGILK	Lys2	-14.1	-10.8	-8.6	-0.6
PKACa	UniRef100_P17612	DLKPENLLIDQQGYIQVTDFGFAK	Lys2		-9.8		-8.4
PKCa, PKCb	UniRef100_P05771, UniRef100_P17252	DLKLDNVMLDSEGHIK	Lys2	2.4	16.9	3.3	25.3
PKCe	UniRef100_Q02156	DLKLDNILLDAEGHCK	Lys2		-38.2		-7
PKCi	UniRef100_P41743	IYAMKVVK	Lys1		16.5		18.6
PKCt	UniRef100_Q04759	GSFGKVFLAEFK	ATP Loop	-5.2		23.5	
PKD2	UniRef100_Q9BZL6	DVAVKVIDK	Lys1	5.5	-11	-1.4	-4.2
PKD3	UniRef100_O94806	DVAIKVIDK	Lys1		-15.2		-9.2
PKN1	UniRef100_Q16512	VLLSEFRPSGELFAIKALK	Lys1	-3.3	-4.9	-29.4	-0.9
PKN2	UniRef100_Q16513	DLKLDNLLLDTEGFVK	Lys2		-4.5		13.6
PKR	UniRef100_P19525	DLKPSNIFLVDTK	Lys2	-3.6	-8	-17.6	-3.8
PLK1	UniRef100_P53350	CFEISDADTKEVFAGKIVPK	Lys1	0.2	2.1	-23	9.6
PRP4	UniRef100_Q13523	CNILHADIKPDNILVNESK	Lys2	5.9	-24.8	-6.2	-15.7

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
PRPK	UniRef100_Q96S44	FLSGLELVKQGAEAR	ATP Loop	2.1	-2	17.3	-1.2
PYK2	UniRef100_Q14289	YIEDEDYYKASVTR	Activation Loop	1	5.1	-12.1	-0.9
QSK	UniRef100_Q9Y2K2	DLKAENLLLDANLNIK	Lys2		-1.8		2.5
RAF1	UniRef100_P04049	DMKSNNIFLHEGLTVK	Lys2	-18.8	9.9	9.9	-9.2
RIPK3	UniRef100_Q9Y572	DLKPSNVLLDPELHVK	Lys2	13.4	-15	22	-27
ROCK1	UniRef100_Q13464	KLQLELNQER	Protein Kinase Domain	2.6	-7.3	-16.9	-2.1
ROCK1, ROCK2	UniRef100_O75116, UniRef100_Q13464	DVKPDNMLLDK	Lys2	-22.2	24.4	12.5	1.7
RSK1 domain1	UniRef100_Q15418	DLKPENILLDEEGHIKLTDFGLSKEAIDHEK	Lys2	9	-2	-16.9	-5.1
RSK1 domain1, RSK2 domain1, RSK3 domain1	UniRef100_P51812, UniRef100_Q15418, UniRef100_Q15349	DLKPENILLDEEGHIK	Lys2	-14.8	-12	-7.3	-6.1
RSK1 domain2	UniRef100_Q15418	DLKPSNILYVDESGNPECLR	Lys2	-1.9	-9.7	-20.8	-4.1
RSK2 domain1	UniRef100_P51812	DLKPENILLDEEGHIKLTDFGLSKESIDHEK	Lys2	-2	-5.6	-15.5	-8.4
RSK2 domain2	UniRef100_P51812	DLKPSNILYVDESGNPESIR	Lys2	-10.2	-9.7	-16.5	1.6
RSK3 domain1	UniRef100_Q15349	DLKPENILLDEEGHIKITDFGLSK	Lys2	7.6	-1.4	-19	-4.1
RSK4 domain1	UniRef100_Q9UK32	DLKPENILLDEIGHIK	Lys2		9.1		15.8
RSKL1	UniRef100_Q96S38	VLGVIDKVLLVMDTR	ATP	-17	13.5	-25.8	1.8
SGK3	UniRef100_Q96BR1	FYAVKVLQK	Lys1	-0.4	1.1	-18.5	-1.1
SLK	UniRef100_Q9H2G2	DLKAGNILFTLDGDIK	Lys2	13	-6	1.6	4.3
SMG1	UniRef100_Q96Q15	DTVTIHSVGGTITILPTKTKPK	ATP	0.6	-11.6	-36.7	-1
SNRK	UniRef100_Q9NRH2	DLKPENVVFFEK	Lys2	46.4	28.6	40.2	30.1
SRC	UniRef100_P12931	VAIKTLKPGTMSPEAFLQEAQVMKK	Lys1	91.7	78.6	96.7	86.1
SRPK1	UniRef100_Q96SB4	IIHTDIKPENILLSVNEQYIR	Lys2	-7.8	-4	-16.8	-0.4
SRPK1, SRPK2	UniRef100_P78362, UniRef100_Q96SB4	FVAMKVVK	Lys1	-3	10	22.3	2.5

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 µM	I-9 1 µM	I-3 1 µM	I-9 1 µM
				no GF	GF	no GF	GF
STK33	UniRef100_Q9BYT3	DLKLENIMVK	Lys2	-6.1	20.2	11.8	16.1
STLK5	UniRef100_Q7RTN6	YSVKVLPWLSPEVLQQNLQGYDAK	Activation Loop	10.4	-12.9	-17.7	-9.4
STLK6	UniRef100_Q9C0K7	HTPTGTLVTIKITNLENCNEER	Lys1		7.2		4.8
SYK	UniRef100_P43405	ISDFGLSKALR	Activation Loop	-1.2	-6.5	-1.1	-6.1
TAK1	UniRef100_O43318	DLKPPNLLLVAGGTVLK	Lys2	2.3	-1.4	-2.5	1
TAO1, TAO3	UniRef100_Q7L7X3, UniRef100_Q9H2K8	DIKAGNILLTEPGQVK	Lys2	7.8	5.1	14.3	9.3
TAO2	UniRef100_Q9UL54	DVKAGNILLSEPGLVK	Lys2	5	4.3	8	11.5
TBK1	UniRef100_Q9UHD2	TGDLFAIKVFNNISFLRPVDVQMR	Lys1	-25.1	23	-1.6	10.8
TEC	UniRef100_P42680	YVLDDQYTSSSGAKFPVK	Activation Loop	>91	97.4	>91	40.8
TLK1	UniRef100_Q9UKI8	YLNEIKPPIIHYDLKPGNILLVDGTACGEIK	Lys2	-0.7	-7.9	-6.9	-2.3
TLK2	UniRef100_Q86UE8	YLNEIKPPIIHYDLKPGNILLVNGTACGEIK	Lys2	-3	-13.3	4.7	-1.9
TYK2 domain2	UniRef100_P29597	IGDFGLAKAVPEGHEYYR	Activation Loop	-10.1	-17.7	-5.5	-16.8
ULK1	UniRef100_O75385	DLKPQNILLSNPAGR	Lys2	9.9	-5.7	-8.2	-1.7
ULK3	UniRef100_D3DW67	NISHLDLKPQNILLSSLEKPHLK	Lys2	8.2	-16.4	-47.2	-9.6
VRK2	UniRef100_Q86Y07	MLDVLEYIHENEYVHGDIKAANLLLGYK	Lys2	-13.9	6.2	5.7	-1.6
Wee1	UniRef100_P30291	YIHSMSLVHMDIKPSNIFISR	Lys2	-32.7	14.3	-6.5	8.6
Wnk1, Wnk2	UniRef100_Q9Y3S1, UniRef100_D3DUP1	GSFKTVYK	ATP Loop	13.1	-6.3	6.8	7.6
Wnk1, Wnk2, Wnk3	UniRef100_Q9Y3S1, UniRef100_D3DUP1, UniRef100_Q9BYP7	DLKCDNIFITGPTGSVK	Lys2	14.9	-10.8	-1.2	4.4
YANK3	UniRef100_Q86UX6	DVKPDNILLDER	Lys2		-8.6		-13.2
YSK1	UniRef100_O00506	EVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSPYITR	Lys1		-11.5		-20.8
ZAK	UniRef100_Q9NYL2	WISQDKEVAVKK	Lys1	1.6	-9.3	21.2	12.1

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Kinase	Reference	Sequence	Labeling Site	% change of MS signal compared to control sample			
				I-3 1 μM	I-9 1 μM	I-3 1 μM	I-9 1 μM
				no GF	GF	no GF	GF
ZC1/HGK	UniRef100_O95819	TGQLAAIKVMDV TEDEEEEIKLEINM LKK	Lys1	-14.8	20.9	-16.8	15.3
ZC1/HGK, ZC2/TNIK, ZC3/MINK	UniRef100_O95819 , UniRef100_Q9UK E5, UniRef100_Q8N4C 8	DIKGQNVLLTENA EVK	Lys2	2.7	-2	-0.1	1.8
ZC2/TNIK	UniRef100_Q9UK E5	TGQLAAIKVMDV TGDEEEEIKQEIN MLKK	Lys1	-15.6	23.4	32.9	11.4

Labeling Site Key:

- Lys1: Conserved Lysine 1;
- Lys2: Conserved Lysine 2;
- ATP Loop: ATP binding loop;
- Activation Loop: Activation loop;
- ATP: ATP site in non-canonical kinase (*e.g.* lipid kinase);
- Protein Kinase Domain: Other lysine within kinase domain, possibly not in ATP binding site; and
- Other: Labeling of residue outside of the protein kinase domain, possibly not in ATP binding site.

*Example 24. KINATIV assay of compounds **I-4, I-7, I-8,** and **II-1***

[00353] BCWM.1 cells were treated with compound **I-4, I-7, I-8,** or **II-1** (1 μM) for 90 minutes. The cells were harvested and lysed. The lysates were directly labeled with an ATP-biotin probe. Bound kinases were identified and quantitated by ACTIVX as described in Patricelli *et al.*, *Biochemistry*, **2007**, 46(2): 350-358. The compounds were tested in duplicates against duplicate or quadruplicate control samples. Exemplary results are shown in *Table 3*, where the % changes of MS signals of compounds **I-4, I-7, I-8, or II-1**, compared to the control samples, are reported. The results shown in *Table 3* were statistically significant (Student T-test score <0.04). A compound inhibited the kinase activity when a % change of the MS signal shown in *Table 3* is positive (*e.g.*, greater than 0%) or increased the kinase activity when a % change of the MS signal shown in *Table 3* is negative (*e.g.*, lower than 0%).

[00354] *Table 3*. Exemplary KINATIV assay results of compounds **I-4**, **I-7**, **I-8**, and **II-1**.

