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Li, S. et al, "Synthesis and biological evaluation of 4-[3-chloro-4-(3-fluorobenzyloxy_anilino]-6-3-substituted-phenoxy)pyrimidines and dual EGFR/ErbB-2 kinase inhibitors", Bioorganic & Medicinal Chemistry, 2012, 20, 877-885
WO 2011/090738 A2
WO 2010/026095 A1
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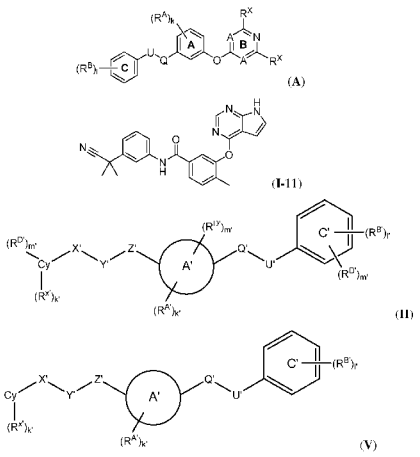
(54) Title: METHODS TO TREAT LYMPHOPLASMACYTIC LYMPHOMA



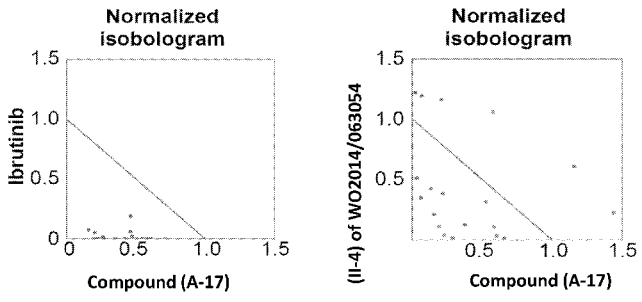


Figure 1

(57) Abstract: The present invention provides compounds of any one of Formulae (A), (I-11), (II), and (V) (*e.g.*, compounds of Formula (A-1)-(A-18)), and methods for treating Waldenström's macroglobulinemia (WM) and other B cell neoplams in a subject using the compounds. The methods comprise administering to a subject in need thereof an effective amount of the compounds. Also provided are methods to treat B cell neoplasms using the compounds in combination with inhibitors of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase 4 (IRAK4), bone marrow on X chromosome kinase (BMX), phosphoinositide 3-kinase (PI3K), transforming growth factor b-activated kinase-1 (TAK1), and/or a Src family kinase.

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METHODS TO TREAT LYMPHOPLASMACYTIC LYMPHOMA

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent applications, U.S.S.N. 62/036,934, filed August 13, 2014 and U.S.S.N. 61/915,684, filed December 13, 2013, the entire contents of which are incorporated herein by reference.

GOVERNMENT SUPPORT

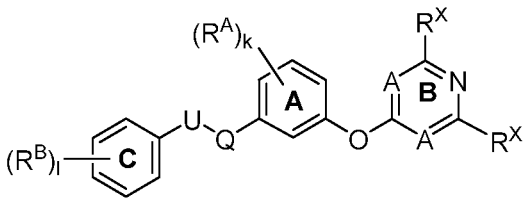
[0002] This invention was made with U.S. Government support under grants 5R01CA130876-05, 5P50CA090578-10, 5R01CA136851-04, 2R01CA136851-05, and 1R01CA172592-01A1 awarded by the National Cancer Institute. The U.S. Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity resulting from the accumulation, predominantly in the bone marrow, of clonally related lymphoplasmacytic cells which secrete a monoclonal IgM protein. This condition is considered to correspond to lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organization classification system. WM is a rare disorder, with fewer than 1,500 cases occurring in the United States annually. There is a 2- to 3-fold risk increase of developing WM in people with a personal history of autoimmune diseases with autoantibodies and particularly elevated risks associated with hepatitis, human immunodeficiency virus, and rickettsiosis (*Arch. Intern. Med.*, **2008**, *168*(17), 1903-9). There is no single accepted treatment for WM, and there can be a marked variation in clinical outcome. Objective response rates are high (>80%) but complete response rates are low (0-15%) (*Clin. Adv. Hematol. Oncol.*, **2009**, *7*(10), 677-81, 687-90). Thus, there is a need for effective treatment of WM.

SUMMARY OF THE INVENTION

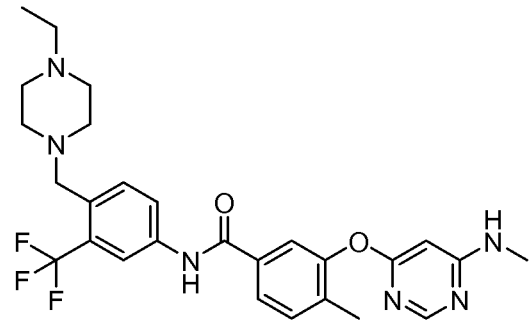
[0004] The present invention is based, at least in part, on the discovery of compounds of the Formula (**A**):



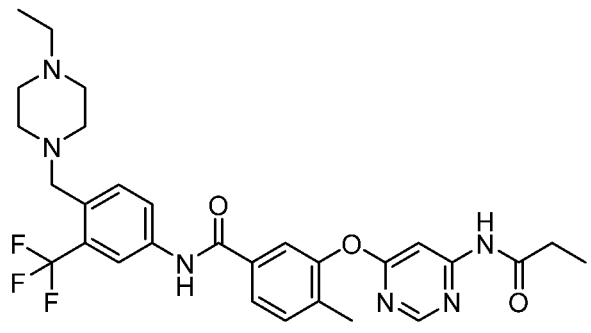
(**A**)

or a pharmaceutically acceptable salt thereof, wherein Q, U, R^A, R^B, R^X, k, and l are defined herein, for the treatment of Waldenström's macroglobulinemia. The activity of these compounds was established by *in vitro* screening against several kinases (*e.g.*, BTK, HCK, TAK1, HPK1).

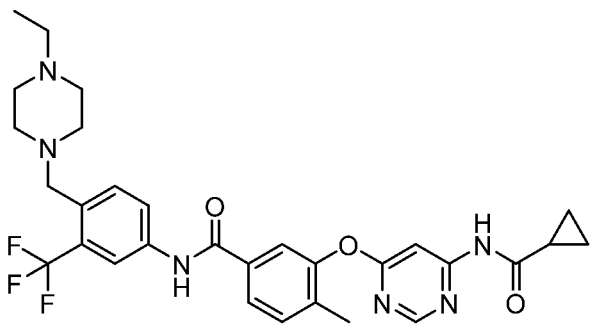
[0005] In certain embodiments, compounds of Formula (**A**) are of formula:



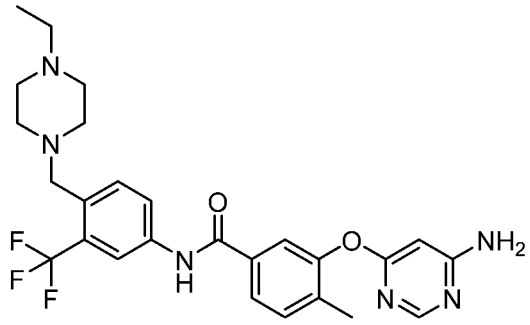
(**A-1**),



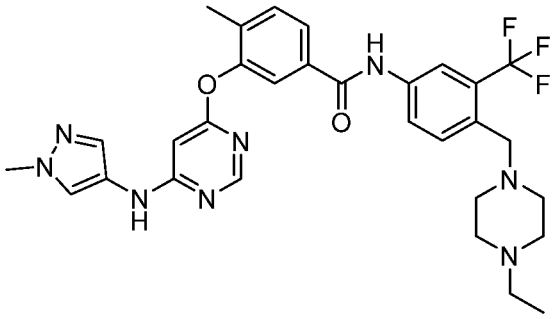
(**A-2**),



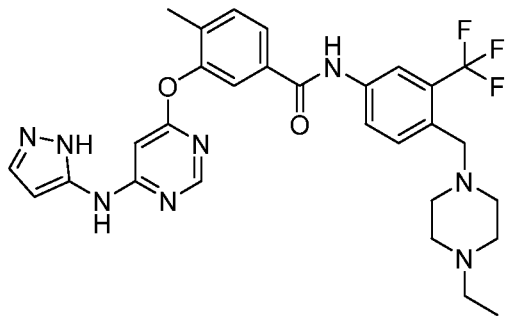
(**A-3**),



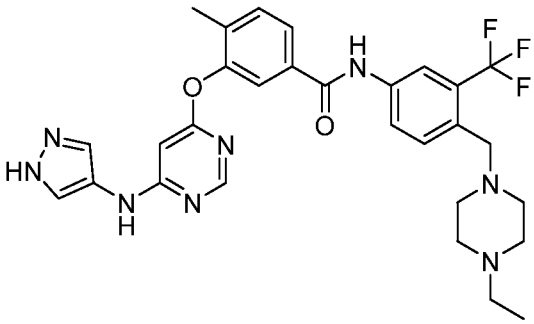
(**A-4**),



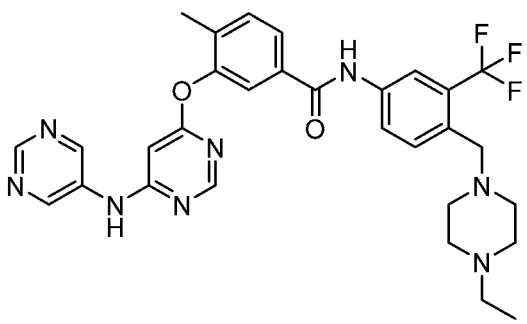
(**A-5**),



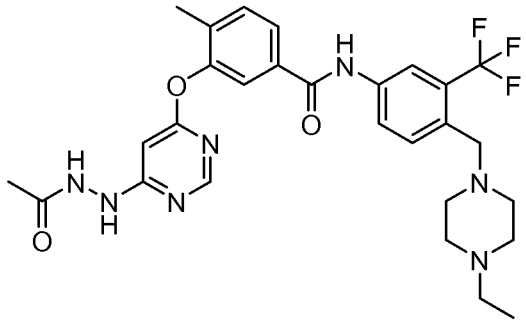
(**A-6**),



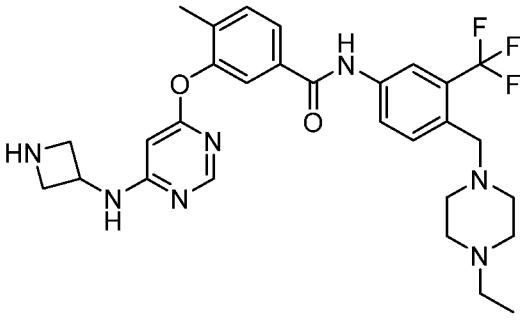
(**A-7**),



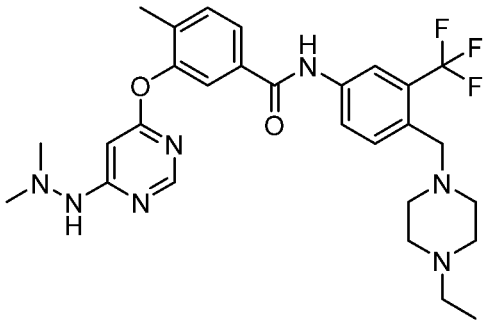
(**A-8**),



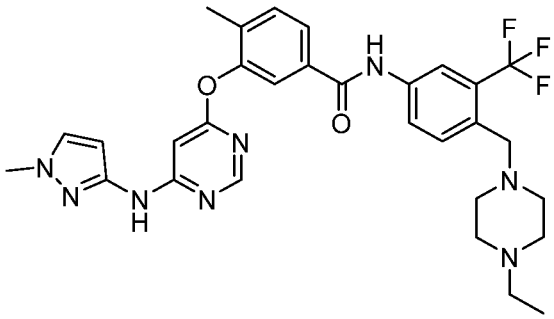
(**A-9**),



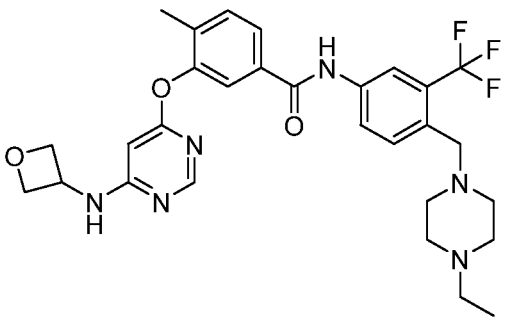
(**A-10**),



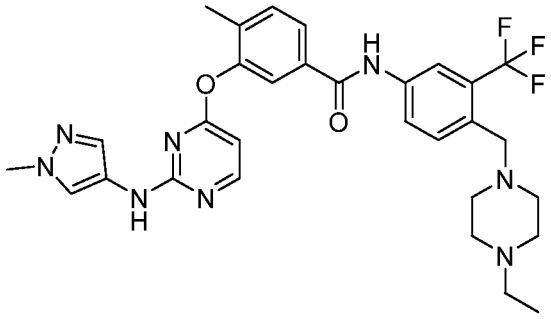
(**A-11**),



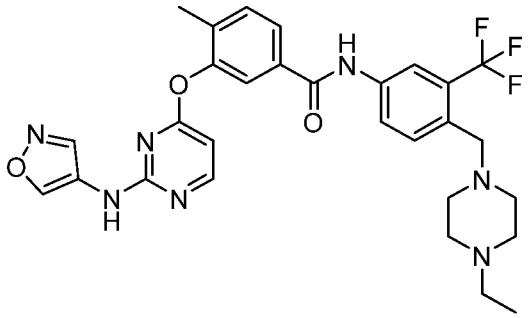
(**A-12**),



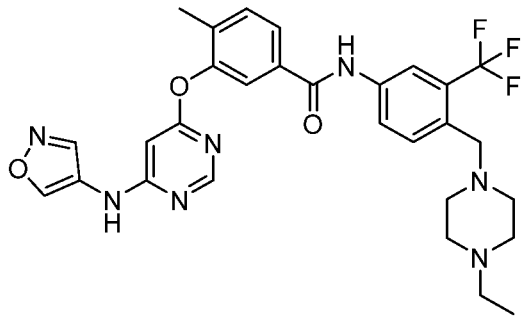
(**A-13**),



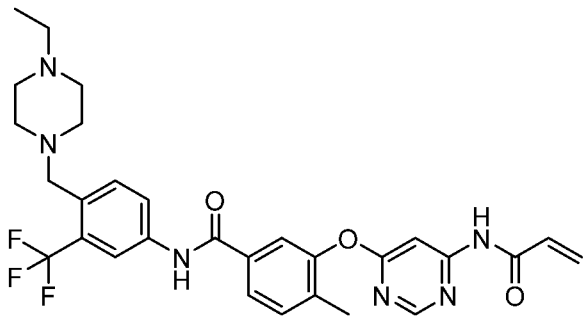
(**A-14**),



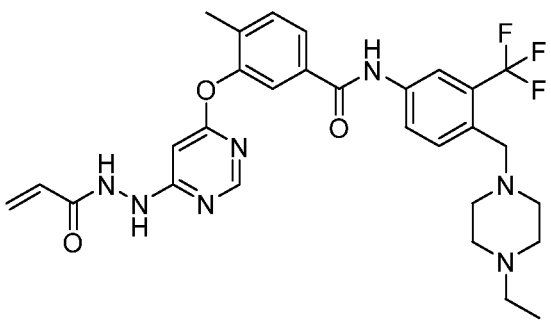
(**A-15**),



(**A-16**),



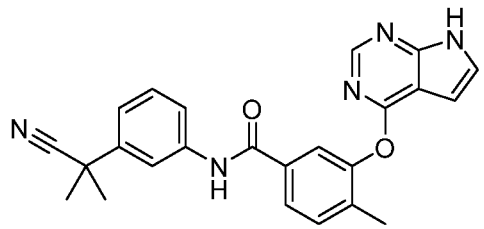
(**A-17**), and



(**A-18**),

and pharmaceutically acceptable salts thereof.

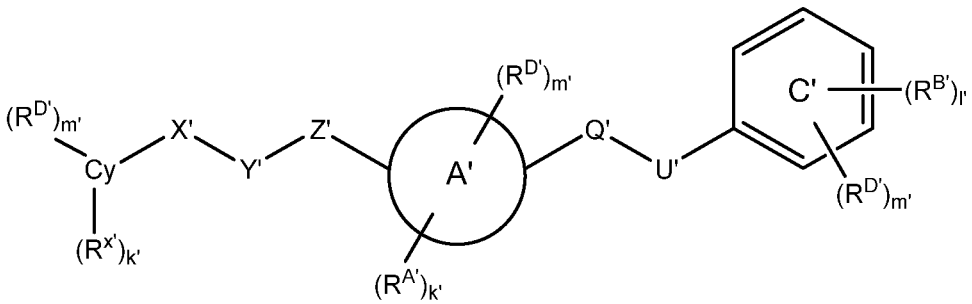
[0006] Another aspect of the invention relates to the compound of Formula (**I-11**):



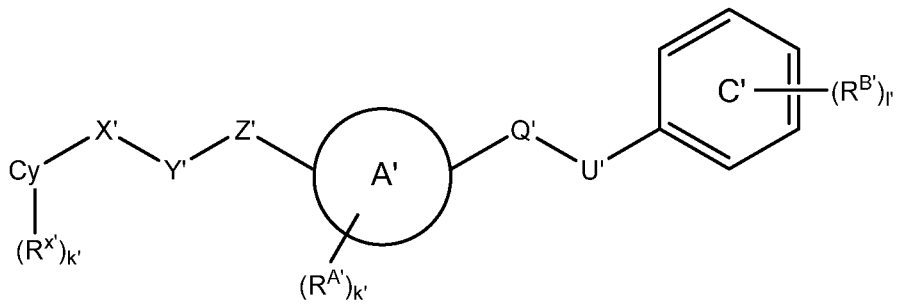
(**I-11**),

and pharmaceutically acceptable salts thereof.

[0007] The present invention also provides compounds of Formula (**II**) or (**V**):



(**II**),



(**V**),

and pharmaceutically acceptable salts thereof, wherein Ring A′, Ring C′, Cy, X′, Y′, Z′, Q′, U′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

[0008] The present invention is also based, at least in part, on the discovery that Waldenström's macroglobulinemia may be treated by administration of a compound of the invention to a subject in need thereof. The activity of these compounds was established by *in vitro* screening against several kinases (*e.g.*, BTK, HCK, TAK1, HPK1) that are involved in the regulation of aberrant cell growth, as well as cell-based screening against several cell lines (*e.g.*, BCWM.1, MWCL-1) that are disease state models of Waldenström's macroglobulinemia (Ditzel et al. *Exp Hematol.* 2007 Sep;35(9):1366-75; Hodge et al. *Blood.* 2011 May 12;117(19)).

[0009] The methods of treatment utilizing a compound of the invention also apply to B cell neoplasms of the group consisting of Hodgkin's lymphomas and most non-Hodgkin's lymphomas, such as diffuse large B cell lymphoma, Follicular lymphoma, mucosa-associated

lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma (overlaps with chronic lymphocytic leukemia), mantle cell lymphoma (MCL), Burkitt lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), Intravascular large B-cell lymphoma, Primary effusion lymphoma, and Lymphomatoid granulomatosis.

[0010] The present invention is also based, at least in part, on pharmaceutical compositions comprising a compound of the invention (*e.g.*, a compound of Formula (**A**), (**I-11**), (**II**), or (**V**) (*e.g.*, compounds of Formula (**A-1**)-(**A-18**))) and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition may be useful for modulating the activity of a kinase *in vitro* or in a subject in need thereof, and/or for treating and/or preventing in a subject in need thereof a condition associated with aberrant activity of a kinase (*e.g.*, a proliferative disease). In certain embodiments, the pharmaceutical composition may be useful for treatment of Waldenström's macroglobulinemia in a subject in need thereof.

[0011] The present invention also provides kits comprising a container with a compound of the invention (*e.g.*, a compound of Formula (**A**), (**I-11**), (**II**), or (**V**) (*e.g.*, compounds of Formula (**A-1**)-(**A-18**))), or a pharmaceutical composition thereof. The kits may include a single dose or multiple doses of a compound described herein or a pharmaceutical composition thereof. The kits may be useful for modulating the activity of a kinase in a subject in need thereof. The kits may also be useful for treating and/or preventing in a subject in need thereof a condition associated with aberrant activity of a kinase. In certain embodiments, the kits further include instructions for using the kit (*e.g.*, for administering a compound described herein, or a pharmaceutical composition thereof).

[0012] The details of particular embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Figures, the Examples, and the Claims.

DEFINITIONS

Chemical Definitions

[0013] 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 *Organic Chemistry*, Thomas Sorrell, 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.

[0014] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0015] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0016] 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} alkyl" 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} alkyl.

[0017] The term "aliphatic," as used herein, refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term "heteroaliphatic" as used herein, refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

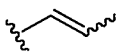
[0018] The term "alkyl" refers to a radical of a straight–chain or branched saturated hydrocarbon group having from 1 to 10 carbon atoms ("C_{1-10} alkyl"). In some embodiments,

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.*, $-CH_3$ (Me), unsubstituted ethyl (Et), unsubstituted propyl (Pr, *e.g.*, unsubstituted *n*-propyl (*n*-Pr), unsubstituted isopropyl (*i*-Pr)), unsubstituted butyl (Bu, *e.g.*, unsubstituted n-butyl (*n*-Bu), unsubstituted *tert*-butyl (*tert*-Bu or *t*-Bu), unsubstituted *sec*-butyl (*sec*-Bu), unsubstituted isobutyl (*i*-Bu)). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl (such as substituted C_{1-6} alkyl, *e.g.*, $-CF_3$, Bn).