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 µM)	I-7 (1 µM)	I-8 (1 µM)	II-1 (1 µM)
ABL,ARG	91.7	>97	>97	39.5
ABL,ARG	> 90	> 90	> 90	76.1
ACK	27.0	80.7	69.9	51.7
ACK	22.8	88.5	82.4	50.8
AKT1	-11.0	-16.4	-19.5	-17.8
AMPKa1	10.1	2.7	-0.6	5.1
AMPKa1,AMPKa2	-11.0	-20.7	-29.2	-19.4
AMPKa1,AMPKa2	-40.3	-22.3	-13.2	-27.3
ATR	-66.1	-48.0	-24.9	-55.3
AurA	3.7	-15.7	-15.2	-10.8
AurA	1.7	7.2	-0.1	3.6
AurA,AurB,AurC	2.3	0.4	-2.9	-3.6
AurB	-10.1	-6.1	-14.3	-7.2
BARK1	-8.1	-29.7	-19.6	-23.3
BLK	> 95	> 95	> 95	> 95
BRAF	17.8	21.7	11.1	6.9
BTK	97.0	98.9	98.0	97.1
BTK	> 90	> 90	> 90	> 90
CaMK1d	-12.5	-19.1	-14.1	-7.9
CaMK1d	-4.0	-16.0	-8.7	-2.8
CaMK2a,CaMK2b,CaMK2d,CaMK2g	10.0	7.4	10.4	2.5
CaMK2d	-8.5	-22.5	-22.3	-14.8
CaMK2g	-19.8	-12.8	-9.4	-17.5
CaMK4	-7.1	-24.9	-26.3	-10.3
CaMKK2	-1.5	28.6	17.3	16.1
CaMKK2	-10.2	-29.6	-27.8	-18.7
CASK	23.2	37.7	43.0	29.4
CDC2	-24.9	-0.9	14.5	-5.2
CDC2	5.1	-16.2	-10.9	2.7
CDK11,CDK8	-36.1	-3.5	19.6	-9.2
CDK2	18.8	15.3	21.5	19.5
CDK2	3.5	-2.1	-4.9	-1.1
CDK4	6.8	16.7	6.1	2.2
CDK5	-7.1	-27.5	-31.8	-11.2
CDK5	-7.2	-14.0	-3.8	-8.0
CDK6	7.8	4.1	4.5	6.0
CDK7	21.6	0.7	-8.2	8.6
CDK7	16.8	22.2	20.6	22.6
CDK9	-41.9	-37.0	-5.2	-57.0
CHK1	-8.6	13.5	15.3	9.0
CHK1	24.1	27.2	24.7	29.6
CHK2	-7.9	-18.6	-14.3	-8.3
CHK2	1.0	-5.6	-10.9	10.3

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 µM)	I-7 (1 µM)	I-8 (1 µM)	II-1 (1 µM)
CK1a	-41.3	-0.7	14.9	-14.4
CK1g2	-4.5	-3.7	-6.1	-1.1
CK2a1	24.6	14.3	13.9	24.7
CK2a2	-3.6	-6.4	27.5	13.8
CLK3	-1.3	-15.7	-14.9	-22.6
CSK	35.7	76.5	88.1	26.2
CSK	35.7	75.7	86.2	32.5
DNAPK	-80.8	-155.4	-153.0	-117.2
DNAPK	-12.9	-17.6	-26.7	-17.7
eEF2K	0.3	4.9	-1.5	-3.8
EphB1	> 97	> 97	> 97	91.0
EphB2	> 90	> 90	> 90	> 90
Erk1	-10.9	-23.1	-19.7	-17.6
Erk2	-3.2	-4.7	-0.1	-5.8
Erk5	-9.0	-13.8	-11.4	-14.2
FER	-13.4	-5.8	-7.7	-10.0
FER	1.8	-5.3	-4.8	0.1
FES	-15.6	-20.9	-13.3	-15.0
FGR	87.0	94.7	86.0	87.8
FRAP	4.9	-3.5	-5.2	8.6
FRK	87.5	93.3	95.3	84.0
FYN,SRC,YES	97.4	98.4	97.9	88.1
GCK	-13.9	-12.2	2.0	-10.9
GCK	11.6	-4.1	2.4	-22.5
GCN2	-11.0	-13.3	-20.3	-6.2
GCN2	-5.7	-6.3	-13.6	-4.1
GSK3A	-10.5	-11.3	-14.2	-11.8
GSK3B	0.7	-1.9	-10.7	-5.1
HPK1	0.4	23.4	32.8	23.0
HPK1	26.6	19.8	24.6	12.1
IKKa	6.4	-3.5	-4.2	-2.1
IKKb	3.1	10.9	23.2	15.1
IKKb	4.4	-29.2	-24.5	-3.2
IKKe	2.2	0.4	-5.9	-1.0
IKKe,TBK1	-38.7	-10.7	5.5	-27.2
ILK	6.7	17.1	19.4	13.8
ILK	-19.1	28.2	36.6	-0.3
IRAK1	20.3	19.0	13.6	26.3
IRAK4	17.8	7.6	11.9	15.9
IRAK4	25.9	25.6	26.7	18.5
IRE1	-44.3	-15.7	-1.5	-29.5
ITPK1	12.8	-17.5	-16.4	14.0
JAK1	-5.7	7.5	-1.9	5.4
JAK1 domain2	-17.6	-17.9	-22.7	-19.8

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 µM)	I-7 (1 µM)	I-8 (1 µM)	II-1 (1 µM)
JAK1 domain2	-1.2	-6.4	-11.2	-2.3
JAK3 domain2	-30.8	-66.2	-109.0	-83.2
JAK3 domain2	-19.2	-32.6	-49.6	-36.2
JNK1,JNK2,JNK3	6.3	-4.8	-9.5	-23.5
KHS1	-2.1	-5.9	-8.4	-0.6
KSR1,KSR2	-8.9	-10.1	-8.8	-8.7
LATS2	-9.2	-6.6	10.6	-2.9
LCK	96.1	96.5	94.8	92.4
LKB1	-4.5	1.2	-1.8	-1.2
LOK	-4.1	-15.0	-14.7	-5.5
LOK	-27.4	2.9	19.2	-15.4
LRRK2	-5.7	-9.6	-12.2	-20.9
LYN	> 97	> 97	> 97	88.1
LYN	> 90	> 90	> 90	> 90
MAP2K1	-31.6	-3.7	1.0	-23.4
MAP2K1,MAP2K2	9.9	7.4	9.8	20.5
MAP2K1,MAP2K2	-4.8	-4.1	-2.3	-2.2
MAP2K3	-12.3	-2.9	5.7	-19.5
MAP2K3	-18.8	-14.1	-23.1	-15.9
MAP2K4	-48.8	-25.3	-8.5	-28.3
MAP2K4	-6.9	-14.5	-6.1	1.2
MAP2K5	33.0	37.6	19.2	14.8
MAP2K5	-13.3	45.7	30.9	-10.9
MAP2K6	-18.0	5.9	3.8	-8.3
MAP2K6	-10.7	2.5	-8.3	-12.6
MAP2K7	-10.1	11.2	-7.5	-0.6
MAP3K1	18.4	7.9	15.5	-1.2
MAP3K15,MAP3K5,MAP3K6	2.8	4.0	2.2	7.5
MAP3K2	12.1	4.9	3.5	21.3
MAP3K2,MAP3K3	24.8	15.6	19.4	17.1
MAP3K3	-0.7	42.8	7.9	13.7
MAP3K4	-20.5	-24.2	12.8	-23.9
MAP3K5	-10.7	-9.3	-0.7	-22.9
MAP3K6	10.9	-21.3	-8.1	18.9
MAPKAPK3	7.0	0.9	0.5	6.2
MARK1,MARK2	17.1	7.9	14.6	20.9
MARK2	3.6	7.7	12.1	15.4
MARK2,MARK3	-31.5	-11.0	7.5	-10.1
MARK3	13.5	12.7	7.8	18.4
MARK3,MARK4	19.1	20.7	5.8	17.4
MARK4	-0.5	4.9	-0.4	12.8
MARK4	12.4	14.1	1.6	9.7
MAST1,MAST2	-62.1	-35.0	-32.5	-81.3
MAST3	2.0	-1.6	-8.3	3.8

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 µM)	I-7 (1 µM)	I-8 (1 µM)	II-1 (1 µM)
MASTL	-2.9	-10.9	-16.9	-16.7
MASTL	-0.3	-13.8	-9.5	-8.2
MELK	-11.7	-11.0	-10.0	4.2
MLK3	-27.2	-4.6	11.7	-18.0
MLKL	-9.4	-6.3	-17.5	-0.8
MPSK1	-17.4	-15.5	-10.0	-4.0
MPSK1	-79.7	-39.7	-25.7	-39.6
MSK1 domain1	-15.8	-40.5	-45.5	-35.0
MSK1,MSK2 domain1	-28.9	-40.4	-29.7	-37.4
MSK2 domain1	-9.6	-45.3	-47.7	-33.9
MST1	7.0	3.0	2.4	13.2
MST1,MST2	3.8	9.5	8.7	3.1
MST2	12.3	6.5	4.3	14.7
MST3	-17.6	5.0	-1.5	5.9
MST3	5.2	-5.6	-7.7	2.0
MST4	-13.2	11.6	-0.8	21.1
MST4,YSK1	20.5	12.7	19.3	9.2
MYO3A,MYO3B	15.9	17.2	23.1	12.9
NDR1	-38.8	-18.1	-0.8	-21.2
NDR1	-4.7	4.5	2.2	3.9
NDR2	-42.0	-20.0	1.9	-11.0
NDR2	7.2	7.4	9.1	18.7
NEK1	7.3	11.4	12.8	14.9
NEK2	22.3	8.5	-3.0	-6.0
NEK3	3.5	15.6	3.2	8.1
NEK4	12.3	7.9	15.2	18.5
NEK6,NEK7	3.7	-8.4	-11.0	-0.2
NEK7	-7.7	10.0	-1.0	-8.5
NEK8	14.6	12.2	13.1	6.5
NEK9	-0.1	2.5	-1.3	-1.0
NEK9	4.4	1.1	-0.3	-0.1
NLK	6.7	4.2	6.1	3.7
OSR1	26.7	22.0	27.9	16.4
p38a	47.9	69.8	79.0	36.4
p38a	6.2	51.2	30.5	-8.7
p38b	-29.6	-1.5	12.0	-19.0
p38d,p38g	-2.7	1.7	3.3	-6.6
p70S6K	-102.3	-70.1	-36.8	-65.4
p70S6Kb	-72.4	-42.7	-22.7	-57.1
PAN3	-29.0	-0.2	18.3	-7.0
PCTAIRE1	19.0	38.2	32.9	38.4
PCTAIRE1,PCTAIRE3	12.7	14.9	19.8	11.4
PCTAIRE2	13.4	9.9	8.5	7.7
PCTAIRE2,PCTAIRE3	27.9	27.0	28.8	31.8

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 µM)	I-7 (1 µM)	I-8 (1 µM)	II-1 (1 µM)
PEK	-44.9	2.6	3.3	-31.0
PFTAIRE1	15.3	19.1	22.1	24.3
PFTAIRE1	6.3	4.8	7.3	6.0
PHKg2	-15.6	0.6	6.4	-9.1
PI4KA,PI4KAP2	-37.7	-17.4	-9.9	-45.7
PI4KB	20.0	36.0	44.2	7.2
PI4KB	16.7	35.3	41.9	13.7
PIK3C2B	-5.8	39.9	12.5	-5.8
PIK3C3	-14.1	-7.4	-2.6	-4.7
PIK3C3	-5.5	10.9	8.6	-11.6
PIK3CB	-61.3	-42.6	-10.1	-64.9
PIK3CD	-14.5	-19.1	-16.2	-9.5
PIK3CG	-46.3	-51.9	-55.4	-45.9
PIP4K2A	-8.9	-36.0	-37.8	-20.5
PIP4K2A	-21.4	-7.4	9.0	1.3
PIP4K2C	71.0	70.9	97.6	-17.6
PIP4K2C	43.0	60.1	85.7	-32.0
PIP5K3	14.5	4.3	4.2	16.3
PITSLRE	-13.6	-9.3	-16.1	-16.1
PKD1,PKD2	-4.7	-8.3	-15.3	-19.8
PKD2	12.9	10.0	8.7	12.7
PKN1	17.4	4.2	13.7	20.9
PKR	-0.1	-2.8	-8.0	-3.2
PKR	16.9	21.9	21.3	22.3
PLK1	1.9	2.7	-7.8	0.5
PLK1	17.4	16.1	12.8	-0.2
PRP4	6.9	-4.1	-10.7	6.9
PRPK	-13.6	-3.8	3.7	-5.2
PYK2	6.7	16.6	20.3	12.5
PYK2	27.3	28.4	25.5	36.6
ROCK1	6.7	6.6	4.4	12.8
RSK1 domain1	-62.2	-97.5	-108.2	-76.3
RSK1 domain1	-53.4	-75.8	-91.8	-76.3
RSK1 domain2	12.5	4.9	0.5	14.0
RSK1,RSK2,RSK3 domain1	-44.0	-58.3	-55.6	-52.0
RSK2 domain1	-90.2	-128.5	-163.6	-132.7
RSK2 domain1	-72.7	-102.7	-122.4	-100.2
RSK2 domain2	13.8	-0.3	-6.8	9.7
RSK3	16.8	12.6	2.9	22.3
RSK3 domain1	-26.9	-48.6	-62.5	-58.4
RSK4 domain1	3.5	-13.5	-8.2	-22.4
RSKL1	10.7	29.7	35.0	13.7
SGK3	4.4	10.0	6.5	8.1
SGK3	8.2	-17.5	-5.4	-3.8

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Kinase	% change of MS signal compared to control sample			
	I-4 (1 μM)	**I-7 (1 μM)**	**I-8 (1 μM)**	**II-1 (1 μM)**
SLK	-2.4	-21.1	-13.7	0.0
SLK	20.5	15.2	16.2	-3.6
SMG1	-2.4	-9.9	-8.5	3.1
SMG1	13.1	21.5	23.1	27.8
SNRK	35.3	40.7	45.1	47.8
SNRK	61.9	58.7	59.1	59.8
SRC	> 90	> 90	> 90	> 90
SRPK1	-2.1	1.2	-19.5	-4.7
SRPK1,SRPK2	-14.7	17.3	33.2	0.0
STK33	-23.0	21.1	29.8	11.0
STLK5	2.0	3.3	1.1	2.6
STLK5	-4.4	-13.9	-4.0	3.8
STLK6	7.4	-16.3	-12.9	-0.8
SYK	-2.2	-16.5	-12.5	-3.2
SYK	12.5	5.7	12.4	16.1
TAK1	27.8	14.5	9.7	25.6
TAO1,TAO3	7.6	-1.8	-8.7	-17.2
TAO2	-7.0	-18.0	-4.9	-17.9
TBK1	-34.8	-39.7	-2.9	-30.2
TEC	68.7	85.1	79.5	91.5
TEC	73.7	58.6	71.1	80.8
TLK1	2.2	1.8	-12.5	7.1
TLK1	8.2	5.5	5.7	5.7
TLK2	8.7	7.3	9.4	7.3
TYK2 domain2	-3.8	-46.4	-44.6	-19.0
ULK1	16.2	19.3	16.1	19.7
ULK3	22.5	15.5	23.7	22.4
ULK3	21.9	18.4	11.3	22.8
VRK2	-30.6	-2.3	3.6	5.2
Wnk1,Wnk2	7.8	-8.6	-16.4	-3.8
Wnk1,Wnk2,Wnk3	17.5	10.4	1.7	2.4
Wnk1,Wnk2,Wnk4	-0.5	-6.6	-16.3	-8.1
YSK1	-58.5	-19.9	-29.2	-27.4
ZC1/HGK,ZC2/TNIK,ZC3/MINK	3.3	6.2	13.6	4.2
ZC2/TNIK	48.8	-1.5	19.0	-10.0

*Example 25. Ambit KINOMESCAN™ assay of compounds **I-2** and **I-3***

[00355] Each of compounds **I-2** (1 μM) and **I-3** (1 μM) was subject to an Ambit KINOMESCAN (DISCOVERRX) assay according to the protocols described in Fabian *et al.* (*Nat. Biotechnol.* **2005**, 23(3): 329-336) and/or Davis *et al.* (*Nat. Biotechnol.* **2011**, 29(11):

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1046-1051) to determine the inhibition against a broad panel of kinases. Exemplary results are shown in *Tables 4* and *5*.

[00356] *Table 4*. Exemplary KINOMESCAN assay results of compound **I-3**.

Kinase	**ENTREZ gene symbol**	**% change compared to control**
ABL1(H396P)-phosphorylated	ABL1	0
ABL1-phosphorylated	ABL1	0
BLK	BLK	0
EPHA4	EPHA4	0
EPHB2	EPHB2	0
EPHB3	EPHB3	0
EPHB4	EPHB4	0
FGR	FGR	0
JAK3(JH1domain-catalytic)	JAK3	0
KIT	KIT	0
KIT(L576P)	KIT	0
KIT(V559D)	KIT	0
PDGFRB	PDGFRB	0
SRC	SRC	0
YES	YES1	0
ABL1(H396P)-nonphosphorylated	ABL1	0.05
BTK	BTK	0.05
ABL1(Y253F)-phosphorylated	ABL1	0.1
ABL1-nonphosphorylated	ABL1	0.1
FRK	FRK	0.1
LYN	LYN	0.1
ABL1(Q252H)-nonphosphorylated	ABL1	0.15
DDR1	DDR1	0.15
EPHB1	EPHB1	0.2
ERBB4	ERBB4	0.2
p38-alpha	MAPK14	0.2
ABL2	ABL2	0.25
ABL1(Q252H)-phosphorylated	ABL1	0.3
SIK	SIK1	0.4
EPHA8	EPHA8	0.45
MEK5	MAP2K5	0.45
ABL1(E255K)-phosphorylated	ABL1	0.5
ABL1(F317L)-nonphosphorylated	ABL1	0.5
FYN	FYN	0.5
LCK	LCK	0.55
EPHA2	EPHA2	0.6
HCK	HCK	0.6
ABL1(M351T)-phosphorylated	ABL1	0.7
TXK	TXK	0.7
EGFR(L858R)	EGFR	0.75

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Kinase	ENTREZ gene symbol	% change compared to control
EGFR(L861Q)	EGFR	0.8
ERBB2	ERBB2	0.8
ERBB3	ERBB3	0.8
EPHA5	EPHA5	0.85
ABL1(F317I)-nonphosphorylated	ABL1	1.2
EGFR(L747-E749del, A750P)	EGFR	1.4
CSK	CSK	1.6
EPHA1	EPHA1	1.6
ABL1(F317L)-phosphorylated	ABL1	2
BRAF(V600E)	BRAF	2.1
EGFR	EGFR	2.6
KIT-autoinhibited	KIT	2.6
EGFR(E746-A750del)	EGFR	2.9
CSF1R-autoinhibited	CSF1R	3.2
CSF1R	CSF1R	3.3
TEC	TEC	3.3
EGFR(L747-S752del, P753S)	EGFR	3.6
EGFR(L747-T751del,Sins)	EGFR	4.2
EGFR(S752-I759del)	EGFR	4.6
EPHB6	EPHB6	4.6
BMX	BMX	4.9
ABL1(F317I)-phosphorylated	ABL1	5.2
PDGFRA	PDGFRA	6.5
BRAF	BRAF	6.8
EGFR(G719S)	EGFR	7.6
PFCDPK1(P.falciparum)	CDPK1	8.1
DDR2	DDR2	8.4
BRK	PTK6	9.3
NLK	NLK	9.4
KIT(A829P)	KIT	10
GAK	GAK	11
SRMS	SRMS	12
EGFR(G719C)	EGFR	14
KIT(D816V)	KIT	14
KIT(D816H)	KIT	23
KIT(V559D,V654A)	KIT	25
LIMK1	LIMK1	25
STK36	STK36	25
RAF1	RAF1	26
TYK2(JH2domain-pseudokinase)	TYK2	26
RIPK2	RIPK2	31
PIK4CB	PI4KB	36
TYRO3	TYRO3	41
EGFR(L858R,T790M)	EGFR	42
TNK2	TNK2	43

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Kinase	ENTREZ gene symbol	% change compared to control
TNNI3K	TNNI3K	44
BMPR1B	BMPR1B	45
PIK3C2B	PIK3C2B	47
PKMYT1	PKMYT1	47
ADCK3	CABC1	49
EPHA3	EPHA3	49
NEK11	NEK11	49
QSK	KIAA0999	50
PAK3	PAK3	51
RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	52
EGFR(T790M)	EGFR	56
MARK3	MARK3	57
NDR2	STK38L	58
SBK1	SBK1	58
HPK1	MAP4K1	61
SGK	SGK1	61
ERK4	MAPK4	62
CAMK1	CAMK1	63
p38-beta	MAPK11	63
TRPM6	TRPM6	63
NEK6	NEK6	64
SRPK2	SRPK2	64
LIMK2	LIMK2	65
PIP5K1C	PIP5K1C	65
DMPK2	CDC42BPG	66
MINK	MINK1	66
TAOK2	TAOK2	67
BUB1	BUB1	68
PRKR	EIF2AK2	69
ABL1(T315I)-phosphorylated	ABL1	70
CSNK2A2	CSNK2A2	70
VRK2	VRK2	70
AURKC	AURKC	71
STK39	STK39	71
PIM2	PIM2	72
DYRK1B	DYRK1B	74
DYRK2	DYRK2	74
NDR1	STK38	74
CDK9	CDK9	75
ROCK2	ROCK2	75
ACVRL1	ACVRL1	76
ALK(L1196M)	ALK	76
AXL	AXL	76
ERN1	ERN1	76
PLK2	PLK2	76