[0019] As used herein, "haloalkyl" is a substituted alkyl group as defined herein wherein one or more of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. "Perhaloalkyl" is a subset of haloalkyl, and refers to an alkyl group wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In certain embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In certain embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In certain embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In certain embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In certain embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In certain embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. In certain embodiments, all of the haloalkyl hydrogen atoms are replaced with chloro to provide a "perchloroalkyl" group. Examples of haloalkyl groups include $-CF_3$, $-CF_2CF_3$, $-CF_2CF_2CF_3$, $-CCl_3$, $-CFCl_2$, $-CF_2Cl$, and the like.

[0020] As used herein, "heteroalkyl" refers to an alkyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{1-5} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1or 2 heteroatoms within the parent chain ("heteroC_{1-4} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-3} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain ("heteroC_{1-2} alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkyl"). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an "unsubstituted heteroalkyl") or substituted (a "substituted heteroalkyl") with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC_{1-10} alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC_{1-10} alkyl.

[0021] As used herein, "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In certain embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In certain embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In certain embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In certain embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6}

alkenyl"). In certain embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In certain embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In certain embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In certain 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 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 unsubstituted (an "unsubstituted alkenyl") or substituted (a "substituted alkenyl") with one or more substituents. In certain embodiments, the alkenyl group is an unsubstituted C_{2-10} alkenyl. In certain embodiments, the alkenyl group is a 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

[0022] As used herein, "heteroalkenyl" refers to an alkenyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1or 2 heteroatoms

within the parent chain ("heteroC_{2-4} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkenyl"). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an "unsubstituted heteroalkenyl") or substituted (a "substituted heteroalkenyl") with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC_{2-10} alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC_{2-10} alkenyl.

[0023] As used herein, "alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) ("C_{2-10} alkynyl"). In certain embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In certain embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In certain embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In certain embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In certain embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In certain embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In certain embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In certain 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 unsubstituted (an "unsubstituted alkynyl") or substituted (a "substituted alkynyl") with one or more substituents. In certain embodiments, the alkynyl group is an unsubstituted C_{2-10} alkynyl. In certain embodiments, the alkynyl group is a substituted C_{2-10} alkynyl.

[0024] As used herein, "heteroalkynyl" refers to an alkynyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or

more heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-5} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1or 2 heteroatoms within the parent chain ("heteroC_{2-4} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom within the parent chain ("heteroC_{2-3} alkynyl"). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an "unsubstituted heteroalkynyl") or substituted (a "substituted heteroalkynyl") with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC_{2-10} alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC_{2-10} alkynyl.

[0025] As used herein, "carbocyclyl" or "carbocyclic" refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms ("C_{3-14} carbocyclyl") and zero heteroatoms in the non–aromatic ring system. In certain embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In certain embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In certain embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In certain embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In certain embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms ("C_{4-6} carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms ("C_{5-6} carbocyclyl"). In certain 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 polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic carbocyclyl") or tricyclic system ("tricyclic carbocyclyl")) and can be saturated or can contain one or more carbon–carbon double or triple bonds. "Carbocyclyl" also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl 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 unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3-14} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3-14} carbocyclyl. In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms ("C_{3-14} cycloalkyl"). In certain embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms ("C_{3-10} cycloalkyl"). In certain embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms ("C_{3-8} cycloalkyl"). In certain embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms ("C_{3-6} cycloalkyl"). In certain embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms ("C_{4-6} cycloalkyl"). In certain embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms ("C_{5-6} cycloalkyl"). In certain 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} 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 an unsubstituted C_{3-14} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3-14} cycloalkyl.

[0026] As used herein, "heterocyclyl" or "heterocyclic" refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("3–14 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 polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system ("bicyclic heterocyclyl") or tricyclic system ("tricyclic heterocyclyl")), and can be saturated or can contain one or more carbon–carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. "Heterocyclyl" also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an "unsubstituted heterocyclyl") or substituted (a "substituted heterocyclyl") with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl.

[0027] In certain 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, and sulfur ("5–10 membered heterocyclyl"). In certain 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 certain 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 certain embodiments, the 5–6 membered heterocyclyl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5–6 membered heterocyclyl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the

5–6 membered heterocyclyl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0028] Exemplary 3–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, and thiiranyl. Exemplary 4–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidinyl, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocyclyl groups containing 3 heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, decahydroisoquinolinyl, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridinyl, decahydro–1,8–naphthyridinyl, octahydropyrrolo[3,2–b]pyrrole, indolinyl, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepinyl, 1,4,5,7–tetrahydropyrano[3,4–b]pyrrolyl, 5,6–dihydro–4H–furo[3,2–b]pyrrolyl, 6,7–dihydro–5H–furo[3,2–b]pyranyl, 5,7–dihydro–4H–thieno[2,3–c]pyranyl, 2,3–dihydro–1H–pyrrolo[2,3–b]pyridinyl, 2,3–dihydrofuro[2,3–b]pyridinyl, 4,5,6,7–tetrahydro–1H–pyrrolo[2,3–b]pyridinyl, 4,5,6,7–tetrahydrofuro[3,2–c]pyridinyl, 4,5,6,7–tetrahydrothieno[3,2–b]pyridinyl, 1,2,3,4–tetrahydro–1,6–naphthyridinyl, and the like.

[0029] As used herein, "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 π 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 certain embodiments, an aryl group has 6 ring carbon

atoms ("C_6 aryl"; *e.g.*, phenyl). In certain embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In certain embodiments, an aryl group has 14 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, 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 unsubstituted (an "unsubstituted aryl") or substituted (a "substituted aryl") with one or more substituents. In certain embodiments, the aryl group is an unsubstituted $C_{6–14}$ aryl. In certain embodiments, the aryl group is a substituted $C_{6–14}$ aryl.

[0030] "Aralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by an aryl group, as defined herein, wherein the point of attachment is on the alkyl moiety.

[0031] As used herein, "heteroaryl" refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π 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 ("5–14 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 polycyclic 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 polycyclic (aryl/heteroaryl) ring system. Polycyclic 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).

[0032] In certain 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 certain embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In certain 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 certain embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain 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 unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is an unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5–14 membered heteroaryl.

[0033] Exemplary 5–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyrrolyl, furanyl, and thiophenyl. Exemplary 5–membered heteroaryl groups containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5–membered heteroaryl groups containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6–membered heteroaryl groups containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6–membered heteroaryl groups containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6–membered heteroaryl groups containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7–membered heteroaryl groups containing 1 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. Exemplary tricyclic heteroaryl groups include, without limitation, phenanthridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl and phenazinyl.

[0034] "Heteroaralkyl" is a subset of "alkyl" and refers to an alkyl group, as defined herein, substituted by a heteroaryl group, as defined herein, wherein the point of attachment is on the alkyl moiety.

[0035] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.*, aryl or heteroaryl moieties) as herein defined.

[0036] As used herein, the term "saturated" refers to a ring moiety that does not contain a double or triple bond, *i.e.*, the ring contains all single bonds.

[0037] Affixing the suffix "–ene" to a group indicates the group is a divalent moiety, *e.g.*, alkylene is the divalent moiety of alkyl, alkenylene is the divalent moiety of alkenyl, alkynylene is the divalent moiety of alkynyl, heteroalkylene is the divalent moiety of heteroalkyl, heteroalkenylene is the divalent moiety of heteroalkenyl, heteroalkynylene is the divalent moiety of heteroalkynyl, carbocyclylene is the divalent moiety of carbocyclyl, heterocyclylene is the divalent moiety of heterocyclyl, arylene is the divalent moiety of aryl, and heteroarylene is the divalent moiety of heteroaryl.

[0038] As understood from the above, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are, in certain embodiments, optionally substituted. Optionally substituted refers to a group which may be substituted or unsubstituted (*e.g.*, "substituted" or "unsubstituted" alkyl, "substituted" or "unsubstituted" alkenyl, "substituted" or "unsubstituted" alkynyl, "substituted" or "unsubstituted" heteroalkyl, "substituted" or "unsubstituted" heteroalkenyl, "substituted" or "unsubstituted" heteroalkynyl, "substituted" or "unsubstituted" carbocyclyl, "substituted" or "unsubstituted" heterocyclyl, "substituted" or "unsubstituted" aryl or "substituted" or "unsubstituted" heteroaryl group). In general, the term "substituted" means that at least one hydrogen present on a group 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, and includes any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0039] 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, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–OC(=NR^{bb})N(R^{bb})_2$, $–NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–NR^{bb}SO_2R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $–SO_2OR^{aa}$, $–OSO_2R^{aa}$, $–S(=O)R^{aa}$, $–OS(=O)R^{aa}$, $–Si(R^{aa})_3$, $–OSi(R^{aa})_3$ $–C(=S)N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=S)SR^{aa}$, $–SC(=S)SR^{aa}$, $–SC(=O)SR^{aa}$, $–OC(=O)SR^{aa}$, $–SC(=O)OR^{aa}$, $–SC(=O)R^{aa}$, $–P(=O)_2R^{aa}$, $–OP(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, $–OP(=O)_2N(R^{bb})_2$, $–P(=O)(NR^{bb})_2$, $–OP(=O)(NR^{bb})_2$, $–NR^{bb}P(=O)(OR^{cc})_2$, $–NR^{bb}P(=O)(NR^{bb})_2$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–B(R^{aa})_2$, $–B(OR^{cc})_2$, $–BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$ alkenyl, hetero$C_{2–10}$ alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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

each instance of R^{aa} is, independently, selected from $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, hetero$C_{1–10}$ alkyl, hetero$C_{2–10}$alkenyl, hetero$C_{2–10}$alkynyl, $C_{3–10}$ carbocyclyl, 3–14 membered heterocyclyl, $C_{6–14}$ 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, heteroalkyl, heteroalkenyl, heteroalkynyl, 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, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, –

$C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{2-10}alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, 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, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$,$-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)_2R^{ee}$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{2-6}alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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, heteroC_{1-6} alkyl, heteroC_{2-6}alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, 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, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{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 3–10 membered heterocyclyl or 5–10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{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), $–CO_2H$, $–CO_2(C_{1-6}$ 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, $–P(=O)_2(C_{1-6}$ alkyl), $–P(=O)(C_{1-6}$ 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, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{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.

[0040] As used herein, the term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0041] In certain embodiments, the substituent present on the nitrogen atom is an nitrogen protecting group (also referred to herein 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.*, alkyl, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} heteroalkyl, C_{2-10} heteroalkenyl, C_{2-10} heteroalkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14

membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, 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 described 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, incorporated herein by reference.

[0042] 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.

[0043] Nitrogen protecting groups such as carbamate groups (*e.g.*, –C(=O)OR^{aa}) include, but are not limited to, methyl carbamate, ethyl carbamante, 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), 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–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.

[0044] 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.

[0045] 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*–[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).

[0046] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to herein as an "hydroxyl protecting group"). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as described herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0047] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxylmethyl (MOM), methylthiomethyl (MTM), *t*–butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*–

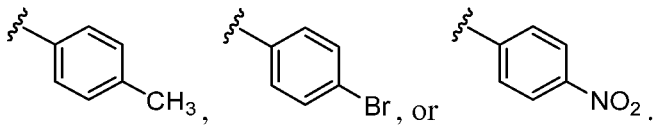
methoxybenzyloxymethyl (PMBM), (4–methoxyphenoxy)methyl (*p*–AOM), guaiacolmethyl (GUM), *t*–butoxymethyl, 4–pentenyloxymethyl (POM), siloxymethyl, 2–methoxyethoxymethyl (MEM), 2,2,2–trichloroethoxymethyl, bis(2–chloroethoxy)methyl, 2–(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3–bromotetrahydropyranyl, 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*–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–benzodithiolan–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), methyl carbonate, 9–fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2–trichloroethyl carbonate (Troc), 2–(trimethylsilyl)ethyl carbonate (TMSEC), 2–(phenylsulfonyl) ethyl carbonate (Psec), 2–(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl

carbonate, *t*–butyl carbonate (BOC), *p*–nitrophenyl carbonate, benzyl carbonate, *p*–methoxybenzyl carbonate, 3,4–dimethoxybenzyl carbonate, *o*–nitrobenzyl carbonate, *p*–nitrobenzyl carbonate, *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).

[0048] In certain embodiments, the substituent present on an sulfur atom is a sulfur protecting group (also referred to as a "thiol protecting group"). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as described herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0049] As used herein, a "leaving group", or "LG", is a term understood in the art to refere to a molecular fragment that departs with a pair of electrons upon heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Examples of suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, or iodide), alkoxycarbonyloxy, aryloxycarbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (*e.g.*, acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, haloformates, $-NO_2$, trialkylammonium, and aryliodonium salts. In certain embodiments, the leaving group is a sulfonic acid ester. In certain embodiments, the sulfonic acid ester comprises the formula $-OSO_2R^{LG1}$ wherein R^{LG1} is selected from the group consisting alkyl optionally, alkenyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, arylalkyl optionally substituted, and heterarylalkyl optionally substituted. In

certain embodiments, R^{LG1} is substituted or unsubstituted C_1-C_6 alkyl. In certain embodiments, R^{LG1} is methyl. In certain embodiments, R^{LG1} is $-CF_3$. In certain embodiments, R^{LG1} is substituted or unsubstituted aryl. In certain embodiments, R^{LG1} is substituted or unsubstituted phenyl. In certain embodiments R^{LG1} is:



[0050] In some cases, the leaving group is toluenesulfonate (tosylate, Ts), methanesulfonate (mesylate, Ms), *p*-bromobenzenesulfonyl (brosylate, Bs), or trifluoromethanesulfonate (triflate, Tf). In some cases, the leaving group is a brosylate (*p*-bromobenzenesulfonyl). In some cases, the leaving group is a nosylate (2-nitrobenzenesulfonyl). In certain embodiments, the leaving group is a sulfonate-containing group. In certain 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.

[0051] These and other exemplary substituents are described in more detail in the Detailed Description, Figures, Examples, and Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other Definitions

[0052] The following definitions are more general terms used throughout the present application.

[0053] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids, such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods

known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}\ alkyl)_4^-$ 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.

[0054] The term "solvate" refers to forms of the compound, or a salt thereof, 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. Compounds of the invention may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates, and methanolates.

[0055] 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 wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R{\cdot}0.5\ H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R{\cdot}2\ H_2O$) and hexahydrates ($R{\cdot}6\ H_2O$)).

[0056] The term "tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0057] 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".

[0058] 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".

[0059] The term "polymorphs" refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof). All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[0060] The term "prodrugs" refers to compounds that have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, 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 of this invention have activity in both their acid and acid derivative forms, but in

the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, H., *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly the 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 of the invention (*e.g.*, the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**)).

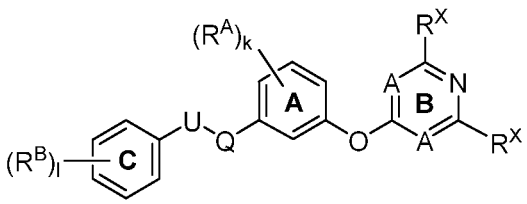
BRIEF DESCRIPTION OF THE DRAWINGS

[0061] *Figure 1* shows isobolograms demonstrating the synergy between compound (**A-17**) and a BTK inhibitor. Points below the 1 to 1 line connecting the X and Y axes are 'synergistic', points near the line are 'additive', and points above it are antagonistic.

DETAILED DESCRIPTION OF THE INVENTION

[0062] In an effort to identify novel treatments for Waldenström's macroglobulinemia, *in vitro* screens were carried out against several kinases (*e.g.*, BTK, HCK, TAK1, HPK1). These kinases are involved in the regulation of aberrant cell growth associated with this condition. Cell-based screening was also carried out in several disease state model lines of Waldenström's macroglobulinemia (*e.g.*, BCWM.1, MWCL-1). Based on these screening efforts and subsequent lead optimization, compounds of any one of Formulae (**A**), (**I-11**), (**II**), and (**V**) (*e.g.*, compounds of Formula (**A-1**)-(**A-18**)) were identified.

[0063] In one aspect, the present invention provides compounds of Formula (**A**):



(**A**)

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

wherein:

each instance of R^A is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, $–OR^{A1}$, $–N(R^{A1})_2$, –CN, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}S(=O)_2R^{A1}$, $–S(=O)_2R^{A1}$, or $–S(=O)_2N(R^{A1})_2$;

each instance of R^B is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–OR^{A1}$, $–N(R^{A1})_2$,–CN, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}S(=O)_2R^{A1}$, $–S(=O)_2R^{A1}$, or $–S(=O)_2N(R^{A1})_2$;

each instance of R^{A1} is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form an optionally substituted heterocyclic ring;

one instance of A that is included in Ring B is CR^Y;

the other instance of A that is included in Ring B is CR^Y or N;

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

each instance of R^X is independently selected from the group consisting of R^D, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and $–N(R^{A1})(R^{Xa})$;

each instance of R^{Xa} is 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, optionally substituted heteroaryl, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–S(=O)R^{A1}$, $–S(=O)N(R^{A1})_2$, $–S(=O)_2R^{A1}$, $–S(=O)_2OR^{A1}$, $–S(=O)_2N(R^{A1})_2$, $–N(R^{A1})_2$, and a nitrogen protecting group;

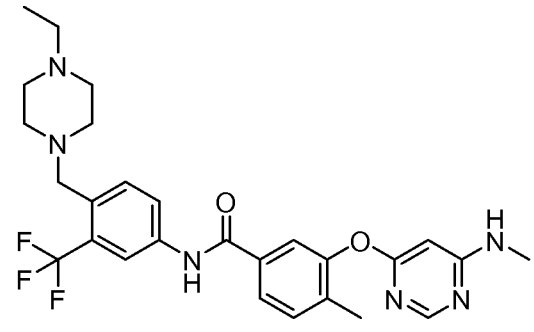
k is 0, 1, 2, 3, or 4;

l is 1, 2, 3, 4, or 5;

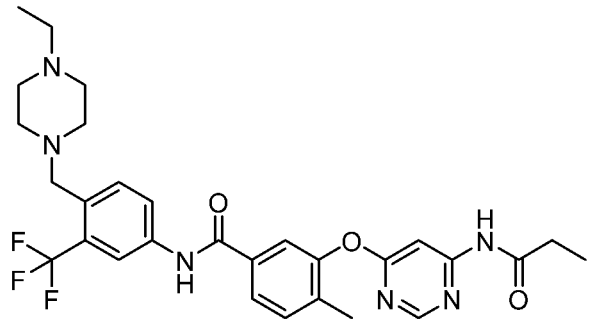
Q and U are taken together to be $–NR^A(C=O)–$ or $–(C=O)NR^A–$; and

R^D is an electrophilic moiety as described herein.

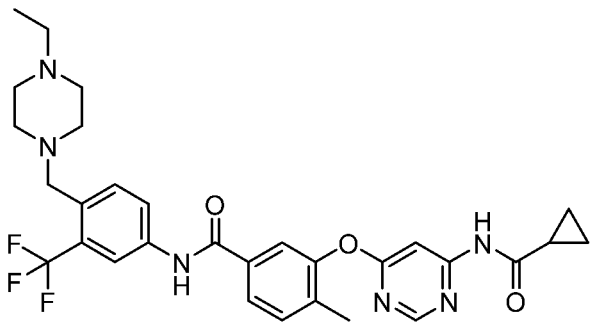
[0064] In certain embodiments, the present invention provides compounds from the group consisting of:



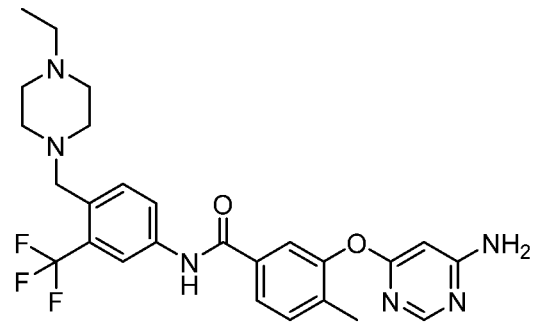
(**A-1**),



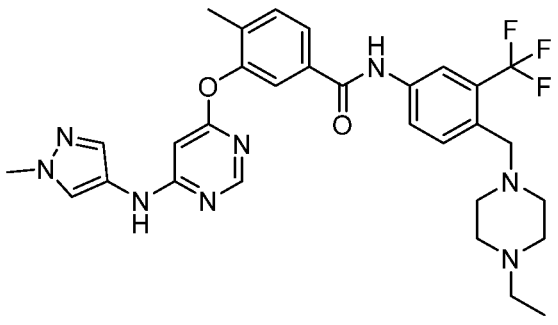
(**A-2**),



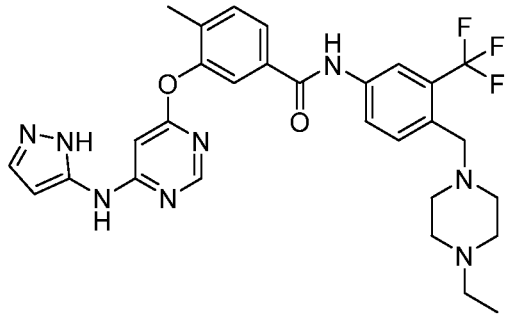
(**A-3**),



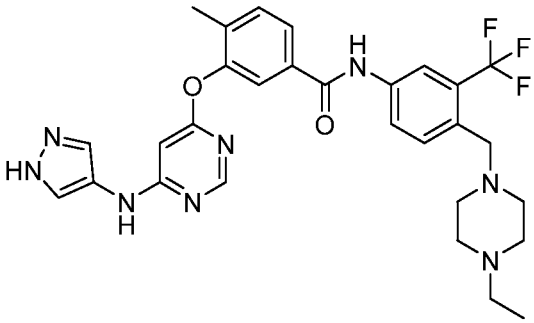
(**A-4**),



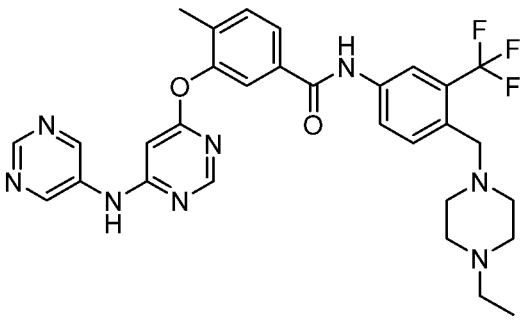
(**A-5**),



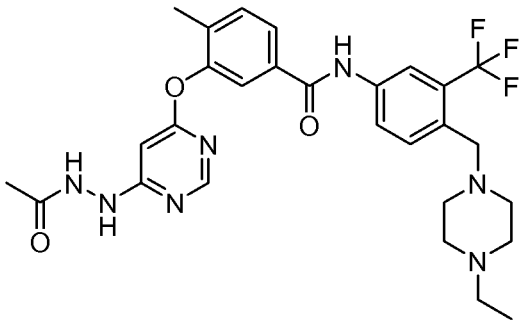
(**A-6**),



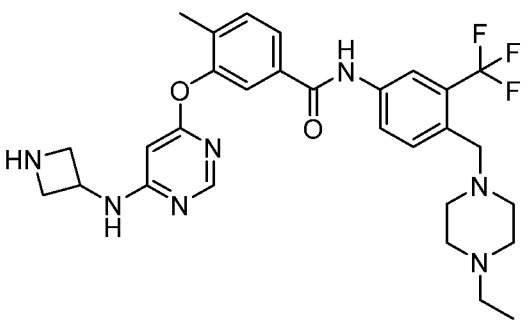
(**A-7**),



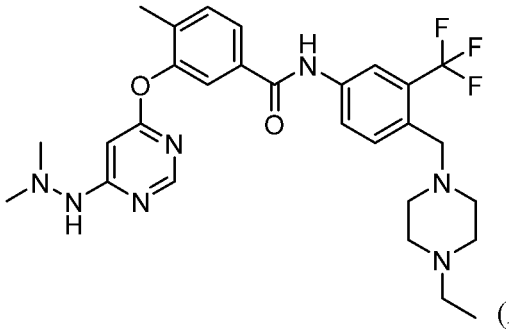
(**A-8**),



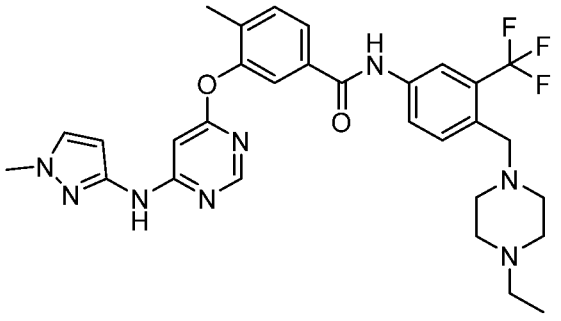
(**A-9**),



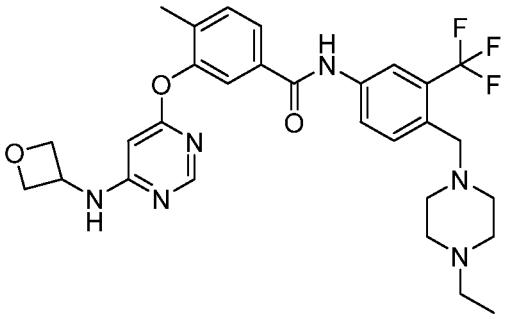
(**A-10**),



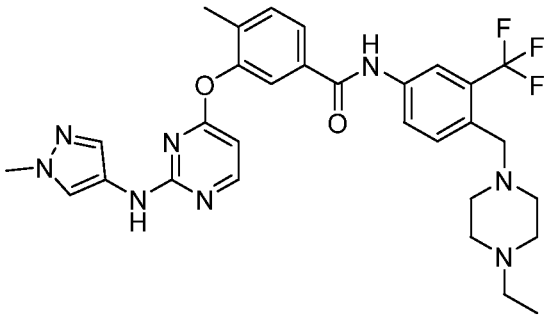
(**A-11**),



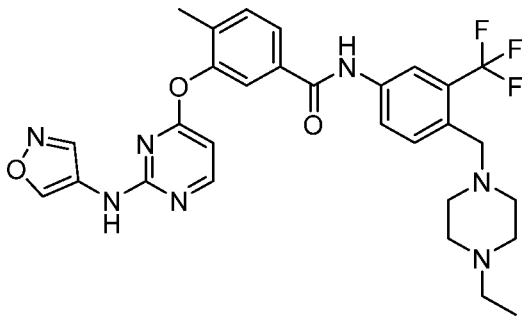
(**A-12**),



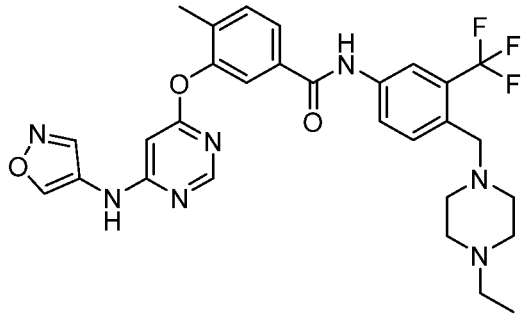
(**A-13**),



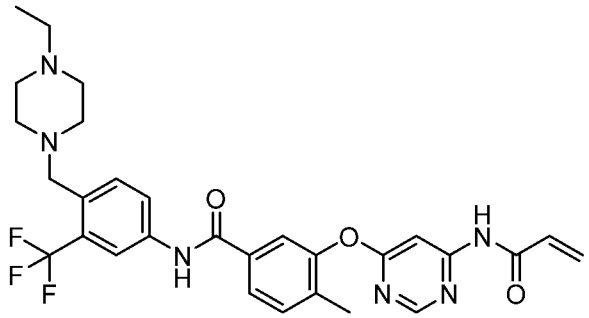
(**A-14**),



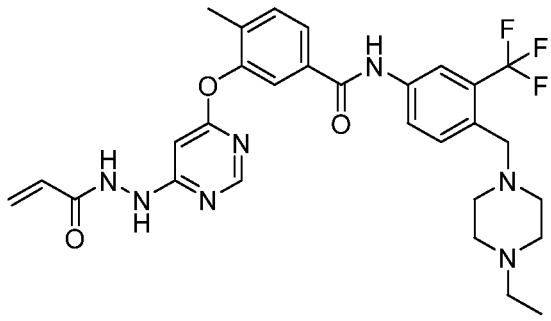
(**A-15**),



(**A-16**),



(**A-17**), and



(**A-18**),

and pharmaceutically acceptable salts thereof.

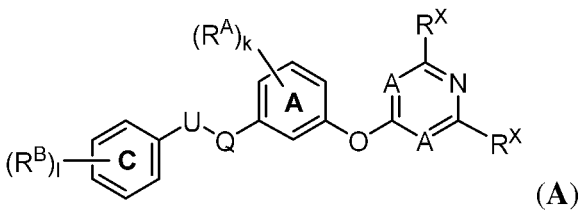
[0065] In another aspect, the present invention provides methods for treating Waldenström's macroglobulinemia (WM) in a subject using compounds of the invention. The methods comprise administering to a subject in need thereof an effective amount of a compound of the invention. Also provided are methods to treat other B cell neoplasms using compounds of the invention in combination with inhibitors of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase 4 (IRAK4), bone marrow on X chromosome kinase (BMX), phosphoinositide 3-kinase (PI3K), transforming growth factor b-activated kinase-1 (TAK1), and/or a Src family kinase. In certain embodiments, one or more compounds of the invention are used in combination with an inhibitor of the phosphoinositide 3-kinase delta isoform (PI3Kδ). In certain embodiments, combinations of 2, 3, 4, 5, 6,7, 8, 9, 10, or more of the agents described herein are used for treating WM. In certain embodiments, the agents described herein are used in combination with kinase inhibitors such as inhibitors of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase

4 (IRAK4), bone marrow on X chromosome kinase (BMX), and/or phosphoinositide 3-kinase (PI3K), transforming growth factor b-activated kinase-1 (TAK1), and/or a Src family kinase.

[0066] Waldenstrom's macroglobulinemia (WM) is a distinct clinicopathological entity resulting from the accumulation, predominantly in the bone marrow, of clonally related lymphoplasmacytic cells which secrete a monoclonal IgM protein. This condition is considered to correspond to lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organization classification system. Genetic factors play an important role in the pathogenesis of WM, with 25% of patients demonstrating a family history. IgM monoclonal gammopathy of unknown significance (MGUS) often precedes the development of WM.

[0067] As used herein, a B cell neoplasm includes both Hodgkin's lymphoma and non-Hodgkin's lymphomas. Classical Hodgkin's lymphoma (HL) includes various subtypes such as Nodular sclerosing HL, Mixed-cellularity subtype, Lymphocyte-rich or Lymphocytic predominance and Lymphocyte depleted. Examples of B cell non-Hodgkin's lymphomas include, but are not limited to, Waldenström's macroglobulinemia, diffuse large B cell lymphoma, follicular lymphoma, mucosa-associated lymphatic tissue lymphoma (MALT), small cell lymphocytic lymphoma (overlaps with chronic lymphocytic leukemia), mantle cell lymphoma (MCL), Burkitt lymphoma, mediastinal large B cell lymphoma, nodal marginal zone B cell lymphoma (NMZL), splenic marginal zone lymphoma (SMZL), intravascular large B-cell lymphoma, primary effusion lymphoma, and lymphomatoid granulomatosis.

[0068] In certain embodiments, the subject is administered a compound of Formula (**A**):



(**A**)

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

wherein:

each instance of R^A is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, $-OR^{A1}$, $-N(R^{A1})_2$, $-CN$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}S(=O)_2R^{A1}$, $-S(=O)_2R^{A1}$, or $-S(=O)_2N(R^{A1})_2$;

each instance of R^B is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally

substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$,$-CN$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}S(=O)_2R^{A1}$, $-S(=O)_2R^{A1}$, or $-S(=O)_2N(R^{A1})_2$;

each instance of R^{A1} is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form an optionally substituted heterocyclic ring;

each instance of R^X is independently selected from the group consisting of R^D, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and $-N(R^{A1})(R^{Xa})$;

each instance of R^{Xa} is 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, optionally substituted heteroaryl, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-S(=O)R^{A1}$, $-S(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, $-S(=O)_2N(R^{A1})_2$, $-N(R^{A1})_2$, and a nitrogen protecting group;

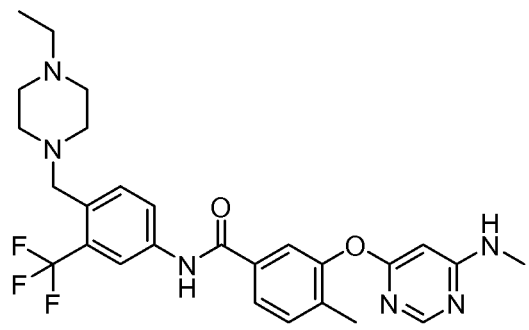
k is 0, 1, 2, 3, or 4;

l is 1, 2, 3, 4, or 5;

Q and U are taken together to be $-NR^A(C=O)-$ or $-(C=O)NR^A-$; and

R^D is an electrophilic moiety as described herein.

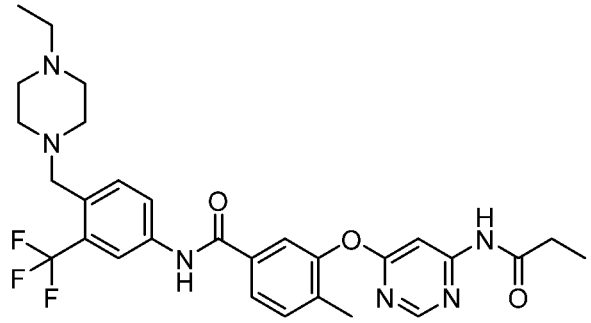
[0069] In certain embodiments, the subject is adminstered compound (**A-1**):



(**A-1**),

or a pharmaceutically acceptable salt thereof.

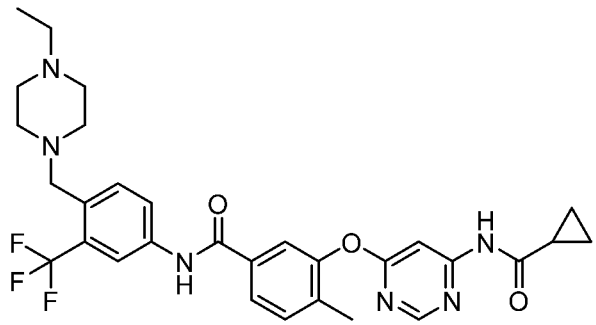
[0070] In certain embodiments, the subject is adminstered compound (**A-2**):



(**A-2**),

or a pharmaceutically acceptable salt thereof.

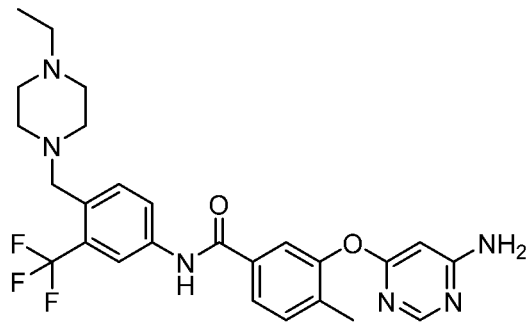
[0071] In certain embodiments, the subject is adminstered compound (**A-3**):



(**A-3**),

or a pharmaceutically acceptable salt thereof.

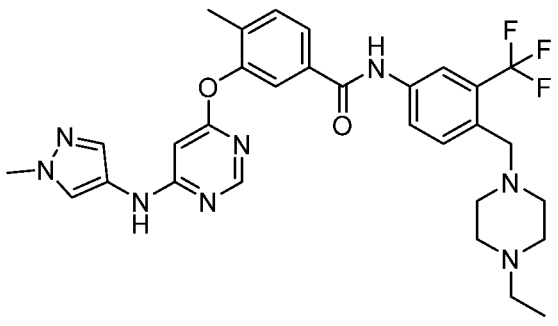
[0072] In certain embodiments, the subject is adminstered compound (**A-4**):



(**A-4**),

or a pharmaceutically acceptable salt thereof.

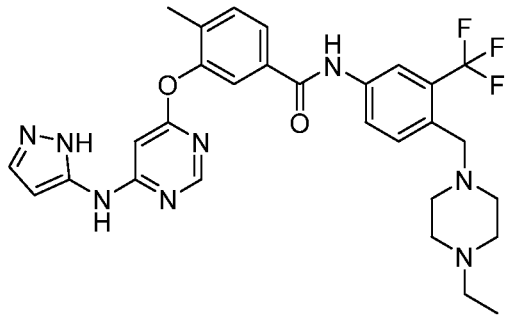
[0073] In certain embodiments, the subject is adminstered compound (**A-5**):



(**A-5**),

or a pharmaceutically acceptable salt thereof.

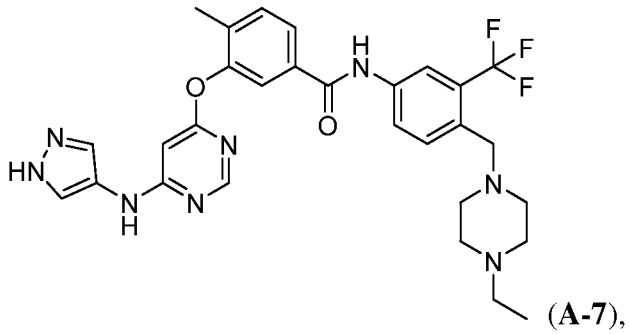
[0074] In certain embodiments, the subject is adminstered compound (**A-6**):



(**A-6**),

or a pharmaceutically acceptable salt thereof.

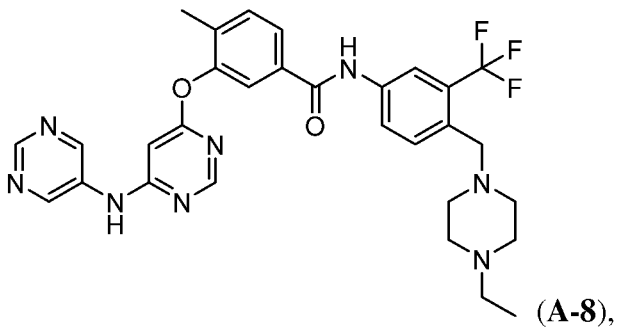
[0075] In certain embodiments, the subject is adminstered compound (**A-7**):



(**A-7**),

or a pharmaceutically acceptable salt thereof.

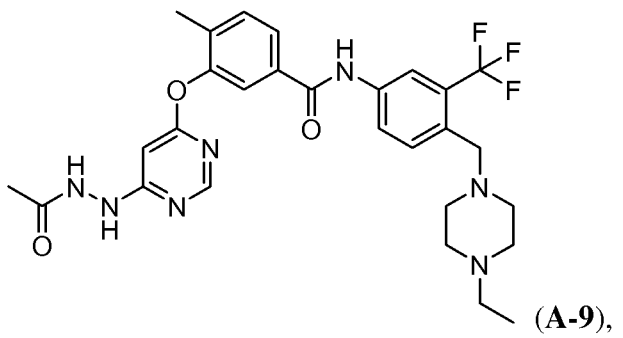
[0076] In certain embodiments, the subject is adminstered compound (**A-8**):



(**A-8**),

or a pharmaceutically acceptable salt thereof.

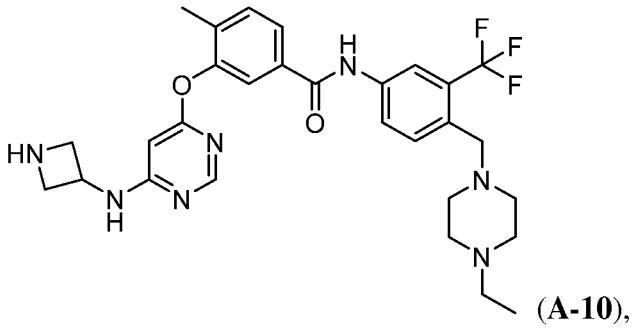
[0077] In certain embodiments, the subject is adminstered compound (**A-9**):



(**A-9**),

or a pharmaceutically acceptable salt thereof.

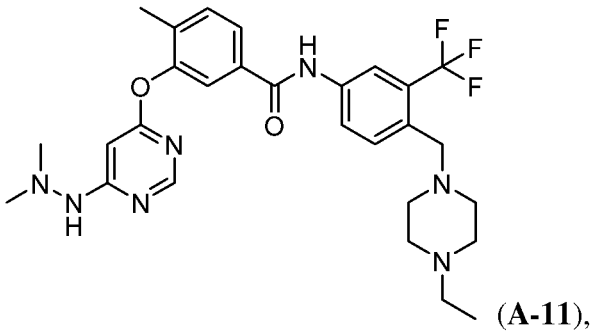
[0078] In certain embodiments, the subject is adminstered compound (**A-10**):



(**A-10**),

or a pharmaceutically acceptable salt thereof.

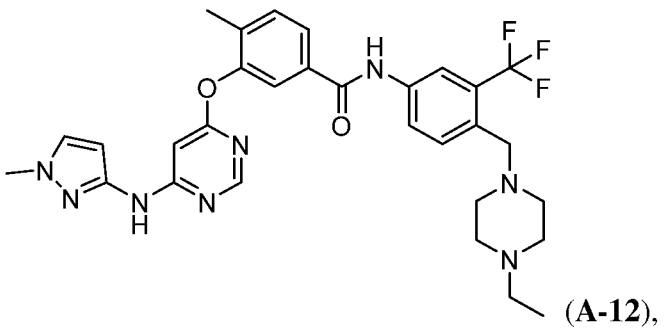
[0079] In certain embodiments, the subject is adminstered compound (**A-11**):



(**A-11**),

or a pharmaceutically acceptable salt thereof.

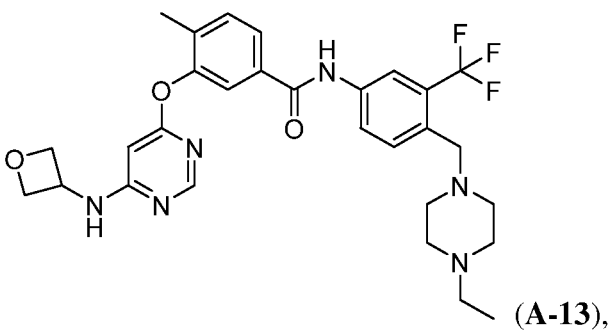
[0080] In certain embodiments, the subject is adminstered compound (**A-12**):



(**A-12**),

or a pharmaceutically acceptable salt thereof.

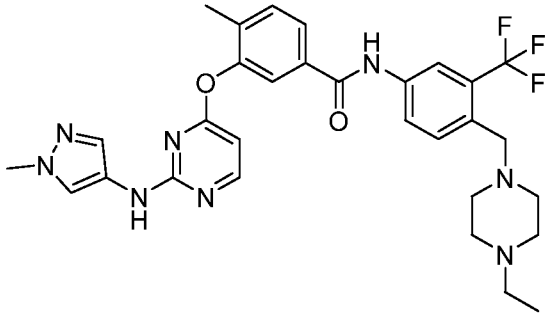
[0081] In certain embodiments, the subject is adminstered compound (**A-13**):



(**A-13**),

or a pharmaceutically acceptable salt thereof.

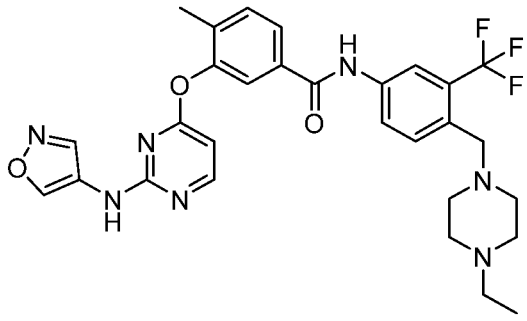
[0082] In certain embodiments, the subject is adminstered compound (**A-14**):



(**A-14**),

or a pharmaceutically acceptable salt thereof.