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Kinase	ENTREZ gene symbol	% change compared to control
SGK2	SGK2	76
RIOK2	RIOK2	77
AMPK-alpha2	PRKAA2	78
CDC2L1	CDK11B	78
CDKL2	CDKL2	78
TTK	TTK	78
AURKA	AURKA	80
DAPK2	DAPK2	80
MAP3K1	MAP3K1	80
MARK2	MARK2	80
MARK4	MARK4	80
AKT3	AKT3	81
CAMK2B	CAMK2B	81
CDKL3	CDKL3	81
CTK	MATK	81
JNK1	MAPK8	81
PCTK2	CDK17	81
PKN1	PKN1	81
PRKD3	PRKD3	81
SYK	SYK	81
ACVR2A	ACVR2A	82
JAK2(JH1domain-catalytic)	JAK2	82
MELK	MELK	82
PLK4	PLK4	82
RIOK1	RIOK1	82
ALK	ALK	83
CAMK2A	CAMK2A	83
CDK11	CDK19	83
HUNK	HUNK	83
PLK1	PLK1	83
ALK(C1156Y)	ALK	84
CAMK4	CAMK4	84
CHEK1	CHEK1	84
DAPK3	DAPK3	84
DCAMKL1	DCLK1	84
FLT3	FLT3	84
NIK	MAP3K14	84
NIM1	MGC42105	84
PAK6	PAK6	84
YANK1	STK32A	84
CLK4	CLK4	85
MKK7	MAP2K7	85
MLK3	MAP3K11	85
NEK1	NEK1	85
PIK3CD	PIK3CD	85

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Kinase	ENTREZ gene symbol	% change compared to control
PKAC-alpha	PRKACA	85
FLT1	FLT1	86
IKK-beta	IKBKB	86
MYO3B	MYO3B	86
RET	RET	86
RIPK5	DSTYK	86
ULK1	ULK1	86
ICK	ICK	87
NEK5	NEK5	87
PDPK1	PDPK1	87
YSK1	STK25	87
CIT	CIT	88
FGFR2	FGFR2	88
HASPIN	GSG2	88
LZK	MAP3K13	88
MRCKA	CDC42BPA	88
PRKCH	PRKCH	88
RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	88
TESK1	TESK1	88
ERK3	MAPK6	89
MEK6	MAP2K6	89
PIK3CA(I800L)	PIK3CA	89
PIM3	PIM3	89
ROCK1	ROCK1	89
RSK3(Kin.Dom.1-N-terminal)	RPS6KA2	89
STK16	STK16	89
BIKE	BMP2K	90
CAMK1D	CAMK1D	90
ERK5	MAPK7	90
JNK2	MAPK9	90
NEK10	NEK10	90
PRKCI	PRKCI	90
RIOK3	RIOK3	90
ROS1	ROS1	90
TAK1	MAP3K7	90
ASK1	MAP3K5	91
JNK3	MAPK10	91
MAP4K2	MAP4K2	91
PIP5K1A	PIP5K1A	91
PKNB(M.tuberculosis)	pknB	91
PRKG2	PRKG2	91
RSK1(Kin.Dom.1-N-terminal)	RPS6KA1	91
TAOK3	TAOK3	91
TYK2(JH1domain-catalytic)	TYK2	91
ULK2	ULK2	91

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Kinase	ENTREZ gene symbol	% change compared to control
YANK3	STK32C	91
ADCK4	ADCK4	92
BMPR1A	BMPR1A	92
CAMK2D	CAMK2D	92
DCAMKL3	DCLK3	92
LATS2	LATS2	92
MET(Y1235D)	MET	92
MLK1	MAP3K9	92
PCTK3	CDK18	92
SNRK	SNRK	92
TRKB	NTRK2	92
CDC2L2	CDC2L2	93
CDKL1	CDKL1	93
CSNK1G2	CSNK1G2	93
DCAMKL2	DCLK2	93
FES	FES	93
FGFR1	FGFR1	93
INSR	INSR	93
IRAK1	IRAK1	93
IRAK3	IRAK3	93
LATS1	LATS1	93
MARK1	MARK1	93
MAST1	MAST1	93
MYLK	MYLK	93
PAK2	PAK2	93
TNIK	TNIK	93
CDK7	CDK7	94
MAP3K3	MAP3K3	94
MET	MET	94
MST2	STK3	94
PHKG2	PHKG2	94
PRKD1	PRKD1	94
SLK	SLK	94
TBK1	TBK1	94
TLK2	TLK2	94
ZAK	ZAK	94
ACVR2B	ACVR2B	95
AKT1	AKT1	95
BRSK2	BRSK2	95
CDK4-cyclinD3	CDK4	95
CLK3	CLK3	95
CSNK1A1L	CSNK1A1L	95
CSNK1G3	CSNK1G3	95
ERK1	MAPK3	95
HIPK1	HIPK1	95

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Kinase	ENTREZ gene symbol	% change compared to control
MAP3K4	MAP3K4	95
MLK2	MAP3K10	95
NEK3	NEK3	95
PAK1	PAK1	95
PFTAIRE2	CDK15	95
PIM1	PIM1	95
PRKCD	PRKCD	95
SgK110	SgK110	95
WNK1	WNK1	95
CLK2	CLK2	96
CSNK1E	CSNK1E	96
GRK7	GRK7	96
IRAK4	IRAK4	96
MAP4K4	MAP4K4	96
MAP4K5	MAP4K5	96
MYO3A	MYO3A	96
NEK2	NEK2	96
PIK3CA(H1047Y)	PIK3CA	96
SRPK1	SRPK1	96
STK33	STK33	96
TRKC	NTRK3	96
YANK2	STK32B	96
CAMK1G	CAMK1G	97
CAMK2G	CAMK2G	97
CAMKK1	CAMKK1	97
CHEK2	CHEK2	97
EIF2AK1	EIF2AK1	97
GRK1	GRK1	97
GSK3A	GSK3A	97
HIPK4	HIPK4	97
LOK	STK10	97
MST1	STK4	97
PAK7	PAK7	97
PIK3C2G	PIK3C2G	97
PLK3	PLK3	97
RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	97
RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	97
RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	97
S6K1	RPS6KB1	97
SRPK3	SRPK3	97
TGFBR1	TGFBR1	97
WEE2	WEE2	97
AMPK-alpha1	PRKAA1	98
ASK2	MAP3K6	98
CASK	CASK	98

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Kinase	ENTREZ gene symbol	% change compared to control
CDK8	CDK8	98
CSNK2A1	CSNK2A1	98
DMPK	DMPK	98
FLT3(ITD)	FLT3	98
ITK	ITK	98
MAP3K2	MAP3K2	98
MKNK2	MKNK2	98
NEK7	NEK7	98
OSR1	OXSR1	98
PRKCQ	PRKCQ	98
SIK2	SIK2	98
TAOK1	TAOK1	98
ULK3	ULK3	98
CDK4-cyclinD1	CDK4	99
CSNK1D	CSNK1D	99
ERK8	MAPK15	99
FER	FER	99
FGFR3(G697C)	FGFR3	99
LRRK2(G2019S)	LRRK2	99
PFTK1	CDK14	99
PHKG1	PHKG1	99
PIK3CA(C420R)	PIK3CA	99
RET(M918T)	RET	99
TRKA	NTRK1	99
AAK1	AAK1	100
ABL1(T315I)-nonphosphorylated	ABL1	100
ACVR1	ACVR1	100
ACVR1B	ACVR1B	100
AKT2	AKT2	100
ANKK1	ANKK1	100
ARK5	NUAK1	100
AURKB	AURKB	100
BMPR2	BMPR2	100
BRSK1	BRSK1	100
CAMKK2	CAMKK2	100
CDC2L5	CDK13	100
CDK2	CDK2	100
CDK3	CDK3	100
CDK5	CDK5	100
CDKL5	CDKL5	100
CLK1	CLK1	100
CSNK1A1	CSNK1A1	100
CSNK1G1	CSNK1G1	100
DAPK1	DAPK1	100
DLK	MAP3K12	100

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Kinase	ENTREZ gene symbol	% change compared to control
DRAK1	STK17A	100
DRAK2	STK17B	100
DYRK1A	DYRK1A	100
EPHA6	EPHA6	100
EPHA7	EPHA7	100
ERK2	MAPK1	100
FAK	PTK2	100
FGFR3	FGFR3	100
FGFR4	FGFR4	100
FLT3(D835H)	FLT3	100
FLT3(D835Y)	FLT3	100
FLT3(K663Q)	FLT3	100
FLT3(N841I)	FLT3	100
FLT3(R834Q)	FLT3	100
FLT3-autoinhibited	FLT3	100
FLT4	FLT4	100
GCN2(Kin.Dom.2,S808G)	EIF2AK4	100
GRK4	GRK4	100
GSK3B	GSK3B	100
HIPK2	HIPK2	100
HIPK3	HIPK3	100
IGF1R	IGF1R	100
IKK-alpha	CHUK	100
IKK-epsilon	IKBKE	100
INSRR	INSRR	100
JAK1(JH1domain-catalytic)	JAK1	100
JAK1(JH2domain-pseudokinase)	JAK1	100
KIT(V559D,T670I)	KIT	100
LKB1	STK11	100
LRRK2	LRRK2	100
LTK	LTK	100
MAK	MAK	100
MAP3K15	MAP3K15	100
MAP4K3	MAP4K3	100
MAPKAPK2	MAPKAPK2	100
MAPKAPK5	MAPKAPK5	100
MEK1	MAP2K1	100
MEK2	MAP2K2	100
MEK3	MAP2K3	100
MEK4	MAP2K4	100
MERTK	MERTK	100
MET(M1250T)	MET	100
MKNK1	MKNK1	100
MLCK	MYLK3	100
MRCKB	CDC42BPB	100

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Kinase	ENTREZ gene symbol	% change compared to control
MST1R	MST1R	100
MST3	STK24	100
MST4	MST4	100
MTOR	MTOR	100
MUSK	MUSK	100
MYLK2	MYLK2	100
MYLK4	MYLK4	100
NEK4	NEK4	100
NEK9	NEK9	100
p38-delta	MAPK13	100
p38-gamma	MAPK12	100
PAK4	PAK4	100
PCTK1	CDK16	100
PFPK5(P.falciparum)	MAL13P1.279	100
PIK3CA	PIK3CA	100
PIK3CA(E542K)	PIK3CA	100
PIK3CA(E545A)	PIK3CA	100
PIK3CA(E545K)	PIK3CA	100
PIK3CA(H1047L)	PIK3CA	100
PIK3CA(M1043I)	PIK3CA	100
PIK3CA(Q546K)	PIK3CA	100
PIK3CB	PIK3CB	100
PIK3CG	PIK3CG	100
PIP5K2B	PIP4K2B	100
PIP5K2C	PIP4K2C	100
PKAC-beta	PRKACB	100
PKN2	PKN2	100
PRKCE	PRKCE	100
PRKD2	PRKD2	100
PRKG1	PRKG1	100
PRKX	PRKX	100
PRP4	PRPF4B	100
PYK2	PTK2B	100
RET(V804L)	RET	100
RET(V804M)	RET	100
RIPK1	RIPK1	100
RIPK4	RIPK4	100
RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	100
RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	100
RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	100
RSK2(Kin.Dom.2-C-terminal)	RPS6KA3	100
RSK4(Kin.Dom.1-N-terminal)	RPS6KA6	100
SGK3	SGK3	100
SNARK	NUAK2	100
STK35	STK35	100

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Kinase	ENTREZ gene symbol	% change compared to control
TGFBR2	TGFBR2	100
TIE1	TIE1	100
TIE2	TEK	100
TLK1	TLK1	100
TNK1	TNK1	100
TSSK1B	TSSK1B	100
VEGFR2	KDR	100
WEE1	WEE1	100
WNK3	WNK3	100
YSK4	YSK4	100
ZAP70	ZAP70	100

[00357] *Table 5*. Exemplary KINOMESCAN assay results of compound **I-2**.

Kinase	% change compared to control
ABL1(F317L)-nonphosphorylated	0
ABL1(H396P)-nonphosphorylated	0
ABL1(H396P)-phosphorylated	0
ABL1-phosphorylated	0
BLK	0
BTK	0
EPHA4	0
EPHB2	0
EPHB3	0
EPHB4	0
JAK3(JH1domain-catalytic)	0
KIT	0
KIT(L576P)	0
KIT(V559D)	0
LYN	0
PDGFRB	0
SRC	0
YES	0
ABL1-nonphosphorylated	0.05
ABL1(Y253F)-phosphorylated	0.1
ERBB3	0.1
FGR	0.1
FRK	0.1
p38-alpha	0.1
ABL1(F317I)-nonphosphorylated	0.15
DDR1	0.2
EPHA2	0.2
ABL1(Q252H)-phosphorylated	0.25

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Kinase	% change compared to control
MEK5	0.25
ABL1(Q252H)-nonphosphorylated	0.3
ABL2	0.3
FYN	0.3
EPHB1	0.35
ABL1(E255K)-phosphorylated	0.45
ABL1(F317L)-phosphorylated	0.5
EPHA1	0.5
ABL1(M351T)-phosphorylated	0.6
ERBB4	0.6
TXK	0.6
LCK	0.65
EPHA8	0.75
SIK	0.8
HCK	0.9
EPHA5	0.95
EGFR(L861Q)	1.3
CSF1R-autoinhibited	1.4
BRAF(V600E)	1.6
BRK	1.6
CSK	1.6
KIT(D816V)	1.7
KIT-autoinhibited	1.8
EGFR(L747-T751del,Sins)	2
EGFR(L858R)	2
EGFR(L747-E749del, A750P)	2.2
CSF1R	2.6
STK36	3.5
BMX	3.6
EGFR(L747-S752del, P753S)	3.6
TEC	3.6
EGFR(E746-A750del)	3.7
BRAF	4.4
PDGFRA	4.5
ABL1(F317I)-phosphorylated	5.4
EGFR	5.6
KIT(A829P)	5.8
KIT(V559D,V654A)	7.2
ERBB2	7.5
SRMS	7.6
EPHB6	7.7
DDR2	8.6
ADCK3	9.2
BMPR1B	10
GAK	11

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Kinase	% change compared to control
NLK	11
KIT(D816H)	14
RIPK2	14
TNNI3K	16
EGFR(G719S)	17
EGFR(S752-I759del)	17
EGFR(G719C)	23
PFCDPK1(P.falciparum)	24
RAF1	26
TYK2(JH2domain-pseudokinase)	28
TNK2	31
QSK	36
TYRO3	41
EPHA3	47
EGFR(L858R,T790M)	48
EGFR(T790M)	48
TGFBR1	50
DMPK2	51
HPK1	51
LIMK2	51
LIMK1	52
ACVRL1	54
SBK1	54
SGK	56
CSNK2A2	57
PKMYT1	59
SgK110	59
TESK1	60
TRPM6	61
p38-beta	62
NDR1	63
JAK2(JH1domain-catalytic)	65
MRCKA	65
TAOK2	65
CTK	67
INSR	67
MEK1	67
ACVR1B	68
ABL1(T315I)-phosphorylated	69
MST2	69
MAP3K1	70
MINK	71
ALK(L1196M)	72
PFTK1	72
SGK2	72

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Kinase	% change compared to control
AURKA	73
CDK3	73
FGFR2	73
PKNB(M.tuberculosis)	73
PLK4	73
RSK1(Kin.Dom.1-N-terminal)	73
TSSK1B	73
ACVR1	74
IKK-beta	75
PAK3	75
ACVR2A	76
IRAK4	76
PIK3CA(I800L)	76
ACVR2B	78
MEK2	78
MAP3K3	79
PIK3CD	79
ULK1	79
OSR1	81
PRKD3	81
TAOK3	81
MAP4K5	82
MEK6	82
ERN1	83
MAP3K4	83
NEK11	83
PIK3CA(Q546K)	83
YANK3	83
CAMK2B	84
CSNK1E	84
IRAK1	84
MELK	84
PIK3CA(H1047L)	84
PIM2	84
PKN2	84
BUB1	85
GCN2(Kin.Dom.2,S808G)	85
MYLK	85
PKAC-alpha	85
YSK1	85
CAMK2A	86
DAPK2	86
ICK	86
PIK3C2B	86
STK33	86

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Kinase	% change compared to control
SYK	86
DCAMKL1	87
MAP4K2	87
ZAK	87
AKT2	88
CDC2L1	88
CDKL2	88
CHEK1	88
DYRK2	88
MKK7	88
NEK1	88
ROCK1	88
CAMK1G	89
DAPK3	89
MLK1	89
MRCKB	89
PRKR	89
TBK1	89
TYK2(JH1domain-catalytic)	89
ULK2	89
AKT3	90
AURKC	90
CDK9	90
CSNK2A1	90
ERK4	90
MERTK	90
RIOK1	90
CAMK1	91
CAMK2D	91
CAMK2G	91
ERK5	91
FGFR1	91
MARK4	91
NIK	91
SRPK1	91
AMPK-alpha2	92
ASK2	92
CDC2L2	92
CLK1	92
FLT3(ITD)	92
MAP3K15	92
PAK2	92
PIK3C2G	92
PIK3CA(E542K)	92
PIP5K1A	92

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Kinase	% change compared to control
PKAC-beta	92
PLK1	92
PLK2	92
RET(M918T)	92
RIOK2	92
SIK2	92
SRPK2	92
STK39	92
CDK8	93
FLT1	93
HIPK1	93
IKK-alpha	93
IRAK3	93
MYO3A	93
MYO3B	93
NEK10	93
NIM1	93
PAK6	93
PRKD1	93
RSK3(Kin.Dom.1-N-terminal)	93
TAOK1	93
WEE1	93
ALK(C1156Y)	94
ANKK1	94
CDK4-cyclinD3	94
CDK7	94
CLK4	94
DYRK1B	94
GRK1	94
JNK1	94
LRRK2	94
MARK3	94
NEK3	94
PIK3CA(E545K)	94
PRKCI	94
PRKCQ	94
RPS6KA5(Kin.Dom.2-C-terminal)	94
TGFBR2	94
TRKB	94
VRK2	94
ABL1(T315I)-nonphosphorylated	95
ADCK4	95
AKT1	95
FLT4	95
HIPK3	95

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Kinase	% change compared to control
MET(Y1235D)	95
PRP4	95
RIPK4	95
ROCK2	95
RSK2(Kin.Dom.1-N-terminal)	95
TAK1	95
ASK1	96
AURKB	96
AXL	96
CAMK4	96
CDK4-cyclinD1	96
CSNK1G3	96
FLT3(K663Q)	96
INSRR	96
LOK	96
MAP3K2	96
MAP4K4	96
NDR2	96
NEK5	96
PAK7	96
PHKG2	96
PIK3CA(M1043I)	96
PRKCD	96
RPS6KA4(Kin.Dom.2-C-terminal)	96
SLK	96
AAK1	97
ALK	97
CAMKK2	97
CHEK2	97
CSNK1G2	97
DCAMKL3	97
ERK1	97
ERK8	97
FLT3(D835Y)	97
GRK7	97
HIPK2	97
JNK3	97
LZK	97
MARK1	97
MET	97
PCTK1	97
PIM1	97
PIM3	97
PRKCH	97
ROS1	97

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Kinase	% change compared to control
TLK2	97
TNIK	97
ULK3	97
CDK11	98
CDKL3	98
DCAMKL2	98
DLK	98
DMPK	98
FES	98
MAST1	98
MUSK	98
MYLK4	98
PDPK1	98
PIP5K2B	98
RET(V804L)	98
RIOK3	98
RPS6KA5(Kin.Dom.1-N-terminal)	98
TRKA	98
ARK5	99
FGFR3	99
MEK3	99
MST1R	99
PCTK3	99
PIP5K1C	99
PLK3	99
PRKG2	99
STK16	99
STK35	99
TRKC	99
ZAP70	99
AMPK-alpha1	100
BIKE	100
BMPR1A	100
BMPR2	100
BRSK1	100
BRSK2	100
CAMK1D	100
CAMKK1	100
CASK	100
CDC2L5	100
CDK2	100
CDK5	100
CDKL1	100
CDKL5	100
CIT	100

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Kinase	% change compared to control
CLK2	100
CLK3	100
CSNK1A1	100
CSNK1A1L	100
CSNK1D	100
CSNK1G1	100
DAPK1	100
DRAK1	100
DRAK2	100
DYRK1A	100
EIF2AK1	100
EPHA6	100
EPHA7	100
ERK2	100
ERK3	100
FAK	100
FER	100
FGFR3(G697C)	100
FGFR4	100
FLT3	100
FLT3(D835H)	100
FLT3(N841I)	100
FLT3(R834Q)	100
FLT3-autoinhibited	100
GRK4	100
GSK3A	100
GSK3B	100
HASPIN	100
HIPK4	100
HUNK	100
IGF1R	100
IKK-epsilon	100
ITK	100
JAK1(JH1domain-catalytic)	100
JAK1(JH2domain-pseudokinase)	100
JNK2	100
KIT(V559D,T670I)	100
LATS1	100
LATS2	100
LKB1	100
LRRK2(G2019S)	100
LTK	100
MAK	100
MAP4K3	100
MAPKAPK2	100