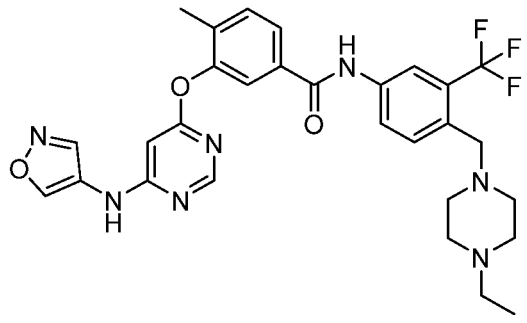
[0083] In certain embodiments, the subject is adminstered compound (**A-15**):



(**A-15**),

or a pharmaceutically acceptable salt thereof.

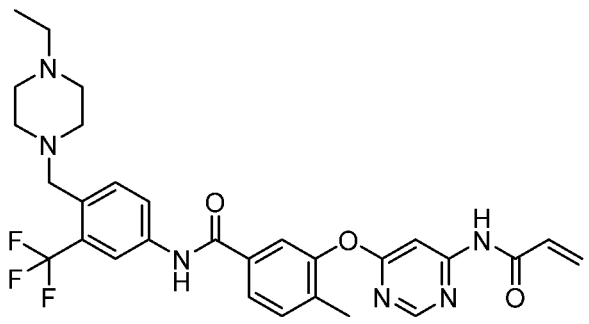
[0084] In certain embodiments, the subject is adminstered compound (**A-16**):



(**A-16**),

or a pharmaceutically acceptable salt thereof.

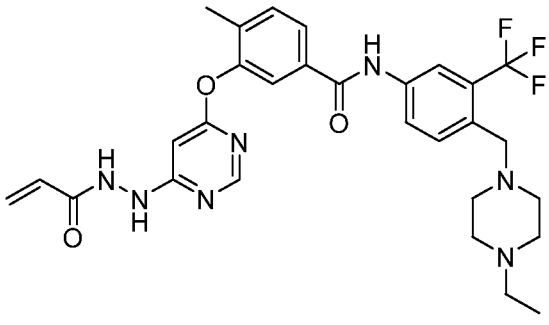
[0085] In certain embodiments, the subject is adminstered compound (**A-17**):



(**A-17**),

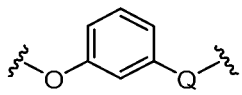
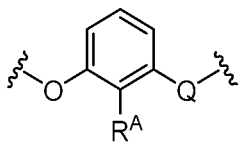
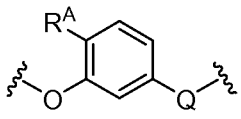
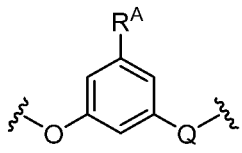
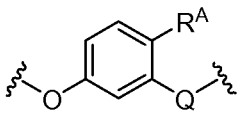
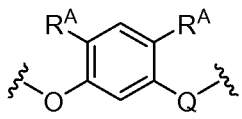
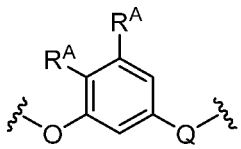
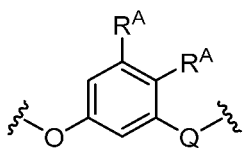
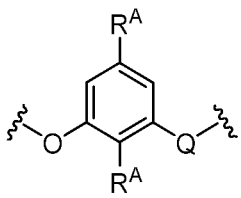
or a pharmaceutically acceptable salt thereof.

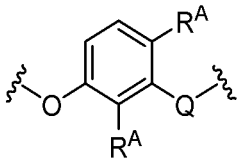
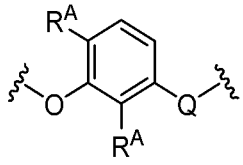
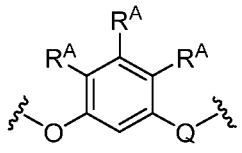
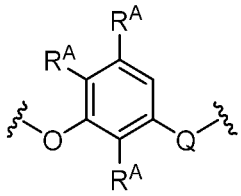
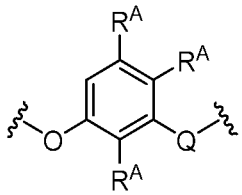
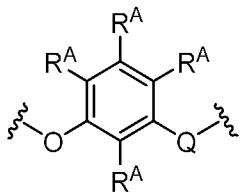
[0086] In certain embodiments, the subject is adminstered compound (**A-18**):



(**A-18**),

or a pharmaceutically acceptable salt thereof.

[0087] Compounds of Formula (**A**) include a phenyl Ring A optionally substituted with one or more R^A groups. In certain embodiments, k is 0. In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, k is 2. In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In

certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, k is 3. In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, Ring A is of the formula:  . In certain embodiments, k is 4. In certain embodiments, Ring A is of the formula:  .

[0088] In compounds of Formula (**A**), Ring A may be substituted with one or more R^A groups. In certain embodiments, at least one R^A is H. In certain embodiments, at least two R^A groups are H. In certain embodiments, at least three R^A groups are H. In certain embodiments, at least four R^A groups are H. In certain embodiments, at least one R^A is not H. In certain embodiments, at least two R^A groups are not H. In certain embodiments, at least three R^A groups are not H. In certain embodiments, at least one R^A is halogen. In certain embodiments, at least one R^A is F. In certain embodiments, at least one R^A is Cl. In certain embodiments, at least one R^A is Br. In certain embodiments, at least one R^A is I (iodine). In certain embodiments, one R^A is F. In certain embodiments, one R^A is Cl. In certain embodiments, at least one R^A is substituted alkyl. In certain embodiments, at least one R^A is unsubstituted alkyl. In certain embodiments, at least one R^A is substituted C_{1-6} alkyl. In

certain embodiments, at least one R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^A is methyl. In certain embodiments, at least one R^A is ethyl. In certain embodiments, at least one R^A is propyl. In certain embodiments, at least one R^A is butyl. In certain embodiments, at least one R^A is substituted carbocyclyl. In certain embodiments, at least one R^A is unsubstituted carbocyclyl. In certain embodiments, at least one R^A is $-OR^{A1}$. In certain embodiments, at least one R^A is $-O(C_{1-6}$ alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^A is –OMe. In certain embodiments, at least one R^A is –OH. In certain embodiments, at least one R^A is $-N(R^{A1})_2$. In certain embodiments, at least one R^A is $-NH_2$. In certain embodiments, at least one R^A is –CN. In certain embodiments, at least one R^A is $-C(=O)R^{A1}$. In certain embodiments, at least one R^A is acetyl. In certain embodiments, at least one R^A is $-C(=O)OR^{A1}$. In certain embodiments, at least one R^A is $-C(=O)N(R^{A1})_2$. In certain embodiments, at least one R^A is $-C(=O)NHR^{A1}$. In certain embodiments, at least one R^A is $-C(=O)NH(C_{1-6}$ alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^A is –C(=O)NHMe. In certain embodiments, at least one R^A is $-C(=O)NH_2$. In certain embodiments, at least one R^A is $-NO_2$. In certain embodiments, at least one R^A is $-NR^{A1}C(=O)R^{A1}$. In certain embodiments, at least one R^A is $-NR^{A1}C(=O)OR^{A1}$. In certain embodiments, at least one R^A is $-NR^{A1}S(=O)_2R^{A1}$. In certain embodiments, at least one R^A is $-NHS(=O)_2R^{A1}$. In certain embodiments, at least one R^A is $-NHS(=O)_2(C_{1-6}$ alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^A is $-NHS(=O)_2$Me. In certain embodiments, at least one R^A is $-S(=O)_2R^{A1}$. In certain embodiments, at least one R^A is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^A is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^A is $-S(=O)_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one R^A is $-S(=O)_2NH(C_{1-6}$ alkyl). In certain embodiments, at least one R^A is $-S(=O)_2NH(t$-Bu). In certain embodiments, at least one R^A is $-S(=O)_2NH_2$.

[0089] In certain embodiments, R^A is $-OR^{A1}$; and k is 1. In certain embodiments, R^A is $-O(C_{1-6}$ alkyl); and k is 1. In certain embodiments, R^A is –OMe; and k is 1. In certain embodiments, R^A is –OH; and k is 1.

[0090] In certain embodiments, R^A is substituted C_{1-6} alkyl; and k is 1. In certain embodiments, R^A is unsubstituted C_{1-6} alkyl; and k is 1. In certain embodiments, R^A is methyl; and k is 1. In certain embodiments, R^A is $-CF_3$; and k is 1. In certain embodiments, R^A is ethyl; and k is 1. In certain embodiments, R^A is propyl; and k is 1. In certain embodiments, R^A is butyl; and k is 1. In certain embodiments, R^A is propyl; and k is 1. In certain embodiments, R^A is butyl; and k is 1.

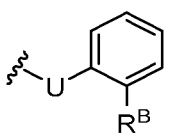
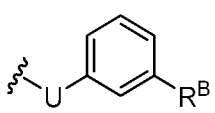
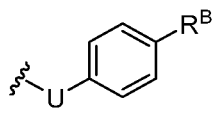
[0091] In certain embodiments, R^A is halogen; and k is 1. In certain embodiments, R^A is F; and k is 1. In certain embodiments, R^A is Cl; and k is 1. In certain embodiments, R^A is Br; and k is 1. In certain embodiments, R^A is I (iodine); and k is 1.

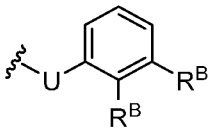
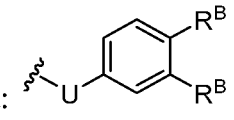
[0092] In certain embodiments, one instance of R^A is halogen; another instance of R^A is substituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is F; another instance of R^A is substituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is Cl; another instance of R^A is substituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is halogen; another instance of R^A is unsubstituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is F; another instance of R^A is unsubstituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is Cl; another instance of R^A is unsubstituted C_{1-6} alkyl; and k is 2. In certain embodiments, one instance of R^A is halogen; another instance of R^A is methyl; and k is 2. In certain embodiments, one instance of R^A is F; another instance of R^A is methyl; and k is 2. In certain embodiments, one instance of R^A is Cl; another instance of R^A is methyl; and k is 2. In certain embodiments, one instance of R^A is halogen; another instance of R^A is $-CF_3$; and k is 2. In certain embodiments, one instance of R^A is F; another instance of R^A is $-CF_3$; and k is 2. In certain embodiments, one instance of R^A is Cl; another instance of R^A is $-CF_3$; and k is 2.

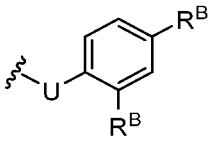
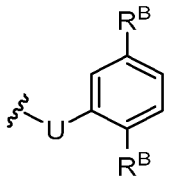
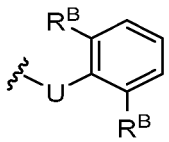
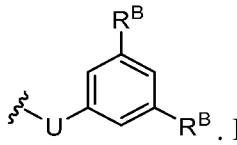
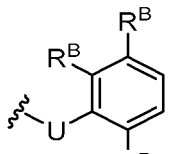
[0093] In certain embodiments, at least one R^{A1} is H. In certain embodiments, at least one R^{A1} is substituted acyl. In certain embodiments, at least one R^{A1} is unsubstituted acyl. In certain embodiments, at least one R^{A1} is acetyl. In certain embodiments, at least one R^{A1} is substituted alkyl. In certain embodiments, at least one R^{A1} is unsubstituted alkyl. In certain embodiments, at least one R^{A1} is C_{1-6} alkyl. In certain embodiments, at least one R^{A1} is methyl. In certain embodiments, at least one R^{A1} is ethyl. In certain embodiments, at least one R^{A1} is propyl. In certain embodiments, at least one R^{A1} is butyl. In certain embodiments, at least one R^{A1} is substituted alkenyl. In certain embodiments, at least one R^{A1} is unsubstituted alkenyl. In certain embodiments, at least one R^{A1} is substituted alkynyl. In certain embodiments, at least one R^{A1} is unsubstituted alkynyl. In certain embodiments, at least one R^{A1} is substituted carbocyclyl. In certain embodiments, at least one R^{A1} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{A1} is substituted heterocyclyl. In certain embodiments, at least one R^{A1} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{A1} is substituted aryl. In certain embodiments, at least one R^{A1} is unsubstituted aryl. In certain embodiments, at least one R^{A1} is substituted phenyl. In certain embodiments, at least one R^{A1} is unsubstituted phenyl. In certain embodiments, at least one R^{A1} is substituted heteroaryl. In certain embodiments, at least one R^{A1} is unsubstituted heteroaryl. In certain

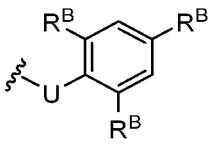
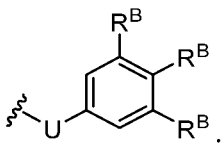
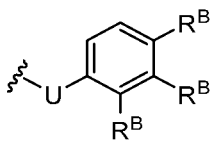
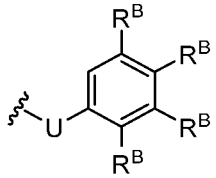
embodiments, at least one R^{A1} is substituted pyridyl. In certain embodiments, at least one R^{A1} is unsubstituted pyridyl. In certain embodiments, at least one R^{A1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one R^{A1} is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{A1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{A1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{A1} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{A1} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

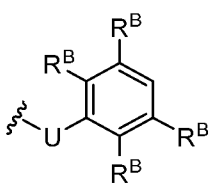
[0094] In compounds of Formula (**A**), two R^{A1} groups may be joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring. In certain embodiments, two R^{A1} groups are joined to form a substituted carbocyclic ring. In certain embodiments, two R^{A1} groups are joined to form an unsubstituted carbocyclic ring. In certain embodiments, two R^{A1} groups are joined to form a substituted heterocyclic ring. In certain embodiments, two R^{A1} groups are joined to form an unsubstituted heterocyclic ring. In certain embodiments, two R^{A1} groups are joined to form a substituted aryl ring. In certain embodiments, two R^{A1} groups are joined to form an unsubstituted aryl ring. In certain embodiments, two R^{A1} groups are joined to form a substituted phenyl ring. In certain embodiments, two R^{A1} groups are joined to form an unsubstituted phenyl ring. In certain embodiments, two R^{A1} groups are joined to form a substituted heteroaryl ring. In certain embodiments, two R^{A1} groups are joined to form an unsubstituted heteroaryl ring.

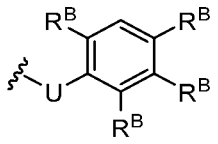
[0095] Compounds of Formula (**A**) include a phenyl Ring C optionally substituted with one or more R^B groups. In certain embodiments, l is 1. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, l is 2. In certain embodiments, Ring C is of the formula:

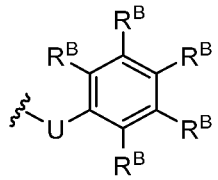

. In certain embodiments, l is 2. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:

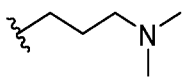
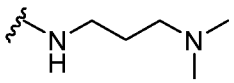
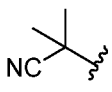

. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, l is 3. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:

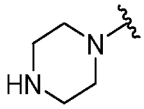
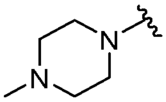
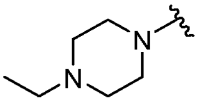
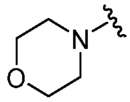
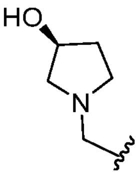
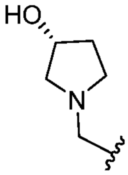
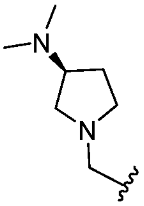
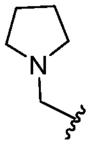
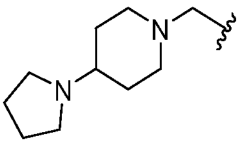
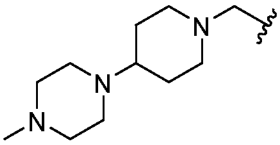
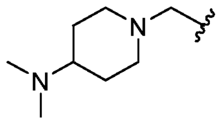
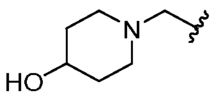
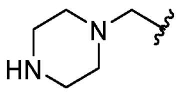
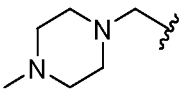
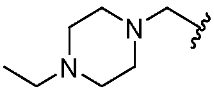
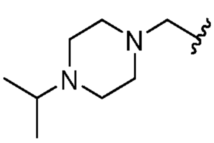
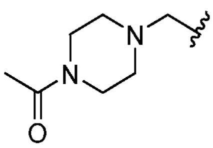

. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:  . In certain embodiments, l is 4. In certain embodiments, Ring C is of the formula:  . In certain embodiments, Ring C is of the formula:

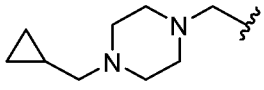
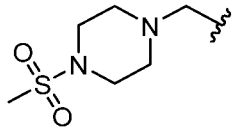
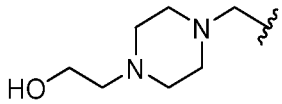
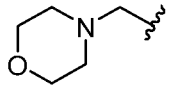
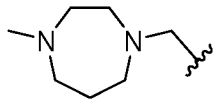
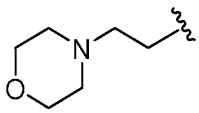
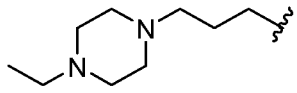
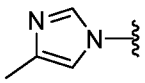
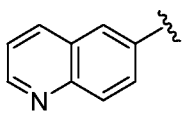
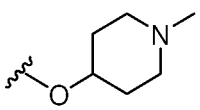
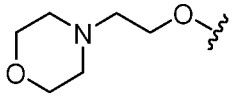

. In certain embodiments, Ring C is of the formula:

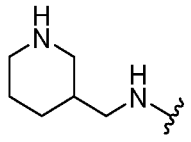
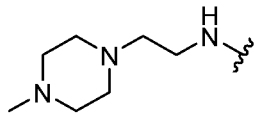
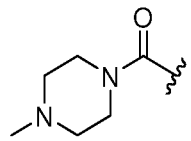
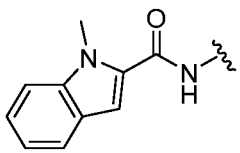
of the formula:  . In certain embodiments, l is 5. In certain embodiments,

Ring C is of the formula:  .

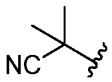
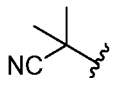
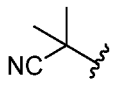
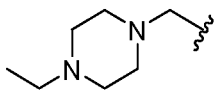
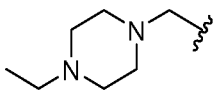
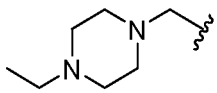
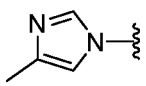
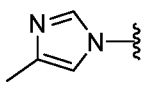
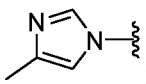
[0096] In compounds of Formula (**A**), Ring C may be substituted with one or more R^B groups. In certain embodiments, at least one R^B is H. In certain embodiments, at least two R^B groups are H. In certain embodiments, at least three R^B groups are H. In certain embodiments, at least four R^B groups are H. In certain embodiments, at least one R^B is not H. In certain embodiments, at least two R^B groups are not H. In certain embodiments, at least three R^B groups are not H. In certain embodiments, at least one R^B is halogen. In certain embodiments, at least one R^B is F. In certain embodiments, at least one R^B is Cl. In certain embodiments, at least one R^B is Br. In certain embodiments, at least one R^B is I (iodine). In certain embodiments, one R^B is F. In certain embodiments, one R^B is Cl. In certain embodiments, at least one R^B is substituted alkyl. In certain embodiments, at least one R^B is unsubstituted alkyl. In certain embodiments, at least one R^B is substituted C_{1-6} alkyl. In certain embodiments, at least one R^B is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^B is methyl. In certain embodiments, at least one R^B is ethyl. In certain embodiments, at least one R^B is propyl. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is butyl. In certain embodiments, at least one R^B is substituted carbocyclyl. In certain embodiments, at least one R^B is unsubstituted carbocyclyl. In certain embodiments, at least one R^B is substituted heterocyclyl. In certain embodiments, at least one R^B is unsubstituted heterocyclyl. In certain embodiments, at least one R^B is substituted piperidine. In certain embodiments, at least one R^B is unsubstituted piperidine. In certain embodiments, at least one R^B substituted piperizine. In certain embodiments, at least one R^B unsubstituted piperizine. In certain embodiments, at least one R^B substituted pyrrolidine. In certain embodiments, at least one R^B unsubstituted pyrrolidine. In certain embodiments, at least one R^B is substituted morpholine. In certain embodiments, at least one R^B is unsubstituted morpholine. In certain

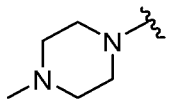
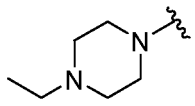
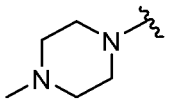
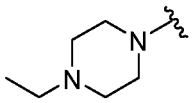
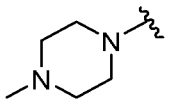
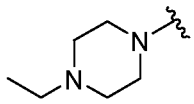
embodiments, at least one R^B is substituted diazapane. In certain embodiments, at least one R^B is unsubstituted diazapane. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is substituted –(CH_2)(heterocyclyl). In certain embodiments, at least one R^B is unsubstituted –(CH_2)(heterocyclyl). In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain