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Kinase	% change compared to control
MAPKAPK5	100
MARK2	100
MEK4	100
MET(M1250T)	100
MKNK1	100
MKNK2	100
MLCK	100
MLK2	100
MLK3	100
MST1	100
MST3	100
MST4	100
MTOR	100
MYLK2	100
NEK2	100
NEK4	100
NEK6	100
NEK7	100
NEK9	100
p38-delta	100
p38-gamma	100
PAK1	100
PAK4	100
PCTK2	100
PFPK5(P.falciparum)	100
PFTAIRE2	100
PHKG1	100
PIK3CA	100
PIK3CA(C420R)	100
PIK3CA(E545A)	100
PIK3CA(H1047Y)	100
PIK3CB	100
PIK3CG	100
PIK4CB	100
PIP5K2C	100
PKN1	100
PRKCE	100
PRKD2	100
PRKG1	100
PRKX	100
PYK2	100
RET	100
RET(V804M)	100
RIPK1	100
RIPK5	100

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Kinase	% change compared to control
RPS6KA4(Kin.Dom.1-N-terminal)	100
RSK1(Kin.Dom.2-C-terminal)	100
RSK2(Kin.Dom.2-C-terminal)	100
RSK3(Kin.Dom.2-C-terminal)	100
RSK4(Kin.Dom.1-N-terminal)	100
RSK4(Kin.Dom.2-C-terminal)	100
S6K1	100
SGK3	100
SNARK	100
SNRK	100
SRPK3	100
TIE1	100
TIE2	100
TLK1	100
TNK1	100
TTK	100
VEGFR2	100
WEE2	100
WNK1	100
WNK3	100
YANK1	100
YANK2	100
YSK4	100

EQUIVALENTS AND SCOPE

[00358] 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.

[00359] 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

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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 it 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.

[00360] This application refers to various issued patents, published patent applications, journal articles, and other publications. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00361] 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.

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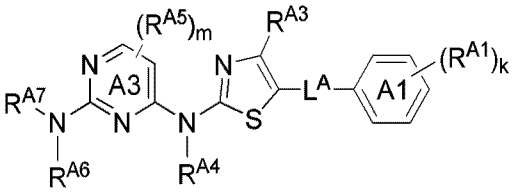
What is claimed is:

1. A compound of Formula (**I**):



(**I**),

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein:

each instance of R^{A1} 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 $–OC(=O)N(R^a)_2$;

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, or 5;

L^A is $–C(=O)–NR^{A2}–$ or $–NR^{A2}–C(=O)–$, wherein R^{A2} is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

R^{A3} 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, $–C(=NR^a)R^a$, $–C(=NR^a)OR^a$, $–C(=NR^a)N(R^a)_2$, –

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$C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, $-NO_2$, $-NR^aC(=O)R^a$, $-NR^aC(=O)OR^a$, $-NR^aC(=O)N(R^a)_2$, $-OC(=O)R^a$, $-OC(=O)OR^a$, or $-OC(=O)N(R^a)_2$;

R^{A4} is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

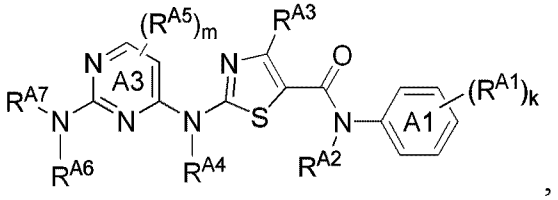
each instance of R^{A5} is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted 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 $-OC(=O)N(R^a)_2$;

m is 0, 1, or 2;

R^{A6} is hydrogen or substituted or unsubstituted, C_{1-6} alkyl; and

R^{A7} is substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl, $-C(=O)R^a$, $-C(=O)OR^a$, or $-C(=O)N(R^a)_2$.

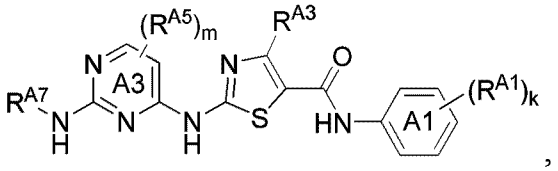
2. The compound of claim 1, wherein the compound is of the formula:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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

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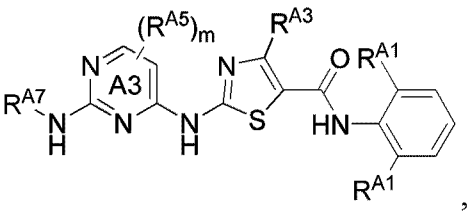
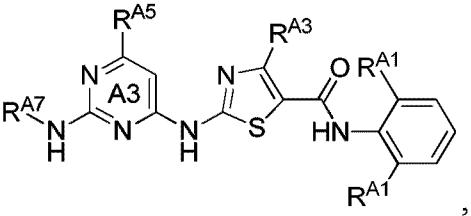


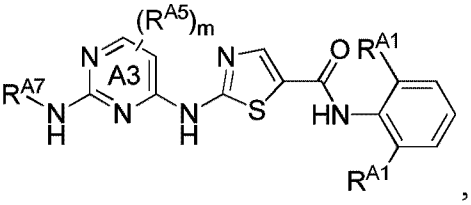
or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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

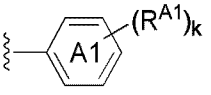
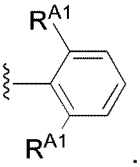


or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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



or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein  is  .

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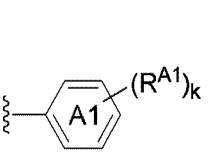
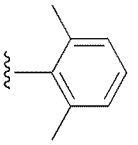
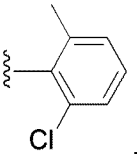
8. The compound of claim 7, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein  is  or  .

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A1} is substituted or unsubstituted alkyl.

10. The compound of claim 9, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A1} is substituted or unsubstituted, C_{1-6} alkyl.

11. The compound of claim 9, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A1} is $–CH_3$.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A1} is halogen.

13. The compound of any one of claims 1-3 and 9-12, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein k is 2.

14. The compound of any one of claims 1 and 7-13, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein L^A is –C(=O)–NH–.

15. The compound of any one of claims 1 and 7-13, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein L^A is $–NR^{A2}–C(=O)–$.

16. The compound of claim 15, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein L^A is –NH–C(=O)–.

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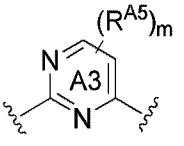
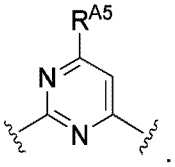
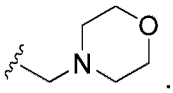
17. The compound of any one of claims 1-5 and 7-16, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A3} is hydrogen.

18. The compound of any one of claims 1, 2, and 7-17, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A4} is hydrogen.

19. The compound of any one of claims 1-4 and 6-18, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein  is  .

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A5} is substituted or unsubstituted alkyl.

21. The compound of claim 20, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A5} is substituted or unsubstituted, C_{1-6} alkyl.

22. The compound of claim 20, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein at least one instance of R^{A5} is of the formula:  .

23. The compound of any one of claims 1-4 and 6-22, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein m is 1.

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24. The compound of any one of claims 1-4 and 6-18, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein m is 0.

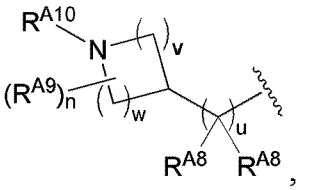
25. The compound of any one of claims 1-2 and 7-24, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A6} is hydrogen.

26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is substituted or unsubstituted alkyl.

27. The compound of claim 26, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is substituted or unsubstituted, C_{1-6} alkyl.

28. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is substituted or unsubstituted, 3- to 9-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms of the heterocyclic ring system are independently nitrogen, oxygen, or sulfur.

29. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



wherein:

each instance of R^{A8} is independently hydrogen, halogen, or substituted or unsubstituted, C_{1-6} alkyl;

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

v is 1, 2, 3, or 4;

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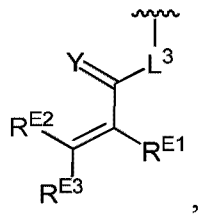
w is 1, 2, or 3;

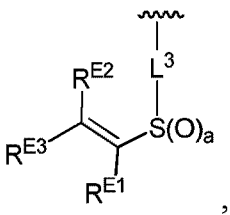
each instance of R^{A9} is independently halogen, or substituted or unsubstituted, C_{1-6} alkyl;

n is an integer between 0 and 13, inclusive; and

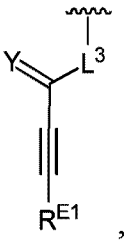
R^{A10} is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, substituted or unsubstituted, C_{2-6} alkenyl, substituted or unsubstituted, C_{2-6} alkynyl, substituted or unsubstituted carbocyclyl, $-C(=O)R^a$, $-C(=O)OR^a$, $-C(=O)N(R^a)_2$, a nitrogen protecting group, or of any one of Formulae **(ii-1)** to **(ii-42)**:



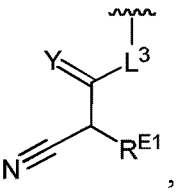
(ii-1)



(ii-2)

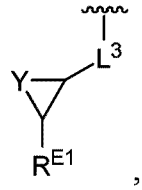


(ii-3)

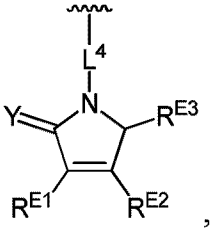


(ii-4)

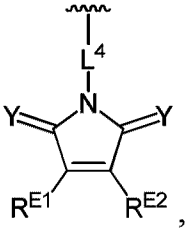
(ii-5)



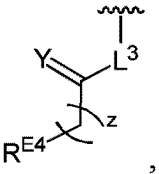
(ii-6)



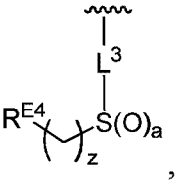
(ii-7)



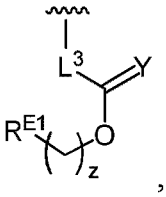
(ii-8)



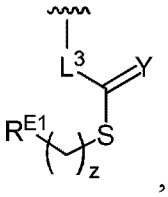
(ii-9)



(ii-10)



(ii-11)