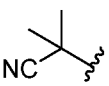
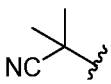
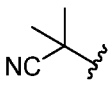
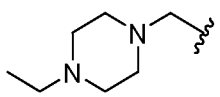
embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is substituted –$(CH_2)_2$(heterocyclyl). In certain embodiments, at least one R^B is unsubstituted –$(CH_2)_2$(heterocyclyl). In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is substituted –$(CH_2)_3$(heterocyclyl). In certain embodiments, at least one R^B is unsubstituted –$(CH_2)_3$(heterocyclyl). In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is substituted aryl. In certain embodiments, at least one R^B is unsubstituted aryl. In certain embodiments, at least one R^B is substituted phenyl. In certain embodiments, at least one R^B is unsubstituted phenyl. In certain embodiments, at least one R^B is substituted heteroaryl. In certain embodiments, at least one R^B is unsubstituted heteroaryl. In certain embodiments, at least one R^B is substituted pyridyl. In certain embodiments, at least one R^B is unsubstituted pyridyl. In certain embodiments, at least one R^B is substituted imidazole. In certain embodiments, at least one R^B is unsubstituted imidazole. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is $–OR^{A1}$. In certain embodiments, at least one R^B is –O(C_{1-6} alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^B is –OMe. In certain embodiments, at least one R^B is –OPh. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is –OH. In certain embodiments, at least one R^B is $–N(R^{A1})_2$. In

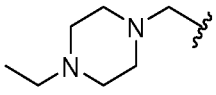
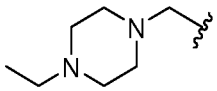
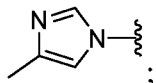
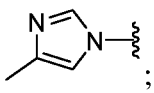
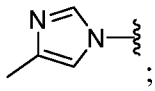
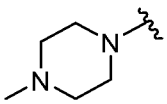
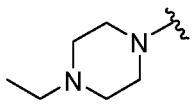
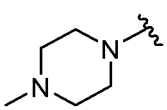
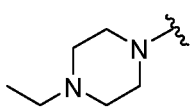
certain embodiments, at least one R^B is $-NEt_2$. In certain embodiments, at least one R^B is $-NMe_2$. In certain embodiments, at least one R^B is $-NHtBu$. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is $-NH_2$. In certain embodiments, at least one R^B is $-CN$. In certain embodiments, at least one R^B is $-C(=O)R^{A1}$. In certain embodiments, at least one R^B is acetyl. In certain embodiments, at least one R^B is $-C(=O)OR^{A1}$. In certain embodiments, at least one R^B is $-C(=O)N(R^{A1})_2$. In certain embodiments, at least one R^B is $-C(=O)NHR^{A1}$. In certain embodiments, at least one R^B is $-C(=O)NH(C_{1-6}$ alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^B is $-C(=O)NHMe$. In certain embodiments, at least one R^B is $-C(=O)NH_2$. In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is  . In certain embodiments, at least one R^B is $-NO_2$. In certain embodiments, at least one R^B is $-NR^{A1}C(=O)R^{A1}$. In certain embodiments, at least one R^B is $-NR^{A1}C(=O)OR^{A1}$. In certain embodiments, at least one R^B is $-NR^{A1}S(=O)_2R^{A1}$. In certain embodiments, at least one R^B is $-NHS(=O)_2R^{A1}$. In certain embodiments, at least one R^B is $-NHS(=O)_2(C_{1-6}$ alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^B is $-NHS(=O)_2Me$. In certain embodiments, at least one R^B is $-S(=O)_2R^{A1}$. In certain embodiments, at least one R^B is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^B is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^B is $-S(=O)_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one R^B is $-S(=O)_2NH(C_{1-6}$ alkyl). In certain embodiments, at least one R^B is $-S(=O)_2NH(t$-Bu). In certain embodiments, at least one R^B is $-S(=O)_2NH_2$.

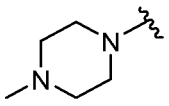
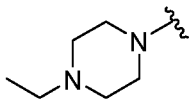
[0097] In certain embodiments, R^B is substituted or unsubstituted C_{1-6}alkyl; and l is 1. In certain embodiments, R^B is substituted or unsubstituted C_{1-6}alkyl; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted C_{1-6}alkyl; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is C_{1-6}alkyl substituted with one –CN group; and l is 1. In certain embodiments, R^B is C_{1-6}alkyl substituted with one –CN group; l is 1; and R^B is *meta* to the point of attachment of U. In

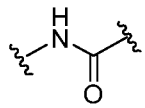
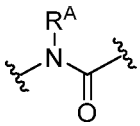
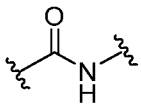
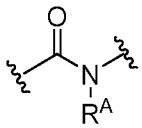
certain embodiments, R^B is C_{1-6}alkyl substituted with one –CN group; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is  ; and l is 1. In certain embodiments, R^B is  ; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is  ; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted –CH_2–(piperazinyl); and l is 1. In certain embodiments, R^B is substituted or unsubstituted –CH_2–(piperazinyl); l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted –CH_2–(piperazinyl); l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is  ; and l is 1. In certain embodiments, R^B is  ; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is  ; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is haloalkyl; and l is 1. In certain embodiments, R^B is haloalkyl; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is haloalkyl; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is –CF_3; and l is 1. In certain embodiments, R^B is –CF_3; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is –CF_3; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted imidazoyl; and l is 1. In certain embodiments, R^B is substituted or unsubstituted imidazoyl; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted imidazoyl; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is  ; and l is 1. In certain embodiments, R^B is  ; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is  ; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted piperazinyl; and l is 1. In certain embodiments, R^B is substituted or unsubstituted piperazinyl; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted piperazinyl; l is 1; and R^B is *para* to the point

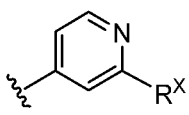
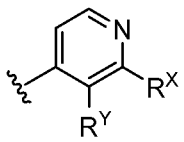
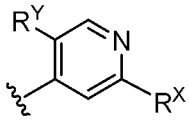
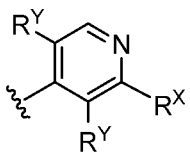
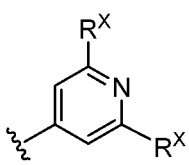
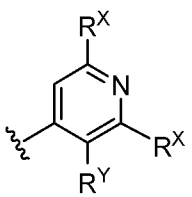
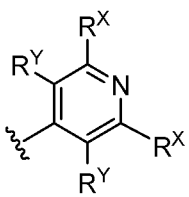
of attachment of U. In certain embodiments, R^B is  or  ; and l is 1. In certain embodiments, R^B is  or  ; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is  or  ; l is 1; and R^B is *para* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted morpholine; and l is 1. In certain embodiments, R^B is substituted or unsubstituted morpholine; l is 1; and R^B is *meta* to the point of attachment of U. In certain embodiments, R^B is substituted or unsubstituted morpholine; l is 1; and R^B is *para* to the point of attachment of U.

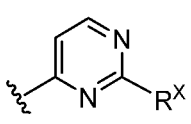
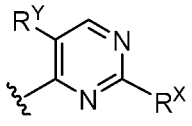
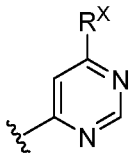
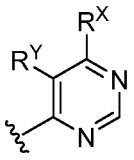
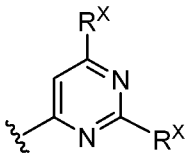
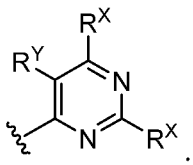
[0098] In certain embodiments, at least one R^B group is substituted or unsubstituted C_{1-6}alkyl; and l is 2. In certain embodiments, at least one R^B group is substituted or unsubstituted C_{1-6}alkyl; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted C_{1-6}alkyl; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is C_{1-6}alkyl substituted with one –CN group; and l is 2. In certain embodiments, at least one R^B group is C_{1-6}alkyl substituted with one –CN group; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is C_{1-6}alkyl substituted with one –CN group; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; and l is 2. In certain embodiments, at least one R^B group is  ; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted –CH_2–(piperazinyl); and l is 2. In certain embodiments, at least one R^B group is substituted or unsubstituted –CH_2–(piperazinyl); l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted –CH_2–(piperazinyl); l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; and l is 2. In certain

embodiments, at least one R^B group is  ; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is haloalkyl; and l is 2. In certain embodiments, at least one R^B group is haloalkyl; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is haloalkyl; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is $-CF_3$; and l is 2. In certain embodiments, at least one R^B group is $-CF_3$; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is $-CF_3$; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted imidazoyl; and l is 2. In certain embodiments, at least one R^B group is substituted or unsubstituted imidazoyl; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted imidazoyl; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; and l is 2. In certain embodiments, at least one R^B group is  ; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is  ; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted piperazinyl; and l is 2. In certain embodiments, at least one R^B group is substituted or unsubstituted piperazinyl; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted piperazinyl; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is  or  ; and l is 2. In certain embodiments, at least one R^B group is  or  ; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is

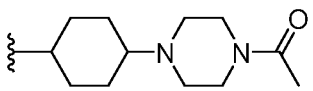
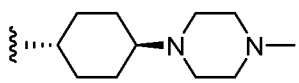
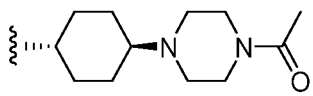
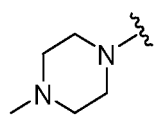
 or  ; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted morpholine; and l is 2. In certain embodiments, at least one R^B group is substituted or unsubstituted morpholine; l is 2; and at least one R^B is *meta* to the point of attachment of U. In certain embodiments, at least one R^B group is substituted or unsubstituted morpholine; l is 2; and one R^B is *para* to the point of attachment of U. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine; l is 2; and both R^B groups are *meta* to the point of attachment of U.

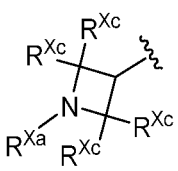
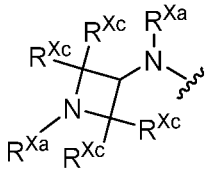
[0099] In compounds of Formula (**A**), Q and U are taken together to represent a divalent linker moiety. In certain embodiments, Q and U are taken together to represent  . In certain embodiments, Q and U are taken together to represent  . In certain embodiments, Q and U are taken together to represent  . In certain embodiments, Q and U are taken together to represent  .

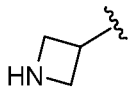
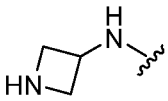
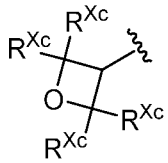
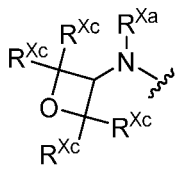
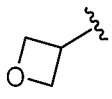
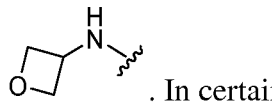
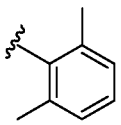
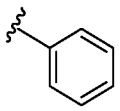
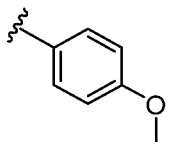
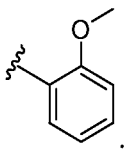
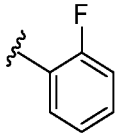
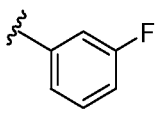
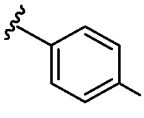
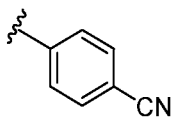
[00100] Formula (**A**) includes a pyridine or pyrimidine ring as Ring B. In certain embodiments, each instance of A included in Ring B is carbon. In certain embodiments, one instance of A included in Ring B is carbon, and the other instance of A included in Ring B is nitrogen. In certain embodiments, Ring B is of the formula:  ,  ,  , or  . In certain embodiments, Ring B is of the formula:  ,  , or  . In certain embodiments, Ring B is of the

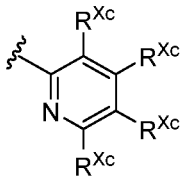
formula:  or  . In certain embodiments, Ring B is of the formula:  or  . In certain embodiments, Ring B is of the formula:  or  .

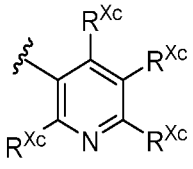
[00101] Formula (**A**) may include one or more R^Y groups. When Formula (**A**) includes two instances of R^Y, the two instances of R^Y may be the same or different from each other. In certain embodiments, at least one instance of R^Y is H. In certain embodiments, each instance of R^Y is H. In certain embodiments, at least one instance of R^Y is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, at least one instance of R^Y is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^Y is Me. In certain embodiments, at least one instance of R^Y is substituted methyl (*e.g.*, $-CF_3$ or Bn). In certain embodiments, at least one instance of R^Y is Et, substituted ethyl (*e.g.*, perfluoroethyl), Pr, substituted propyl (*e.g.*, perfluoropropyl), Bu, or substituted butyl (*e.g.*, perfluorobutyl).

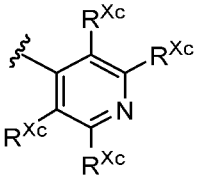
[00102] In compounds of Formula (**A**), the pyridine or pyrimidine ring may be substituted with one or more R^X groups. When Formula (**A**) includes two instances of R^X, the two instances of R^X may be the same or different from each other. In certain embodiments, at least one R^X is substituted carbocyclyl. In certain embodiments, at least one R^X is unsubstituted carbocyclyl. In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is substituted heterocyclyl. In certain embodiments, at least one R^X is unsubstituted heterocyclyl. In certain embodiments, at least one R^X is  . In certain embodiments,

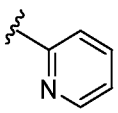
at least one R^X is  . In certain embodiments, at least one R^X is  .

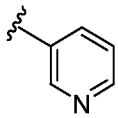
In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is substituted aryl. In certain embodiments, at least one R^X is unsubstituted aryl. In certain embodiments, at least one R^X is substituted phenyl. In certain embodiments, at least one R^X is unsubstituted phenyl. In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is substituted heteroaryl. In certain

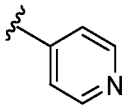


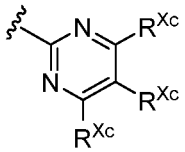


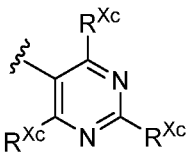


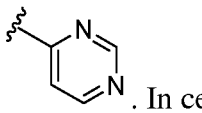


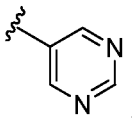


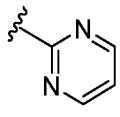


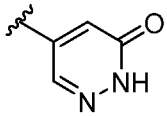


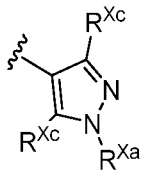


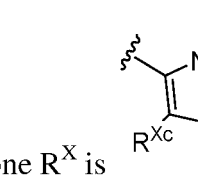


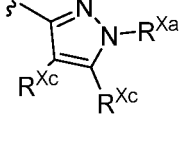




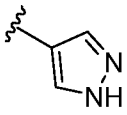


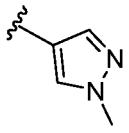


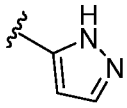


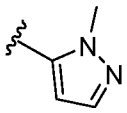


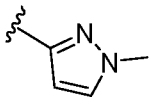
embodiments, at least one R^X is unsubstituted heteroaryl. In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one

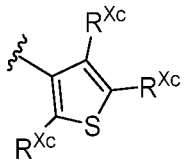


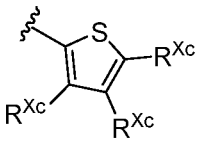


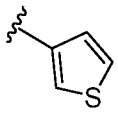


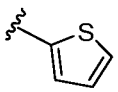


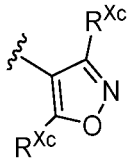


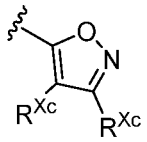


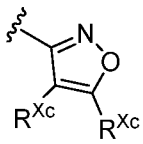


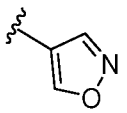


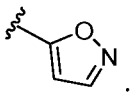


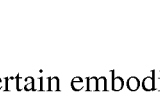


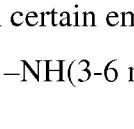


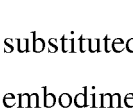


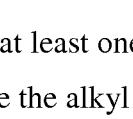


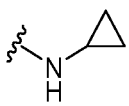




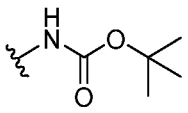
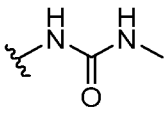
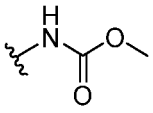
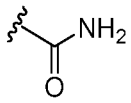
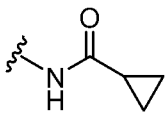
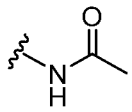
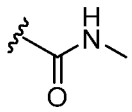
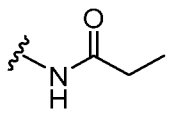
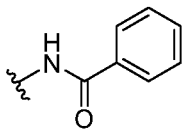
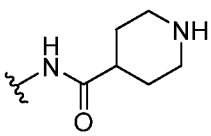
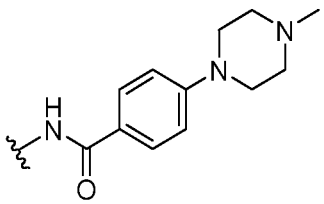


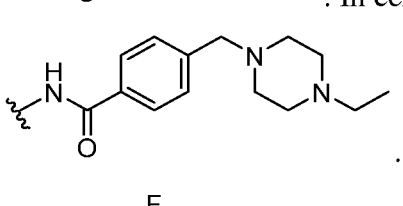


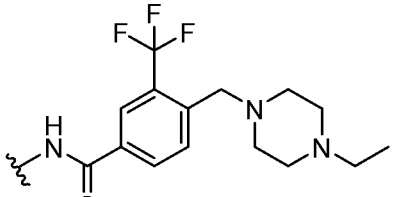




R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is $-N(R^{A1})(R^{Xa})$. In certain embodiments, at least one R^X is $-NH_2$. In certain embodiments, at least one R^X is –NH(3-6 membered cycloalkyl) where the cycloalkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is $-NH(C_{1-6}alkyl)$ where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is $-N(C_{1-6}alkyl)_2$ where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is –NH(acyl). In certain embodiments, at least one R^X is

 . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is –NHC(=O)(3-6 membered cycloalkyl) where the cycloalkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is –NHC(=O)(C_{1-6}alkyl) where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is

 . In certain embodiments, at least one R^X is

 . In certain embodiments, at least one R^X is

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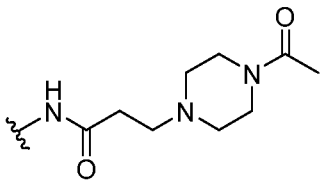
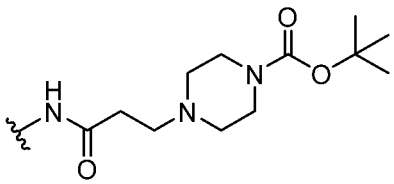
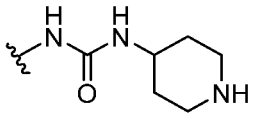


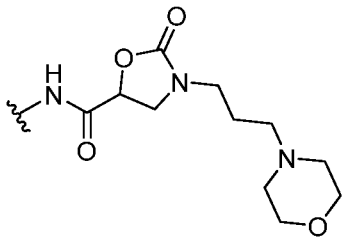
. In certain embodiments, at least one R^X is



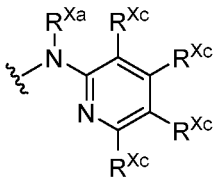
. In certain embodiments, at least one R^X is



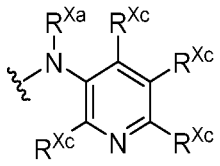
. In certain embodiments, at least one R^X is



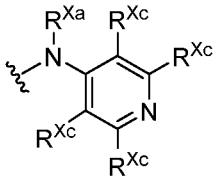
. In certain embodiments, at least one R^X is



. In certain embodiments, at least one R^X is



. In certain embodiments, at least one R^X is



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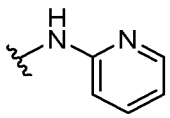

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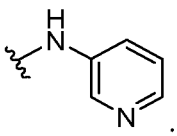

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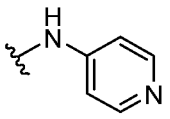

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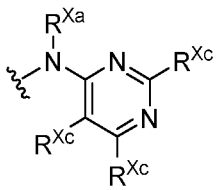

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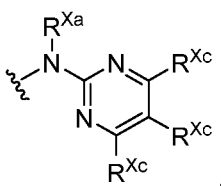

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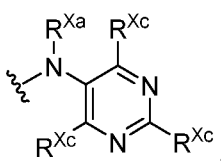
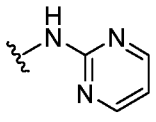
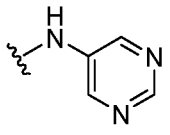
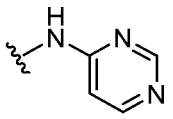
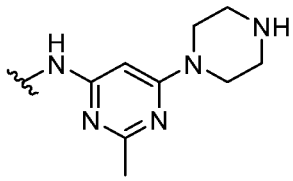


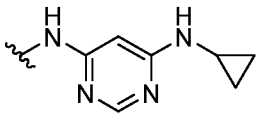
. In certain

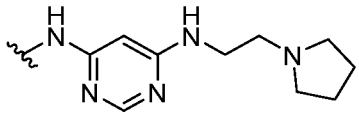


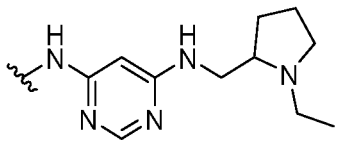


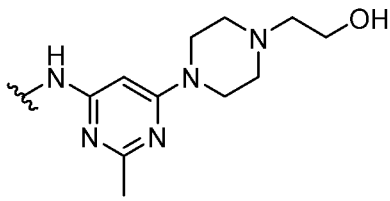


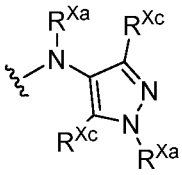


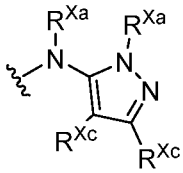


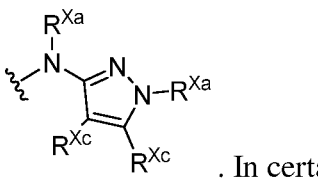


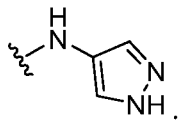


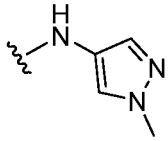


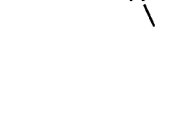




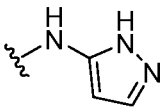


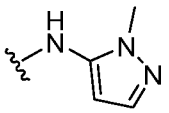


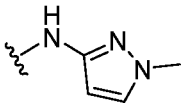


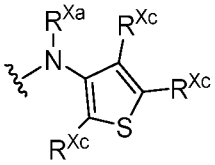


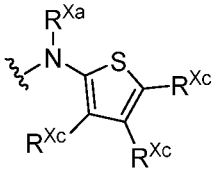
embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is

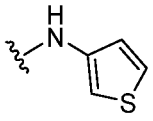


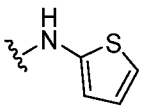


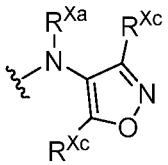


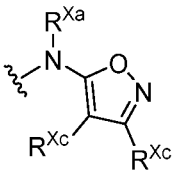


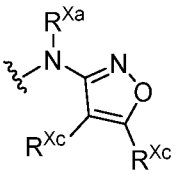


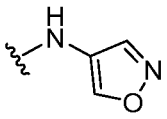


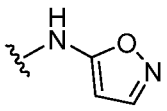


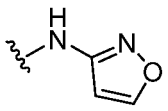


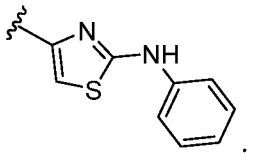


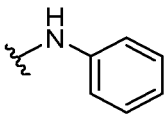


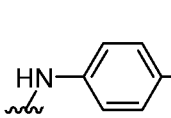


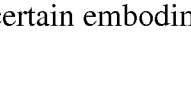


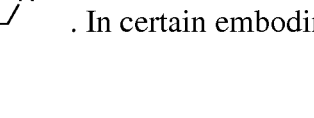




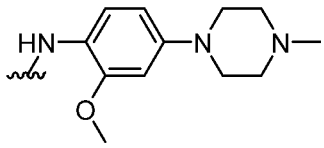
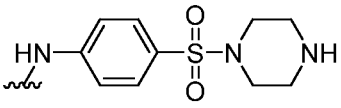








. In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at least one R^X is . In certain embodiments, at

least one R^X is  . In certain embodiments, at least one R^X is  . In certain embodiments, at least one R^X is $-N(R^{A1})N(R^{A1})_2$. In certain embodiments, at least one R^X is $-NHN(R^{A1})_2$. In certain embodiments, at least one R^X is –NHNH(acyl). In certain embodiments, at least one R^X is –NHNHC(=O)Me. In certain embodiments, at least one R^X is $-NHN(C_{1-6}alkyl)_2$ where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^X is $-NHNMe_2$.

[00103] In compounds of Formula (**A**), R^X may be substituted with one or more R^{Xa} groups. Each instance of R^{Xa} is 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, optionally substituted heteroaryl, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-S(=O)R^{A1}$, $-S(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, $-S(=O)_2N(R^{A1})_2$, $-N(R^{A1})_2$, and a nitrogen protecting group; wherein each occurrence of R^{A1} is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form an optionally substituted heterocyclic ring.

[00104] In certain embodiments, at least one R^{Xa} is H. In certain embodiments, all R^{Xa} groups are H. In certain embodiments, at least one R^{Xa} is substituted alkyl. In certain embodiments, at least one R^{Xa} is substituted C_{1-6} alkyl. In certain embodiments, at least one R^{Xa} is substituted methyl. In certain embodiments, at least one R^{Xa} is unsubstituted alkyl. In certain embodiments, at least one R^{Xa} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^{Xa} is methyl. In certain embodiments, at least one R^{Xa} is ethyl. In certain embodiments, at least one R^{Xa} is propyl. In certain embodiments, at least one R^{Xa} is butyl. In certain embodiments, at least one R^{Xa} is substituted alkenyl. In certain embodiments, at least one R^{Xa} is unsubstituted alkenyl. In certain embodiments, at least one R^{Xa} is substituted alkynyl. In certain embodiments, at least one R^{Xa} is unsubstituted alkynyl. In certain

embodiments, at least one R^{Xa} is substituted carbocyclyl. In certain embodiments, at least one R^{Xa} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{Xa} is substituted heterocyclyl. In certain embodiments, at least one R^{Xa} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{Xa} is substituted aryl. In certain embodiments, at least one R^{Xa} is unsubstituted aryl. In certain embodiments, at least one R^{Xa} is substituted phenyl. In certain embodiments, at least one R^{Xa} is unsubstituted phenyl. In certain embodiments, at least one R^{Xa} is substituted heteroaryl. In certain embodiments, at least one R^{Xa} is unsubstituted heteroaryl. In certain embodiments, at least one R^{Xa} is $-C(=O)R^{A1}$. In certain embodiments, at least one R^{Xa} is $-C(=O)H$. In certain embodiments, at least one R^{Xa} is acetyl. In certain embodiments, at least one R^{Xa} is $-C(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-C(=O)OR^{A1}$. In certain embodiments, at least one R^{Xa} is $-C(=O)OH$. In certain embodiments, at least one R^{Xa} is $-C(=O)O(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-C(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xa} is $-C(=O)NHR^{A1}$. In certain embodiments, at least one R^{Xa} is $-C(=O)N(C_{1-6}$ alkyl$)_2$. In certain embodiments, at least one R^{Xa} is $-C(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one R^{Xa} is $-C(=O)NH_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)R^{A1}$. In certain embodiments, at least one R^{Xa} is $-S(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-S(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)NH(R^{A1})$. In certain embodiments, at least one R^{Xa} is $-S(=O)NH_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)NH(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2R^{A1}$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2OR^{A1}$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2OH$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2NH(R^{A1})$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2NH_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xa} is $-S(=O)_2NH(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xa} is $-N(R^{A1})_2$. In certain embodiments, at least one R^{Xa} is $-NH(R^{A1})$. In certain embodiments, at least one R^{Xa} is $-NH(acyl)$. In certain embodiments, at least one R^{Xa} is $-NHC(=O)Me$. In certain embodiments, at least one R^{Xa} is $-N(C_{1-6}alkyl)_2$ where the alkyl is substituted or unsubstituted. In certain embodiments, at least one R^{Xa} is $-NMe_2$.

[00105] In compounds of Formula (**A**), R^X may be substituted with one or more R^{Xc} groups. Each instance of R^{Xc} 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

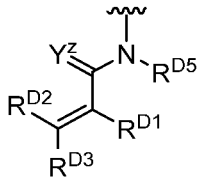
aryl, optionally substituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-N_3$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-NR^{A1}S(=O)_2R^{A1}$, $-NR^{A1}S(=O)R^{A1}$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-S(=O)R^{A1}$, $-S(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2N(R^{A1})_2$; wherein each occurrence of R^{A1} is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form an optionally substituted heterocyclic ring.

[00106] In certain embodiments, at least one R^{Xc} is H. In certain embodiments, all R^{Xc} groups are H. In certain embodiments, at least one R^{Xc} is substituted alkyl. In certain embodiments, at least one R^{Xc} is substituted C_{1-6} alkyl. In certain embodiments, at least one R^{Xc} is substituted methyl. In certain embodiments, at least one R^{Xc} is unsubstituted alkyl. In certain embodiments, at least one R^{Xc} is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^{Xc} is methyl. In certain embodiments, at least one R^{Xc} is ethyl. In certain embodiments, at least one R^{Xc} is propyl. In certain embodiments, at least one R^{Xc} is butyl. In certain embodiments, at least one R^{Xc} is substituted alkenyl. In certain embodiments, at least one R^{Xc} is unsubstituted alkenyl. In certain embodiments, at least one R^{Xc} is substituted alkynyl. In certain embodiments, at least one R^{Xc} is unsubstituted alkynyl. In certain embodiments, at least one R^{Xc} is substituted carbocyclyl. In certain embodiments, at least one R^{Xc} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{Xc} is substituted heterocyclyl. In certain embodiments, at least one R^{Xc} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{Xc} is substituted aryl. In certain embodiments, at least one R^{Xc} is unsubstituted aryl. In certain embodiments, at least one R^{Xc} is substituted phenyl. In certain embodiments, at least one R^{Xc} is unsubstituted phenyl. In certain embodiments, at least one R^{Xc} is substituted heteroaryl. In certain embodiments, at least one R^{Xc} is unsubstituted heteroaryl. In certain embodiments, at least one R^{Xc} is $-OR^{A1}$. In certain embodiments, at least one R^{Xc} is $-OH$. In certain embodiments, at least one R^{Xc} is $-O(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is $-NH(R^{A1})$. In certain embodiments, at least one R^{Xc} is $-N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-NH(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-NH_2$. In certain embodiments, at least one R^{Xc} is $-SR^{A1}$. In certain embodiments, at least one R^{Xc} is –

SH. In certain embodiments, at least one R^{Xc} is $-S(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is –CN. In certain embodiments, at least one R^{Xc} is $-NO_2$. In certain embodiments, at least one R^{Xc} is $-N_3$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}C(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is $-NHC(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is $-NHC(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}C(=O)OR^{A1}$. In certain embodiments, at least one R^{Xc} is $-NHC(=O)OR^{A1}$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}C(=O)O(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}C(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is $-NHC(=O)N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-NHC(=O)NH_2$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}S(=O)_2R^{A1}$. In certain embodiments, at least one R^{Xc} is $-NHS(=O)_2R^{A1}$. In certain embodiments, at least one R^{Xc} is $-NHS(=O)_2(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}S(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is $-NR^{A1}S(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-NHS(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-OC(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is $-OC(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-OC(=O)OR^{A1}$. In certain embodiments, at least one R^{Xc} is $-OC(=O)O(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-OC(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is $-OC(=O)NH(R^{A1})$. In certain embodiments, at least one R^{Xc} is $-OC(=O)N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-C(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is –C(=O)H. In certain embodiments, at least one R^{Xc} is acetyl. In certain embodiments, at least one R^{Xc} is $-C(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-C(=O)OR^{A1}$. In certain embodiments, at least one R^{Xc} is –C(=O)OH. In certain embodiments, at least one R^{Xc} is $-C(=O)O(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-C(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is $-C(=O)NHR^{A1}$. In certain embodiments, at least one R^{Xc} is $-C(=O)N(C_{1-6}$ $alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-C(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one R^{Xc} is $-C(=O)NH_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)R^{A1}$. In certain embodiments, at least one R^{Xc} is $-S(=O)(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-S(=O)N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)NH(R^{A1})$. In certain embodiments, at least one R^{Xc} is $-S(=O)NH_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)NH(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2R^{A1}$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2(C_{1-6}alkyl)$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2OR^{A1}$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2OH$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2N(R^{A1})_2$. In certain embodiments, at least one R^{Xc} is

$-S(=O)_2NH(R^{A1})$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2NH_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2N(C_{1-6}alkyl)_2$. In certain embodiments, at least one R^{Xc} is $-S(=O)_2NH(C_{1-6}alkyl)$.

[00107] In compounds of Formula (**A**), R^D is an optional electrophilic moiety that is attached to the pyridyl ring. In certain embodiments, R^D is any one of Formulae (**i-1**)-(**i-18**):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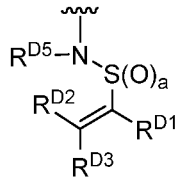
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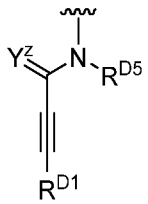
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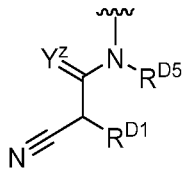
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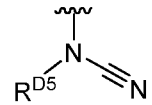
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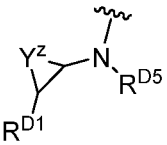
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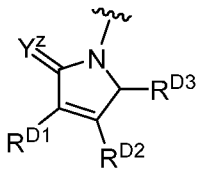
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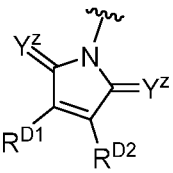
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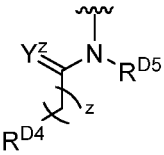
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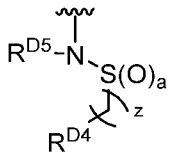
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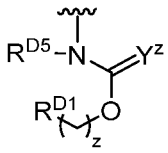
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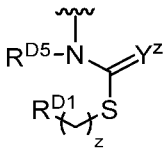
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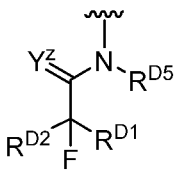
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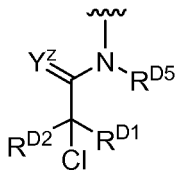
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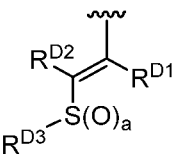
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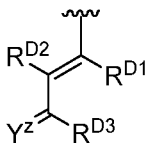
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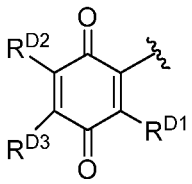
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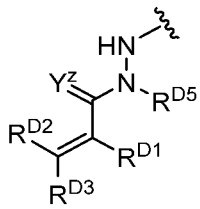

(**i-18**);

R^{D1} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-CN$, $-NO_2$, $-OR^{D1a}$, $-N(R^{D1a})_2$, $-SR^{D1a}$, $-CH_2OR^{D1a}$, $-CH_2N(R^{D1a})_2$, $-CH_2SR^{D1a}$, $-C(=O)R^{D1a}$, $-C(=O)OR^{D1a}$, $-C(=O)SR^{D1a}$, $-C(=O)N(R^{D1a})_2$, $-C(=S)R^{D1a}$, $-C(=S)OR^{D1a}$, $-C(=S)SR^{D1a}$, $-C(=S)N(R^{D1a})_2$, $-C(=NR^{D1a})R^{D1a}$, $-C(=NR^{D1a})OR^{D1a}$, $-C(=NR^{D1a})SR^{D1a}$, and $-C(=NR^{D1a})N(R^{D1a})_2$, wherein each occurrence of R^{D1a} 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^{D1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{D2} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D2a}$, $–N(R^{D2a})_2$, $–SR^{D2a}$, $–CH_2OR^{D2a}$, $–CH_2N(R^{D2a})_2$, $–CH_2SR^{D2a}$, $–C(=O)R^{D2a}$, $–C(=O)OR^{D2a}$, $–C(=O)SR^{D2a}$, $–C(=O)N(R^{D2a})_2$, $–C(=S)R^{D2a}$, $–C(=S)OR^{D2a}$, $–C(=S)SR^{D2a}$, $–C(=S)N(R^{D2a})_2$, $–C(=NR^{D2a})R^{D2a}$, $–C(=NR^{D2a})OR^{D2a}$, $–C(=NR^{D2a})SR^{D2a}$, and $–C(=NR^{D2a})N(R^{D2a})_2$, wherein each occurrence of R^{D2a} 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^{D2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{D3} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D3a}$, $–N(R^{D3a})_2$, $–SR^{D3a}$, $–CH_2OR^{D3a}$, $–CH_2N(R^{D3a})_2$, $–CH_2SR^{D3a}$, $–C(=O)R^{D3a}$, $–C(=O)OR^{D3a}$, $–C(=O)SR^{D3a}$, $–C(=O)N(R^{D3a})_2$, $–C(=S)R^{D3a}$, $–C(=S)OR^{D3a}$, $–C(=S)SR^{D3a}$, $–C(=S)N(R^{D3a})_2$, $–C(=NR^{D3a})R^{D3a}$, $–C(=NR^{D3a})OR^{D3a}$, $–C(=NR^{D3a})SR^{D3a}$, and $–C(=NR^{D3a})N(R^{D3a})_2$, wherein each occurrence of R^{D3a} 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^{D3a} groups are joined to form an optionally substituted heterocyclic ring;

optionally R^{D1} and R^{D3}, or R^{D2} and R^{D3}, or R^{D1} and R^{D2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{D4} is a leaving group;

R^{D5} is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group;

Y^Z is –O–, –S–, or $–NR^{D6}–$, wherein R^{D6} is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group;

a is 1 or 2;

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

optionally R^{D5} and one R^{C} are joined to form an optionally substituted heterocyclic ring.

[00108] In certain embodiments, R^{D} comprises a Michael acceptor moiety. This Michael acceptor moiety may react with a cysteine or other nucleophilic residue to allow covalent attachment of the compound to the target. In certain embodiments, the covalent attachment is irreversible. In other embodiments, the covalent attachment is reversible. In certain embodiments, R^{D} is of Formula (**i-1**). In certain embodiments, R^{D} is of Formula (**i-2**). In certain embodiments, R^{D} is of Formula (**i-3**). In certain embodiments, R^{D} is of Formula (**i-4**). In certain embodiments, R^{D} is of Formula (**i-5**). In certain embodiments, R^{D} is of Formula (**i-6**). In certain embodiments, R^{D} is of Formula (**i-7**). In certain embodiments, R^{D} is of Formula (**i-8**). In certain embodiments, R^{D} is of Formula (**i-9**). In certain embodiments, R^{D} is of Formula (**i-10**). In certain embodiments, R^{D} is of Formula (**i-11**). In certain embodiments, R^{D} is of Formula (**i-12**). In certain embodiments, R^{D} is of Formula (**i-13**). In certain embodiments, R^{D} is of Formula (**i-14**). In certain embodiments, R^{D} is of Formula (**i-15**). In certain embodiments, R^{D} is of Formula (**i-16**). In certain embodiments, R^{D} is of Formula (**i-17**).

[00109] In compounds of Formula (**A**), R^{D} may include a substituent R^{D1}. In certain embodiments, R^{D1} is H. In certain embodiments, R^{D1} is halogen. In certain embodiments, R^{D1} is F. In certain embodiments, R^{D1} is Cl. In certain embodiments, R^{D1} is Br. In certain embodiments, R^{D1} is I (iodine). In certain embodiments, R^{D1} is substituted acyl. In certain embodiments, R^{D1} is unsubstituted acyl. In certain embodiments, R^{D1} is acetyl. In certain embodiments, R^{D1} is substituted alkyl. In certain embodiments, R^{D1} is unsubstituted alkyl. In certain embodiments, R^{D1} is C_{1-6} alkyl. In certain embodiments, R^{D1} is methyl. In certain embodiments, R^{D1} is ethyl. In certain embodiments, R^{D1} is propyl. In certain embodiments, R^{D1} is butyl. In certain embodiments, R^{D1} is substituted alkenyl. In certain embodiments, R^{D1} is unsubstituted alkenyl. In certain embodiments, R^{D1} is substituted alkynyl. In certain embodiments, R^{D1} is unsubstituted alkynyl. In certain embodiments, R^{D1} is substituted carbocyclyl. In certain embodiments, R^{D1} is unsubstituted carbocyclyl. In certain embodiments, R^{D1} is substituted heterocyclyl. In certain embodiments, R^{D1} is unsubstituted heterocyclyl. In certain embodiments, R^{D1} is substituted aryl. In certain embodiments, R^{D1} is unsubstituted aryl. In certain embodiments, R^{D1} is substituted phenyl. In certain embodiments, R^{D1} is unsubstituted phenyl. In certain embodiments, R^{D1} is substituted heteroaryl. In certain embodiments, R^{D1} is unsubstituted heteroaryl. In certain embodiments,

R^{D1} is substituted pyridyl. In certain embodiments, R^{D1} is unsubstituted pyridyl. In certain embodiments, R^{D1} is –CN. In certain embodiments, R^{D1} is $–NO_2$. In certain embodiments, R^{D1} is $–OR^{D1a}$. In certain embodiments, R^{D1} is $–N(R^{D1a})_2$. In certain embodiments, R^{D1} is $–SR^{D1a}$. In certain embodiments, R^{D1} is $–CH_2OR^{D1a}$. In certain embodiments, R^{D1} is $–CH_2N(R^{D1a})_2$. In certain embodiments, R^{D1} is $–CH_2SR^{D1a}$.

[00110] In certain embodiments, at least one R^{D1a} is H. In certain embodiments, at least one R^{D1a} is substituted acyl. In certain embodiments, at least one R^{D1a} is unsubstituted acyl. In certain embodiments, at least one R^{D1a} is acetyl. In certain embodiments, at least one R^{D1a} is substituted alkyl. In certain embodiments, at least one R^{D1a} is unsubstituted alkyl. In certain embodiments, at least one R^{D1a} is C_{1-6} alkyl. In certain embodiments, at least one R^{D1a} is methyl. In certain embodiments, at least one R^{D1a} is ethyl. In certain embodiments, at least one R^{D1a} is propyl. In certain embodiments, at least one R^{D1a} is butyl. In certain embodiments, at least one R^{D1a} is substituted alkenyl. In certain embodiments, at least one R^{D1a} is unsubstituted alkenyl. In certain embodiments, at least one R^{D1a} is substituted alkynyl. In certain embodiments, at least one R^{D1a} is unsubstituted alkynyl. In certain embodiments, at least one R^{D1a} is substituted carbocyclyl. In certain embodiments, at least one R^{D1a} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{D1a} is substituted heterocyclyl. In certain embodiments, at least one R^{D1a} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{D1a} is substituted aryl. In certain embodiments, at least one R^{D1a} is unsubstituted aryl. In certain embodiments, at least one R^{D1a} is substituted phenyl. In certain embodiments, at least one R^{D1a} is unsubstituted phenyl. In certain embodiments, at least one R^{D1a} is substituted heteroaryl. In certain embodiments, at least one R^{D1a} is unsubstituted heteroaryl. In certain embodiments, at least one R^{D1a} is substituted pyridyl. In certain embodiments, at least one R^{D1a} is unsubstituted pyridyl. In certain embodiments, at least one R^{D1a} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one R^{D1a} is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{D1a} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{D1a} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{D1a} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{D1a} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two R^{D1a} groups are joined to form a substituted heterocyclic ring. In certain embodiments, two R^{D1a} groups are joined to form an unsubstituted heterocyclic ring.