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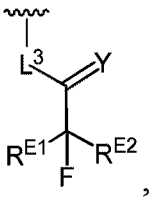
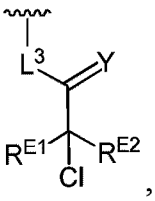
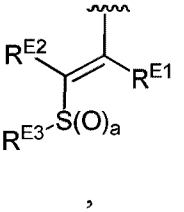


(ii-13)



(ii-14)



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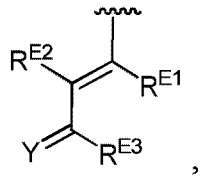
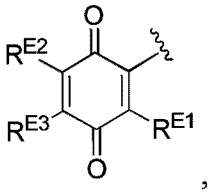
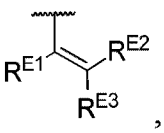


(ii-16)

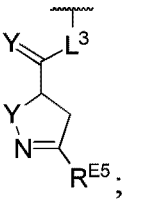


(ii-17)



(ii-18)

(ii-19)



(ii-20);

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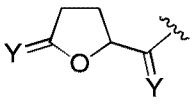
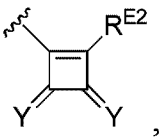


(ii-21)



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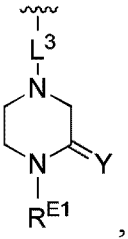

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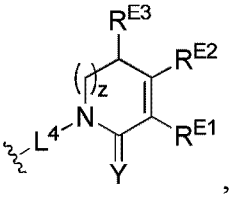

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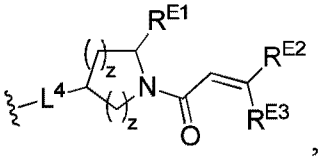
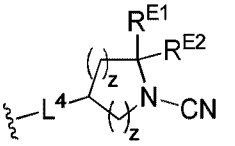


(ii-25)



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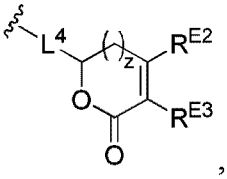

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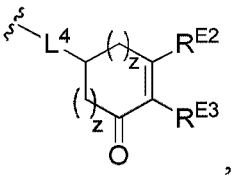

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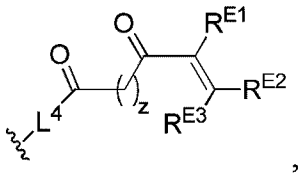

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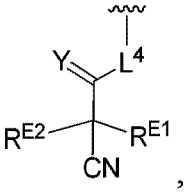

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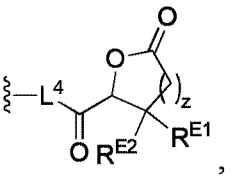

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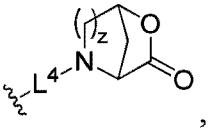

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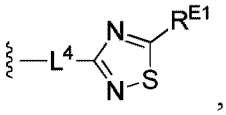

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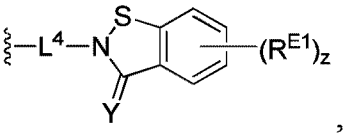

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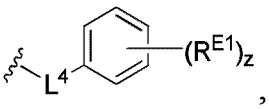

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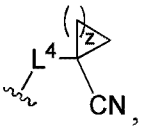

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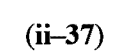

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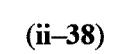

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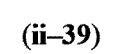
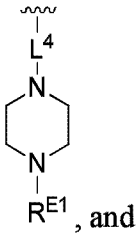
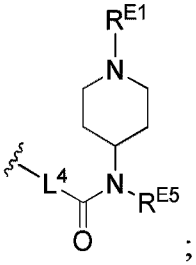


(ii-39)

(ii-40)



(ii-41), and



(ii-42);

wherein:

L^3 is a bond or an optionally substituted C_{1-4} hydrocarbon chain, optionally wherein one or more carbon units of the hydrocarbon chain are independently replaced with –O–, –S–, –NR^{L3a}–, –$NR^{L3a}C(=O)$–, –$C(=O)NR^{L3a}$–, –SC(=O)–, –C(=O)S–, –OC(=O)–, –C(=O)O–, –

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$NR^{L3a}C(=S)–$, $–C(=S)NR^{L3a}–$, *trans*–$CR^{L3b}=CR^{L3b}–$, *cis*–$CR^{L3b}=CR^{L3b}–$, $–C\equiv C–$, $–S(=O)–$, $–S(=O)O–$, $–OS(=O)–$, $–S(=O)NR^{L3a}–$, $–NR^{L3a}S(=O)–$, $–S(=O)_2–$, $–S(=O)_2O–$, $–OS(=O)_2–$, $–S(=O)_2NR^{L3a}–$, or $–NR^{L3a}S(=O)_2–$, wherein R^{L3a} is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group, and wherein each occurrence of R^{L3b} is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{L3b} groups are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

L^4 is a bond or an optionally substituted C_{1-4} hydrocarbon chain;

R^{E1} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E1a}$, $–CH_2N(R^{E1a})_2$, $–CH_2SR^{E1a}$, $–OR^{E1a}$, $–N(R^{E1a})_2$, $–Si(R^{E1a})_3$, and $–SR^{E1a}$, wherein each occurrence of R^{E1a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E2} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–CH_2OR^{E2a}$, $–CH_2N(R^{E2a})_2$, $–CH_2SR^{E2a}$, $–OR^{E2a}$, $–N(R^{E2a})_2$, and $–SR^{E2a}$, wherein each occurrence of R^{E2a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{E3} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally

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substituted heteroaryl, –CN, $–CH_2OR^{E3a}$, $–CH_2N(R^{E3a})_2$, $–CH_2SR^{E3a}$, $–OR^{E3a}$, $–N(R^{E3a})_2$, and $–SR^{E3a}$, wherein each occurrence of R^{E3a} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^{E3a} groups are joined to form an optionally substituted heterocyclic ring;

or R^{E1} and R^{E3}, or R^{E2} and R^{E3}, or R^{E1} and R^{E2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{E4} is a leaving group;

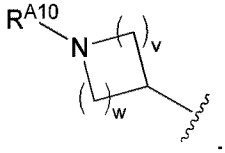
R^{E5} is halogen;

Y is O, S, or NR^{E6}, wherein R^{E6} is hydrogen, substituted or unsubstituted, C_{1-6} alkyl, or a nitrogen protecting group;

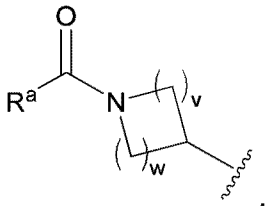
a is 1 or 2; and

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

30. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



31. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



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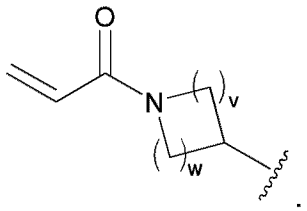
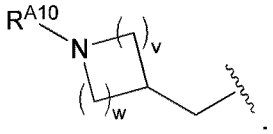
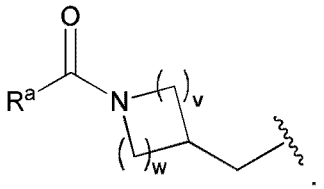
32. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



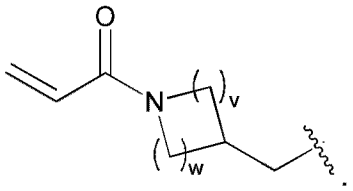
33. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



34. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



35. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A7} is of the formula:



36. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A10} is of Formula (**ii-1**).

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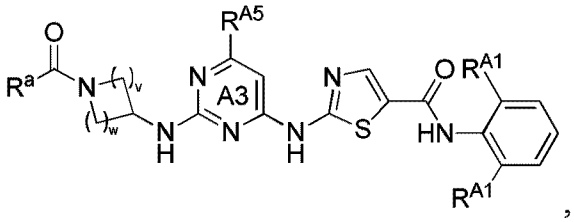
37. The compound of claim 29, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^{A10} is of Formula (**ii-3**).

38. The compound of claim 29, wherein the compound is of the formula:



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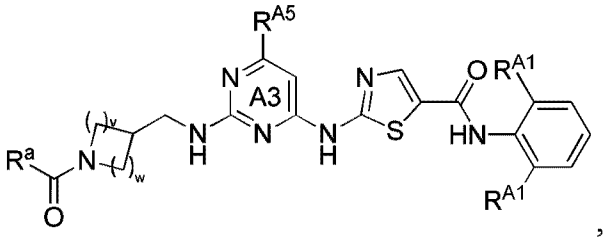
or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^a is substituted or unsubstituted, C_{1-6} alkyl or substituted or unsubstituted, C_{2-6} alkenyl.

39. The compound of claim 29, wherein the compound is of the formula:



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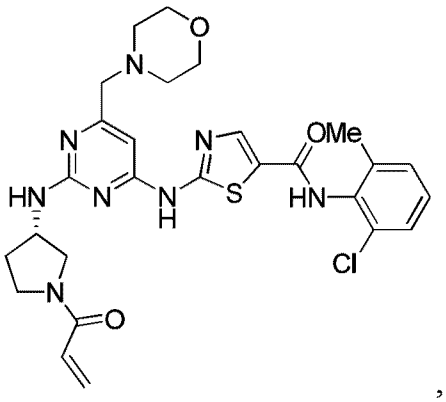
or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, wherein R^a is substituted or unsubstituted, C_{1-6} alkyl or substituted or unsubstituted, C_{2-6} alkenyl.

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



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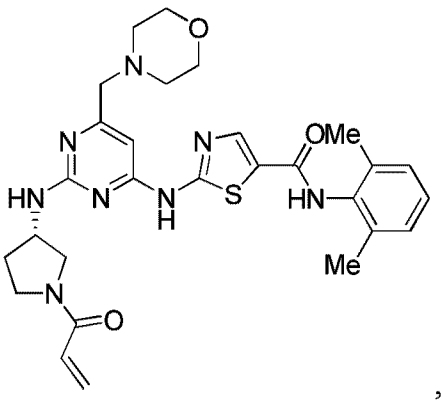

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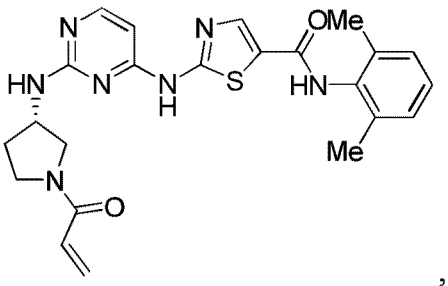
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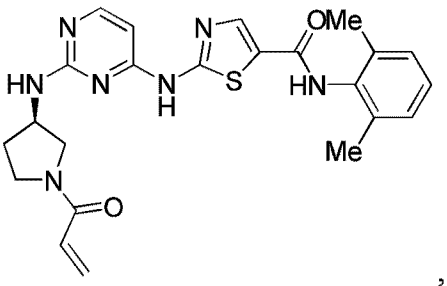
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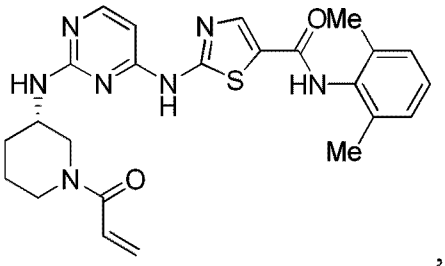
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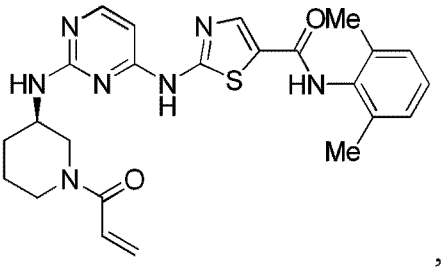
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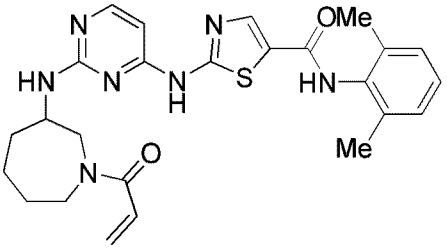
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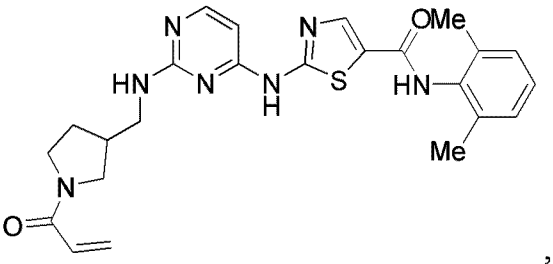
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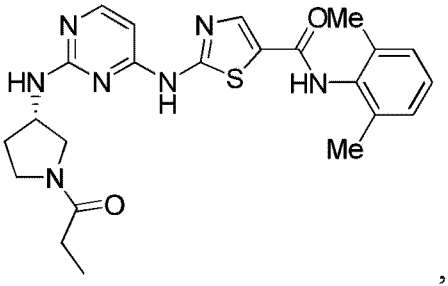
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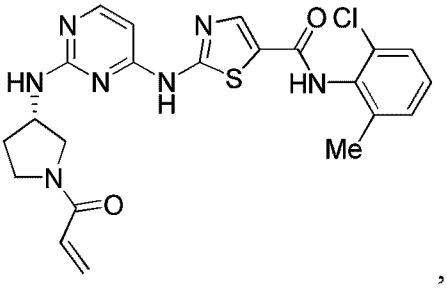
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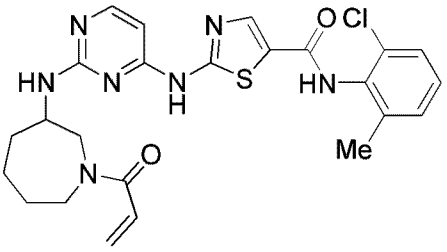
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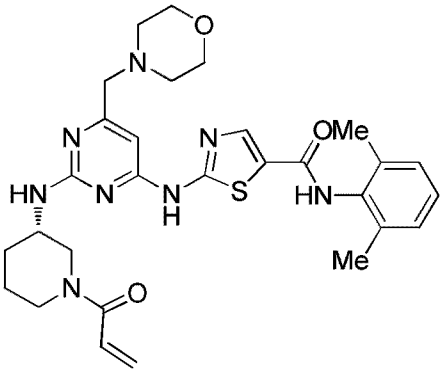
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or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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41. The compound of any one of claims 1-40, or a pharmaceutically acceptable salt thereof.

42. A pharmaceutical composition comprising a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, and a pharmaceutically acceptable excipient.

43. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, for treating a proliferative disease in a subject in need thereof.

44. Use of a pharmaceutical composition of claim 42 for treating a proliferative disease in a subject in need thereof.

45. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, for preventing a proliferative disease in a subject in need thereof.

46. Use of a pharmaceutical composition of claim 42 for preventing a proliferative disease in a subject in need thereof.

47. The use of any one of claims 43-46, wherein the proliferative disease is a proliferative disease associated with a mutation of myeloid differentiation primary response gene 88 (MYD88 gene).

48. The use of claim 47, wherein the mutation is an MYD88 L265P mutation.

49. The use of any one of claims 43-48, wherein the proliferative disease is cancer.

50. The use of claim 49, wherein the proliferative disease is a hematological malignancy.

51. The use of claim 49, wherein the proliferative disease is myelodysplasia.

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52. The use of claim 49, wherein the proliferative disease is leukemia.

53. The use of claim 49, wherein the proliferative disease is chronic lymphocytic leukemia (CLL).

54. The use of claim 49, wherein the proliferative disease is lymphoma.

55. The use of claim 49, wherein the proliferative disease is Waldenström's macroglobulinemia.

56. The use of claim 49, wherein the proliferative disease is activated B-cell (ABC) diffuse large B-cell lymphoma (DLBCL), central nervous system (CNS) lymphoma, lymphoma of an immune privileged site, testicular lymphoma, or marginal zone lymphoma.

57. The use of any one of claims 43-48, wherein the proliferative disease is pathological angiogenesis.

58. The use of any one of claims 43-48, wherein the proliferative disease is a benign neoplasm.

59. The use of any one of claims 43-48, wherein the proliferative disease is an inflammatory disease.

60. The use of any one of claims 43-48, wherein the proliferative disease is an autoimmune disease.

61. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, for inhibiting the activity of a protein kinase in a subject in need thereof.

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62. Use of a pharmaceutical composition of claim 42 for inhibiting the activity of a protein kinase in a subject in need thereof.

63. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, for inhibiting the activity of a protein kinase in a cell or tissue.

64. Use of a pharmaceutical composition of claim 42 for inhibiting the activity of a protein kinase in a cell or tissue.

65. An *in vitro* method of inhibiting the activity of a protein kinase in a cell or tissue, the method comprising contacting the cell or tissue with an effective amount of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

66. An *in vitro* method of inhibiting the activity of a protein kinase in a cell or tissue, the method comprising contacting the cell or tissue with an effective amount of a pharmaceutical composition of claim 42.

67. The use of any one of claims 61-64, wherein the protein kinase is hemopoietic cell kinase (HCK) or Bruton's tyrosine kinase (BTK).

68. The *in vitro* method of claim 65 or 66, wherein the protein kinase is hemopoietic cell kinase (HCK) or Bruton's tyrosine kinase (BTK).

69. The use of any one of claims 61-64, wherein the protein kinase is ABL, ACK, ARG, BLK, CSK, EphB1, EphB2, FGR, FRK, FYN, SRC, YES, LCK, LYN, MAP2K5, NLK, p38a, PIP4K2C, SNRK, SRC, or TEC.

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70. The *in vitro* method of claim 65 or 66, wherein the protein kinase is ABL, ACK, ARG, BLK, CSK, EphB1, EphB2, FGR, FRK, FYN, SRC, YES, LCK, LYN, MAP2K5, NLK, p38a, PIP4K2C, SNRK, SRC, or TEC.

71. The use of any one of claims 61-64, wherein the protein kinase is 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, or EGFR(E746-A750del).

72. The *in vitro* method of claim 65 or 66, wherein the protein kinase is 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, or EGFR(E746-A750del).

73. The use of any one of claims 61-64, wherein the protein kinase is 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)-

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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), or CSF1R.

74. The *in vitro* method of claim 65 or 66, wherein the protein kinase is 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), or CSF1R.

75. The use of any one of claims 43-62, wherein the subject is a human.

76. Use of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, for inducing apoptosis in a cell.

77. Use of a pharmaceutical composition of claim 42 for inducing apoptosis in a cell.

78. An *in vitro* method of inducing apoptosis in a cell, the method comprising contacting the cell with an effective amount of a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

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79. An *in vitro* method of inducing apoptosis in a cell, the method comprising contacting the cell with an effective amount of a pharmaceutical composition of claim 42.

80. The use of claim 76 or 77, wherein the cell is a malignant blood cell.

81. The *in vitro* method of claim 78 or 79, wherein the cell is a malignant blood cell.

82. The use of claim 76 or 77, wherein the cell expresses an MYD88 L265P mutation.

83. The *in vitro* method of claim 78 or 79, wherein the cell expresses an MYD88 L265P mutation.

84. The use of any one of claims 43, 45, 47-61, 63, 67, 69, 71, 73, 75-76, 80, and 82, wherein the compound, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, or pharmaceutical composition is in combination with an additional pharmaceutical agent.

85. The use of any one of claims 44, 46-60, 62, 64, 67, 69, 71, 73, 75, 77, 80, and 82, wherein the pharmaceutical composition is in combination with an additional pharmaceutical agent.

86. The *in vitro* method of any one of claims 65, 68, 70, 74, 78, 81, and 83, wherein the compound, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof, or pharmaceutical composition is in combination with an additional pharmaceutical agent.

87. The *in vitro* method of any one of claims 66, 68, 70, 74, 79, 81, and 83, wherein the pharmaceutical composition is in combination with an additional pharmaceutical agent.

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88. A kit comprising:

a compound of any one of claims 1-40, or a pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof; and

instructions for using the compound, or pharmaceutically acceptable salt, tautomer, stereoisomer, or isotopically labeled derivative thereof.

89. A kit comprising:

a pharmaceutical composition of claim 42; and

instructions for using the pharmaceutical composition.

90. A method of screening a library of compounds, the method comprising:

obtaining at least two different compounds of any one of claims 1-40, or pharmaceutically acceptable salts, tautomers, stereoisomers, or isotopically labeled derivatives thereof; and

performing at least one assay using the different compounds, or pharmaceutically acceptable salts, tautomers, stereoisomers, or isotopically labeled derivatives thereof.

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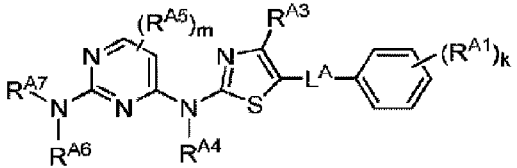

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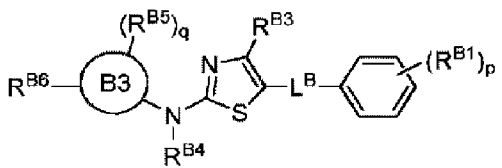

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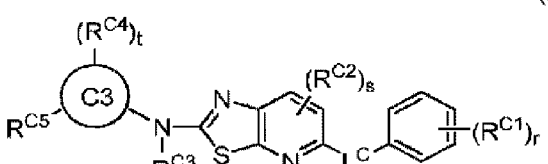

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