[00111] In compounds of Formula (**A**), R^D may include a substituent R^{D2}. In certain embodiments, R^{D2} is H. In certain embodiments, R^{D2} is halogen. In certain embodiments, R^{D2} is F. In certain embodiments, R^{D2} is Cl. In certain embodiments, R^{D2} is Br. In certain embodiments, R^{D2} is I (iodine). In certain embodiments, R^{D2} is substituted acyl. In certain embodiments, R^{D2} is unsubstituted acyl. In certain embodiments, R^{D2} is acetyl. In certain embodiments, R^{D2} is substituted alkyl. In certain embodiments, R^{D2} is unsubstituted alkyl. In certain embodiments, R^{D2} is C_{1-6} alkyl. In certain embodiments, R^{D2} is methyl. In certain embodiments, R^{D2} is ethyl. In certain embodiments, R^{D2} is propyl. In certain embodiments, R^{D2} is butyl. In certain embodiments, R^{D2} is substituted alkenyl. In certain embodiments, R^{D2} is unsubstituted alkenyl. In certain embodiments, R^{D2} is substituted alkynyl. In certain embodiments, R^{D2} is unsubstituted alkynyl. In certain embodiments, R^{D2} is substituted carbocyclyl. In certain embodiments, R^{D2} is unsubstituted carbocyclyl. In certain embodiments, R^{D2} is substituted heterocyclyl. In certain embodiments, R^{D2} is unsubstituted heterocyclyl. In certain embodiments, R^{D2} is substituted aryl. In certain embodiments, R^{D2} is unsubstituted aryl. In certain embodiments, R^{D2} is substituted phenyl. In certain embodiments, R^{D2} is unsubstituted phenyl. In certain embodiments, R^{D2} is substituted heteroaryl. In certain embodiments, R^{D2} is unsubstituted heteroaryl. In certain embodiments, R^{D2} is substituted pyridyl. In certain embodiments, R^{D2} is unsubstituted pyridyl. In certain embodiments, R^{D2} is –CN. In certain embodiments, R^{D2} is $–NO_2$. In certain embodiments, R^{D2} is $–OR^{D2a}$. In certain embodiments, R^{D2} is $–N(R^{D2a})_2$. In certain embodiments, R^{D2} is $–SR^{D2a}$. In certain embodiments, R^{D2} is $–CH_2OR^{D2a}$. In certain embodiments, R^{D2} is $–CH_2N(R^{D2a})_2$. In certain embodiments, R^{D2} is $–CH_2SR^{D2a}$.

[00112] In certain embodiments, at least one R^{D2a} is H. In certain embodiments, at least one R^{D2a} is substituted acyl. In certain embodiments, at least one R^{D2a} is unsubstituted acyl. In certain embodiments, at least one R^{D2a} is acetyl. In certain embodiments, at least one R^{D2a} is substituted alkyl. In certain embodiments, at least one R^{D2a} is unsubstituted alkyl. In certain embodiments, at least one R^{D2a} is C_{1-6} alkyl. In certain embodiments, at least one R^{D2a} is methyl. In certain embodiments, at least one R^{D2a} is ethyl. In certain embodiments, at least one R^{D2a} is propyl. In certain embodiments, at least one R^{D2a} is butyl. In certain embodiments, at least one R^{D2a} is substituted alkenyl. In certain embodiments, at least one R^{D2a} is unsubstituted alkenyl. In certain embodiments, at least one R^{D2a} is substituted alkynyl. In certain embodiments, at least one R^{D2a} is unsubstituted alkynyl. In certain embodiments, at least one R^{D2a} is substituted carbocyclyl. In certain embodiments, at least one R^{D2a} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{D2a} is substituted

heterocyclyl. In certain embodiments, at least one R^{D2a} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{D2a} is substituted aryl. In certain embodiments, at least one R^{D2a} is unsubstituted aryl. In certain embodiments, at least one R^{D2a} is substituted phenyl. In certain embodiments, at least one R^{D2a} is unsubstituted phenyl. In certain embodiments, at least one R^{D2a} is substituted heteroaryl. In certain embodiments, at least one R^{D2a} is unsubstituted heteroaryl. In certain embodiments, at least one R^{D2a} is substituted pyridyl. In certain embodiments, at least one R^{D2a} is unsubstituted pyridyl. In certain embodiments, at least one R^{D2a} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one R^{D2a} is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{D2a} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{D2a} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{D2a} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{D2a} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two R^{D2a} groups are joined to form a substituted heterocyclic ring. In certain embodiments, two R^{D2a} groups are joined to form an unsubstituted heterocyclic ring.

[00113] In compounds of Formula (**A**), R^{D} may include a substituent R^{D3}. In certain embodiments, R^{D3} is H. In certain embodiments, R^{D3} is halogen. In certain embodiments, R^{D3} is F. In certain embodiments, R^{D3} is Cl. In certain embodiments, R^{D3} is Br. In certain embodiments, R^{D3} is I (iodine). In certain embodiments, R^{D3} is substituted acyl. In certain embodiments, R^{D3} is unsubstituted acyl. In certain embodiments, R^{D3} is acetyl. In certain embodiments, R^{D3} is substituted alkyl. In certain embodiments, R^{D3} is unsubstituted alkyl. In certain embodiments, R^{D3} is C_{1-6} alkyl. In certain embodiments, R^{D3} is methyl. In certain embodiments, R^{D3} is ethyl. In certain embodiments, R^{D3} is propyl. In certain embodiments, R^{D3} is butyl. In certain embodiments, R^{D3} is substituted alkenyl. In certain embodiments, R^{D3} is unsubstituted alkenyl. In certain embodiments, R^{D3} is substituted alkynyl. In certain embodiments, R^{D3} is unsubstituted alkynyl. In certain embodiments, R^{D3} is substituted carbocyclyl. In certain embodiments, R^{D3} is unsubstituted carbocyclyl. In certain embodiments, R^{D3} is substituted heterocyclyl. In certain embodiments, R^{D3} is unsubstituted heterocyclyl. In certain embodiments, R^{D3} is substituted aryl. In certain embodiments, R^{D3} is unsubstituted aryl. In certain embodiments, R^{D3} is substituted phenyl. In certain embodiments, R^{D3} is unsubstituted phenyl. In certain embodiments, R^{D3} is substituted heteroaryl. In certain embodiments, R^{D3} is unsubstituted heteroaryl. In certain embodiments,

R^{D3} is substituted pyridyl. In certain embodiments, R^{D3} is unsubstituted pyridyl. In certain embodiments, R^{D3} is –CN. In certain embodiments, R^{D3} is $–NO_2$. In certain embodiments, R^{D3} is $–OR^{D3a}$. In certain embodiments, R^{D3} is $–N(R^{D3a})_2$. In certain embodiments, R^{D3} is $–SR^{D3a}$. In certain embodiments, R^{D3} is $–CH_2OR^{D3a}$. In certain embodiments, R^{D3} is $–CH_2N(R^{D3a})_2$. In certain embodiments, R^{D3} is $–CH_2SR^{D3a}$.

[00114] In certain embodiments, at least one R^{D3a} is H. In certain embodiments, at least one R^{D3a} is substituted acyl. In certain embodiments, at least one R^{D3a} is unsubstituted acyl. In certain embodiments, at least one R^{D3a} is acetyl. In certain embodiments, at least one R^{D3a} is substituted alkyl. In certain embodiments, at least one R^{D3a} is unsubstituted alkyl. In certain embodiments, at least one R^{D3a} is C_{1-6} alkyl. In certain embodiments, at least one R^{D3a} is methyl. In certain embodiments, at least one R^{D3a} is ethyl. In certain embodiments, at least one R^{D3a} is propyl. In certain embodiments, at least one R^{D3a} is butyl. In certain embodiments, at least one R^{D3a} is substituted alkenyl. In certain embodiments, at least one R^{D3a} is unsubstituted alkenyl. In certain embodiments, at least one R^{D3a} is substituted alkynyl. In certain embodiments, at least one R^{D3a} is unsubstituted alkynyl. In certain embodiments, at least one R^{D3a} is substituted carbocyclyl. In certain embodiments, at least one R^{D3a} is unsubstituted carbocyclyl. In certain embodiments, at least one R^{D3a} is substituted heterocyclyl. In certain embodiments, at least one R^{D3a} is unsubstituted heterocyclyl. In certain embodiments, at least one R^{D3a} is substituted aryl. In certain embodiments, at least one R^{D3a} is unsubstituted aryl. In certain embodiments, at least one R^{D3a} is substituted phenyl. In certain embodiments, at least one R^{D3a} is unsubstituted phenyl. In certain embodiments, at least one R^{D3a} is substituted heteroaryl. In certain embodiments, at least one R^{D3a} is unsubstituted heteroaryl. In certain embodiments, at least one R^{D3a} is substituted pyridyl. In certain embodiments, at least one R^{D3a} is unsubstituted pyridyl. In certain embodiments, at least one R^{D3a} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one R^{D3a} is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, R^{D3a} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, R^{D3a} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, R^{D3a} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, R^{D3a} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two R^{D3a} groups are joined to form a substituted heterocyclic ring. In certain embodiments, two R^{D3a} groups are joined to form an unsubstituted heterocyclic ring.

[00115] In compounds of Formula (**A**), R^D may include a substituent R^{D4}. In certain embodiments, R^{D4} is a leaving group. In certain embodiments, R^{D4} is halogen. In certain embodiments, R^{D4} is F. In certain embodiments, R^{D4} is Cl. In certain embodiments, R^{D4} is Br. In certain embodiments, R^{D4} is I (iodine). In certain embodiments, R^{D4} is $-OS(=O)_wR^{D4a}$. In certain embodiments, w is 1. In certain embodiments, w is 2. In certain embodiments, R^{D4} is –OMs. In certain embodiments, R^{D4} is –OTf. In certain embodiments, R^{D4} is –OTs. In certain embodiments, R^{D4} is –OBs. In certain embodiments, R^{D4} is 2-nitrobenzenesulfonyloxy.In certain embodiments, R^{D4} is $-OR^{D4a}$. In certain embodiments, R^{D4} is –OMe. In certain embodiments, R^{D4} is $-OCF_3$. In certain embodiments, R^{D4} is –OPh. In certain embodiments, R^{D4} is $-OC(=O)R^{D4a}$. In certain embodiments, R^{D4} is –OC(=O)Me. In certain embodiments, R^{D4} is $-OC(=O)CF_3$. In certain embodiments, R^{D4} is –OC(=O)Ph. In certain embodiments, R^{D4} is –OC(=O)Cl. In certain embodiments, R^{D4} is $-OC(=O)OR^{D4a}$. In certain embodiments, R^{D4} is –OC(=O)OMe. In certain embodiments, R^{D4} is –OC(=O)O(*t*-Bu).

[00116] In certain embodiments, R^{D4a} is substituted alkyl. In certain embodiments, R^{D4a} is unsubstituted alkyl. In certain embodiments, R^{D4a} is C_{1-6} alkyl. In certain embodiments, R^{D4a} is methyl. In certain embodiments, R^{D4a} is ethyl. In certain embodiments, R^{D4a} is propyl. In certain embodiments, R^{D4a} is butyl. In certain embodiments, R^{D4a} is substituted alkenyl. In certain embodiments, R^{D4a} is unsubstituted alkenyl. In certain embodiments, R^{D4a} is vinyl. In certain embodiments, R^{D4a} is substituted alkynyl. In certain embodiments, R^{D4a} is unsubstituted alkynyl. In certain embodiments, R^{D4a} is ethynyl. In certain embodiments, R^{D4a} is substituted carbocyclyl. In certain embodiments, R^{D4a} is unsubstituted carbocyclyl. In certain embodiments, R^{D4a} is substituted heterocyclyl. In certain embodiments, R^{D4a} is unsubstituted heterocyclyl. In certain embodiments, R^{D4a} is substituted aryl. In certain embodiments, R^{D4a} is unsubstituted aryl. In certain embodiments, R^{D4a} is substituted phenyl. In certain embodiments, R^{D4a} is unsubstituted phenyl. In certain embodiments, R^{D4a} is substituted heteroaryl. In certain embodiments, R^{D4a} is unsubstituted heteroaryl. In certain embodiments, R^{D4a} is substituted pyridyl. In certain embodiments, R^{D4a} is unsubstituted pyridyl.

[00117] In compounds of Formula (**A**), R^D may include a substituent R^{D5}. In certain embodiments, R^{D5} is H. In certain embodiments, R^{D5} is substituted alkyl. In certain embodiments, R^{D5} is unsubstituted alkyl. In certain embodiments, R^{D5} is C_{1-6} alkyl. In certain embodiments, R^{D5} is methyl. In certain embodiments, R^{D5} is ethyl. In certain embodiments, R^{D5} is propyl. In certain embodiments, R^{D5} is butyl. In certain embodiments, R^{D5} is a nitrogen protecting group. In certain embodiments, R^{D5} is Bn, BOC, Cbz, Fmoc, trifluoroacetyl,

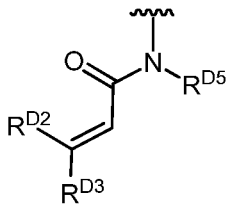
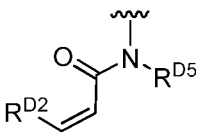
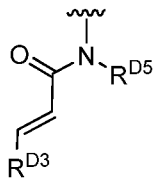
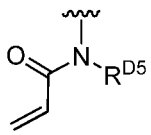
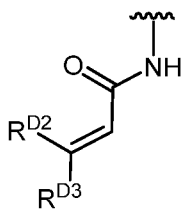
triphenylmethyl, or Ts.

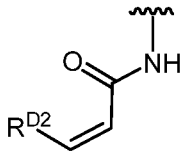
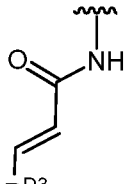
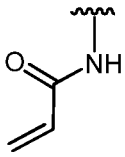
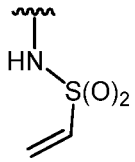
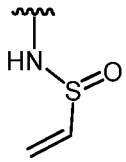
[00118] In certain embodiments, R^{D1} and R^{D2} are each hydrogen. In certain embodiments, R^{D1} and R^{D3} are each hydrogen. In certain embodiments, R^{D2} and R^{D3} are each hydrogen. In certain embodiments, R^{D1}, R^{D2}, and R^{D3} are each hydrogen. In certain embodiments, R^{D1}, R^{D2}, and R^{D3}, and R^{D5} are each hydrogen.

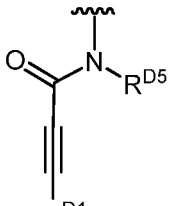
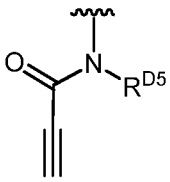
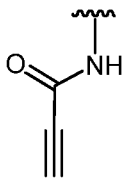
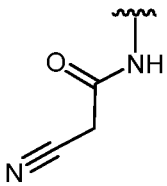
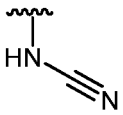
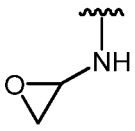
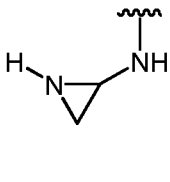
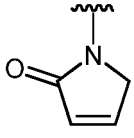
[00119] In certain embodiments, a is 1. In certain embodiments, a is 2.

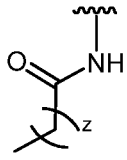
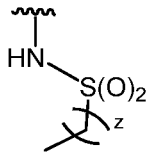
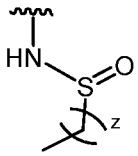
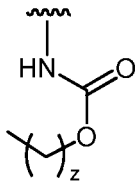
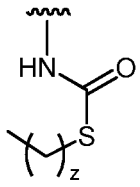
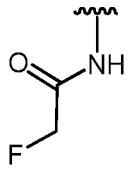
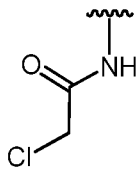
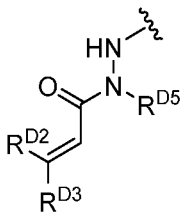
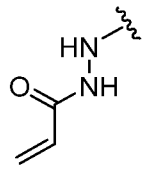
[00120] In certain embodiments, z is 0. In certain embodiments, z is 1. In certain embodiments, z is 2. In certain embodiments, z is 3. In certain embodiments, z is 4. In certain embodiments, z is 5. In certain embodiments, z is 6.

[00121] In certain embodiments, Y is –O–. In certain embodiments, Y is –C(=O)–. In certain embodiments, Y is –S–. In certain embodiments, Y is –C(=S)–. In certain embodiments, Y is $–NR^{D6}–$, wherein R^{D6} is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, Y is –NH–. In certain embodiments, Y is $–NCH_3–$. In certain embodiments, Y is –N(BOC)–. In certain embodiments, Y is –N(Fmoc)–. In certain embodiments, Y is –N(Cbz)–. In certain embodiments, Y is –N(Bn)–. In certain embodiments, Y is $–C(=NR^{D6})–$, wherein R^{D6} is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, Y is –C(=NH)–. In certain embodiments, Y is $–C(=NCH_3)–$. In certain embodiments, Y is –C(=NTs)–. In certain embodiments, Y is –C(=NBn)–. In certain embodiments, Y is $–C(=NCH(Ph)_2)–$.

[00122] In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the

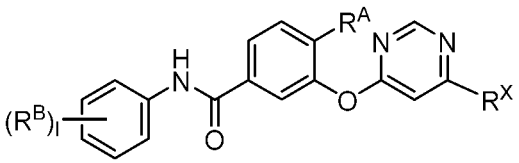
formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  .

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

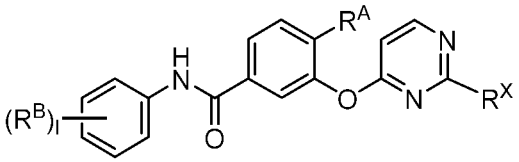
embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments, R^D is of the formula:  . In certain embodiments,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

[00123] Various combinations of certain embodiments of Formula (**A**) are futher contemplated herein.

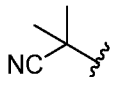
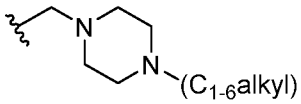
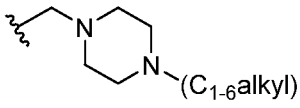
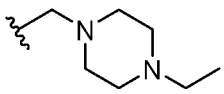
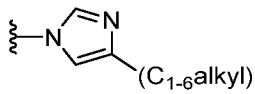
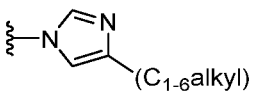
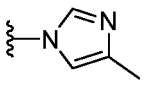
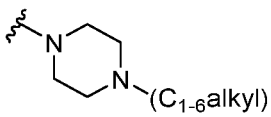
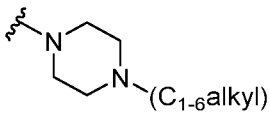
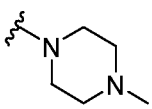
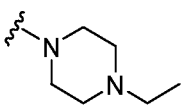
[00124] For example, in certain embodiments, a compound of Formula (**A**) is a compound of Formula (**A1**) or (**A2**):



(**A1**)

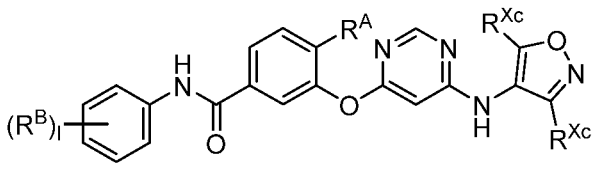


(**A2**)

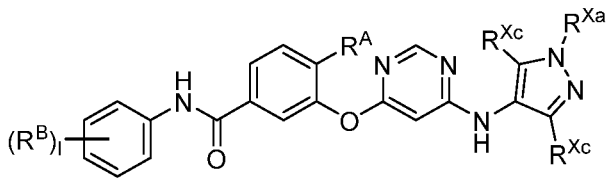
wherein R^X, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted –CH_2–(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is –CF_3. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is

substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, R^X is $-N(R^{A1})N(R^{A1})_2$. In certain embodiments, R^X is $-N(R^{A1})N(R^{A1})_2$; and each instance of R^A is hydrogen, methyl, or acetyl. In certain embodiments, R^X is $-NHNMe_2$ or $-NHNHAc$. In certain embodiments, R^X is $-NH_2$. In certain embodiments, R^X is $-NH(R^{A1})$. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted methyl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is acyl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted $-C(=O)-(C_{1-6}alkyl)$. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is acetyl or propionyl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted $-C(=O)-$(carbocyclyl). In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted $-C(=O)-$(cyclopropyl). In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted heteroaryl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted pyrazole. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted isoxazole. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted pyrimidine. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted heterocyclyl. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted azetidine. In certain embodiments, R^X is $-NH(R^{A1})$; and R^{A1} is substituted or unsubstituted oxetane.

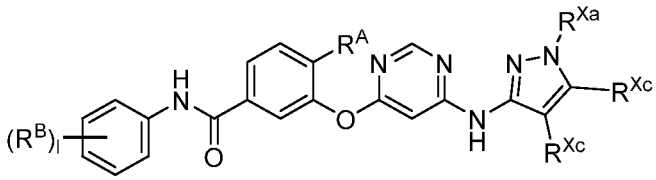
[00125] In certain embodiments, a compound of Formula (**A1**) is a compound of Formula (**A1-a**), (**A1-b**), (**A1-c**), or (**A1-d**):



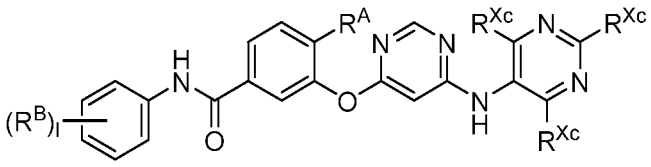
(**A1-a**)



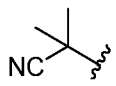
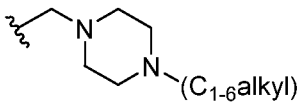
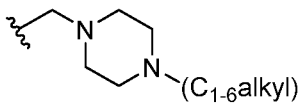
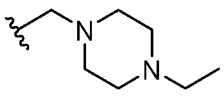
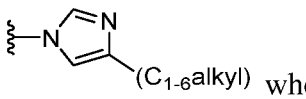
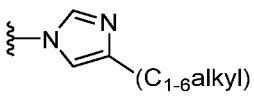
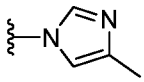
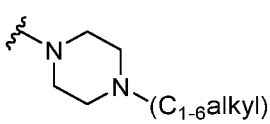
(**A1-b**)

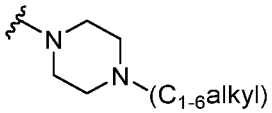
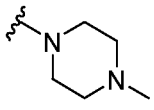
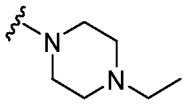


(**A1-c**)

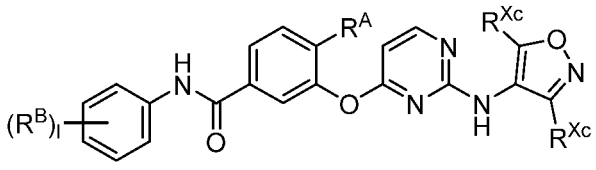


(**A1-d**)

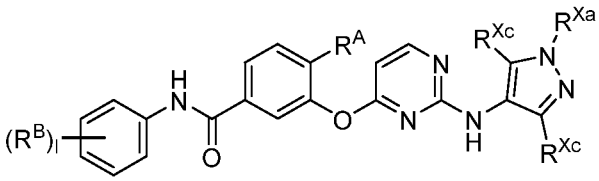
wherein R^{Xa}, R^{Xc}, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted –CH_2–(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is –CF_3. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one

R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, all instances of R^{Xc} are hydrogen. In certain embodiments, R^{Xa} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{Xa} is methyl or ethyl.

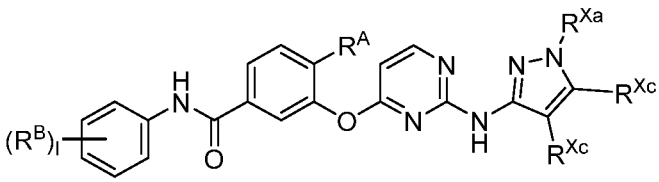
[00126] In certain embodiments, a compound of Formula (**A2**) is a compound of Formula (**A2-a**), (**A2-b**), (**A2-c**), or (**A2-d**):



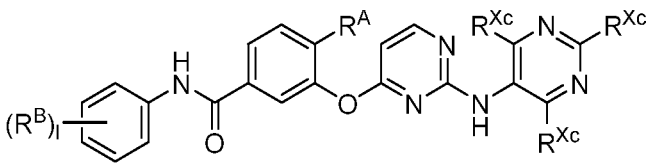
(**A2-a**)



(**A2-b**)

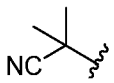
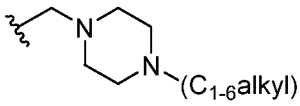
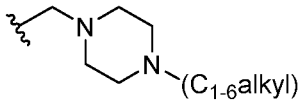
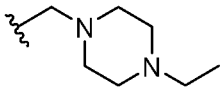
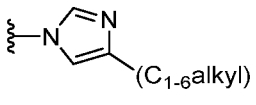
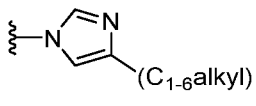
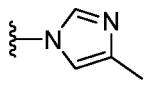
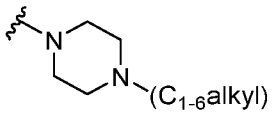
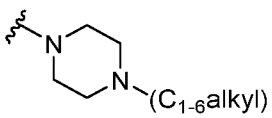
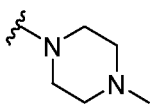
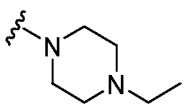


(**A2-c**)

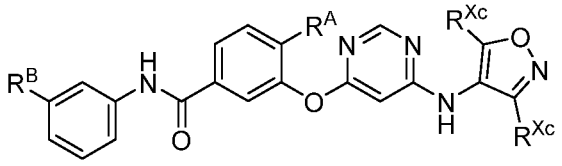


(**A2-d**)

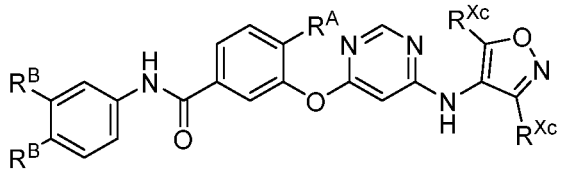
wherein R^{Xa}, R^{Xc}, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl

substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted $–CH_2–$(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is $–CF_3$. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, all instances of R^{Xc} are hydrogen. In certain embodiments, R^{Xa} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{Xa} is methyl or ethyl.

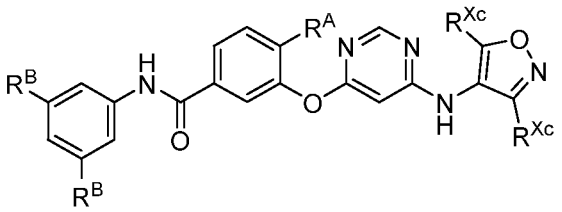
[00127] In certain embodiments, a compound of Formula (**A1**) is a compound of Formula (**A1-e**)-(**A1-p**):



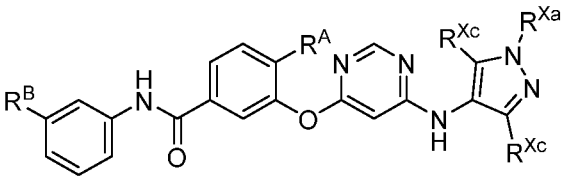
(**A1-e**)



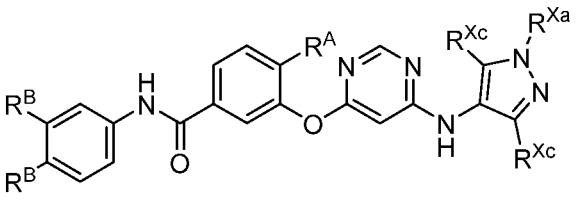
(**A1-f**)



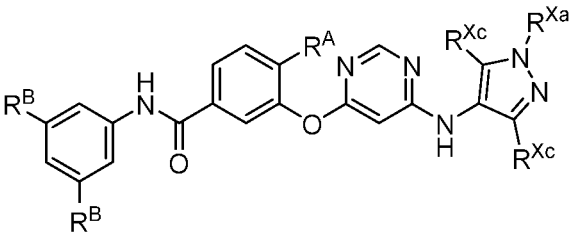
(**A1-g**)



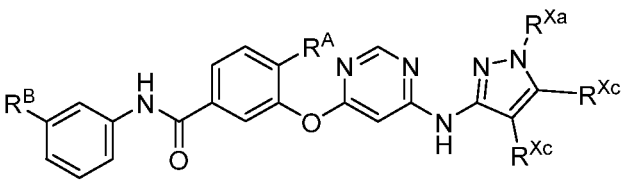
(**A1-h**)



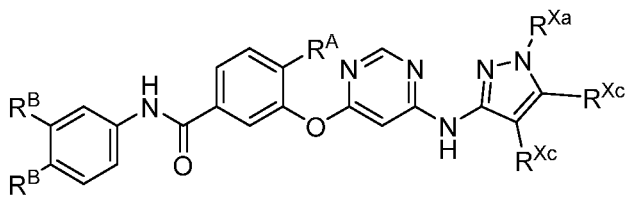
(**A1-i**)



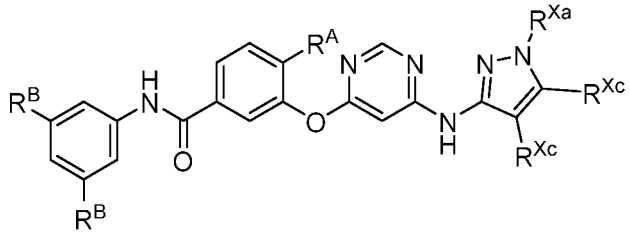
(**A1-j**)



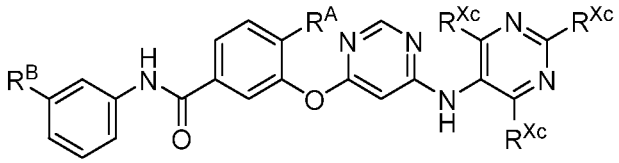
(**A1-k**)



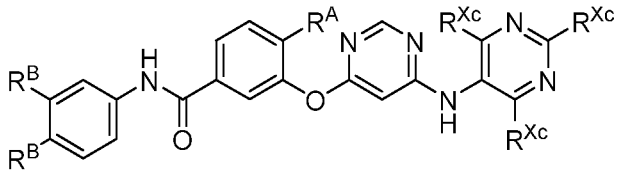
(**A1-l**)



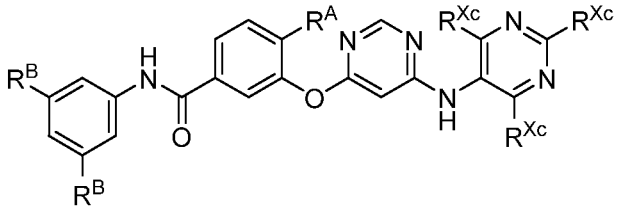
(**A1-m**)



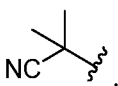
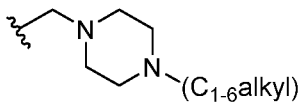
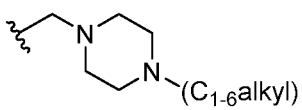
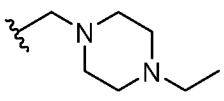
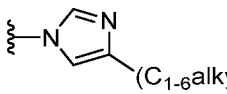
(**A1-n**)

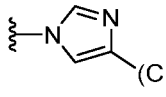
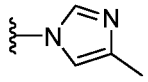
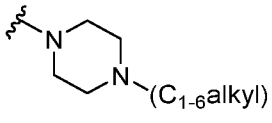
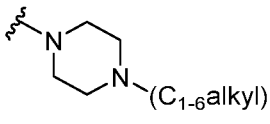
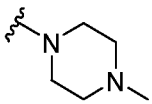
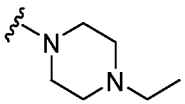


(**A1-o**)

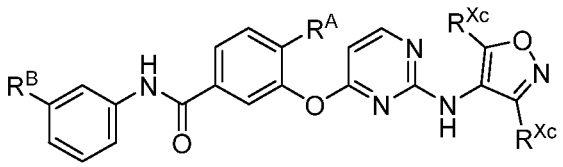


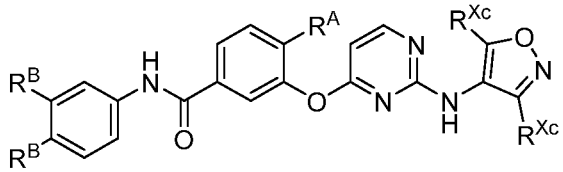
(**A1-p**)

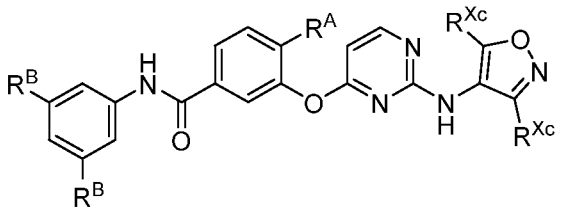
wherein R^{Xa}, R^{Xc}, R^A, and R^B are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted –CH_2–(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is –CF_3. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted.

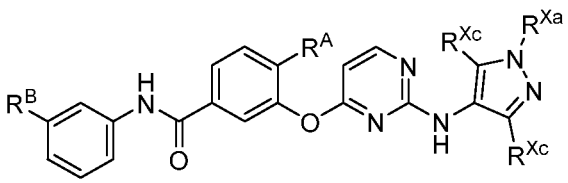
In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, all instances of R^{Xc} are hydrogen. In certain embodiments, R^{Xa} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{Xa} is methyl or ethyl.

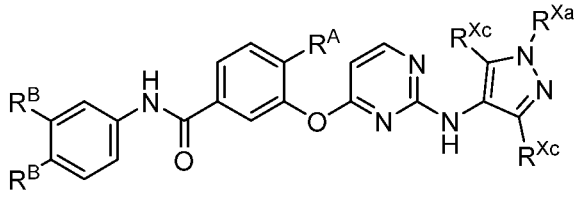
[00128] In certain embodiments, a compound of Formula (**A2**) is a compound of Formula (**A2-e**)-(**A2-p**):


(**A2-e**)

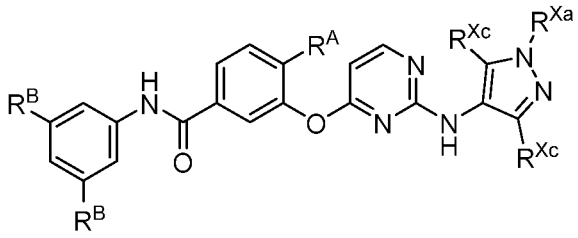

(**A2-f**)


(**A2-g**)

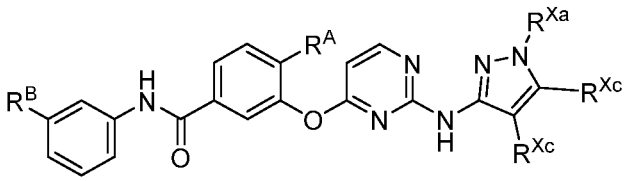

(**A2-h**)



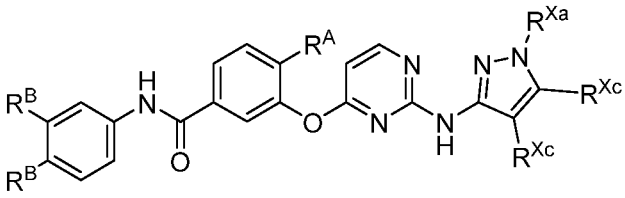
(**A2-i**)



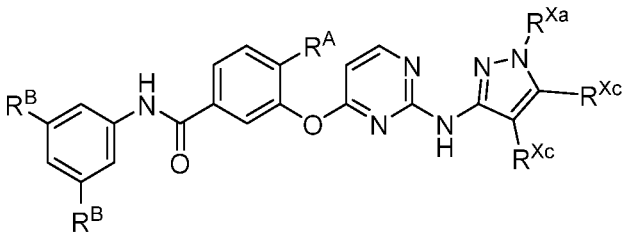
(**A2-j**)



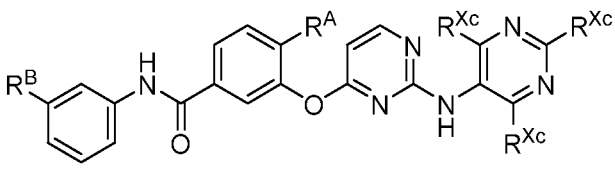
(**A2-k**)



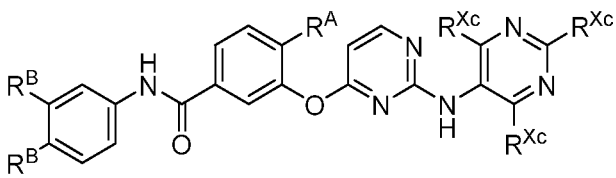
(**A2-l**)



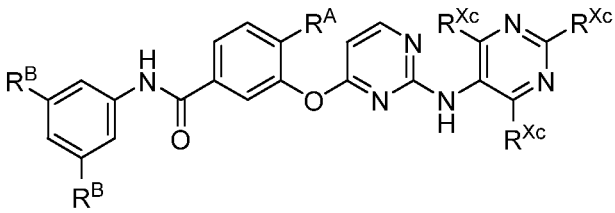
(**A2-m**)



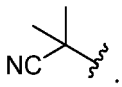
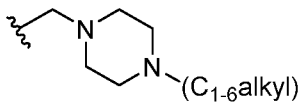
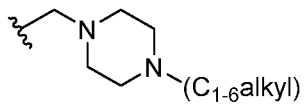
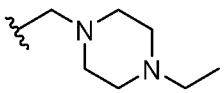
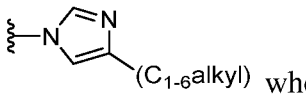
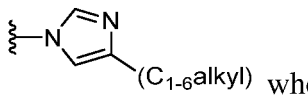
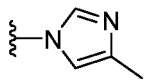
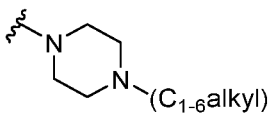
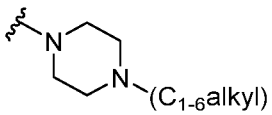
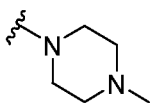
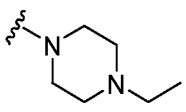
(**A2-n**)



(**A2-o**)

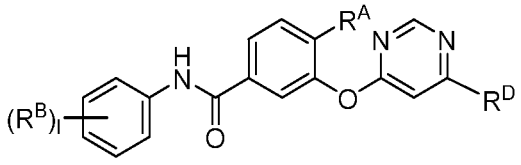


(**A2-p**)

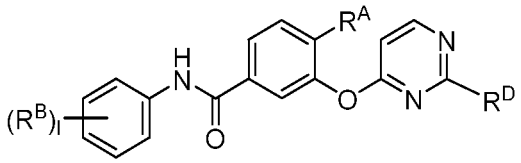
wherein R^{Xa}, R^{Xc}, R^A, and R^B are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted –CH_2–(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is –CF_3. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, all instances of R^{Xc} are hydrogen. In certain embodiments, R^{Xa} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{Xa} is methyl or ethyl.

[00129] In certain embodiments, a compound of Formula (**A**) is a compound of Formula

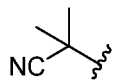
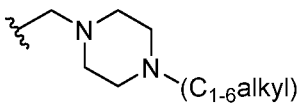
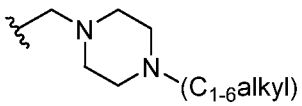
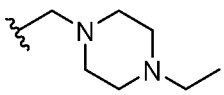
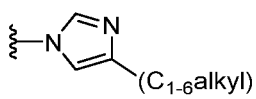
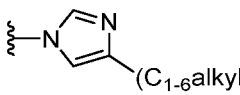
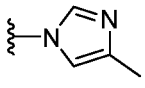
(**A3**) or (**A4**):

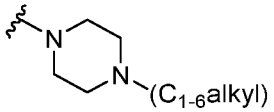
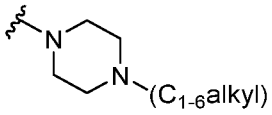
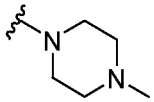
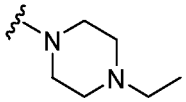
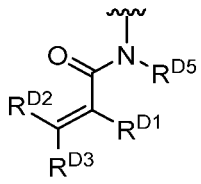
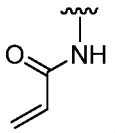
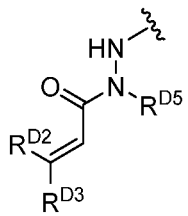
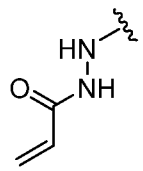


(**A3**)

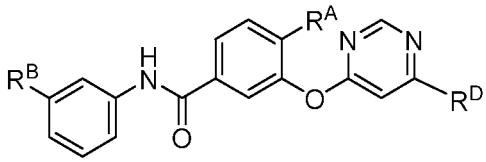


(**A4**)

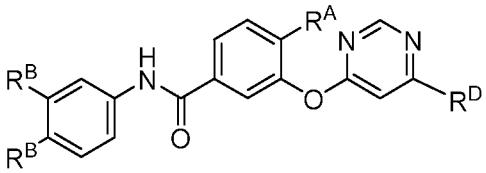
wherein R^D, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted $–CH_2–$(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is $–CF_3$. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is

substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  .

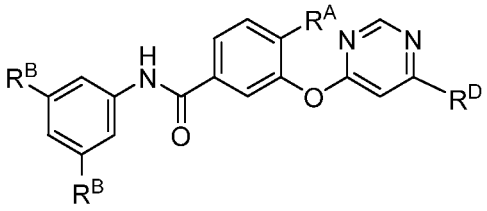
[00130] In certain embodiments, a compound of Formula (**A3**) is a compound of Formula (**A3-a**), (**A3-b**), or (**A3-c**):



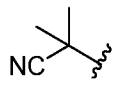
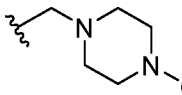
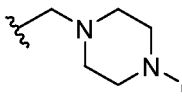
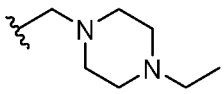
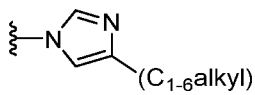
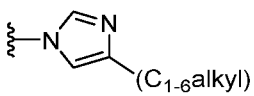
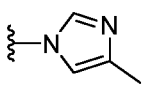
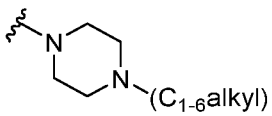
(**A3-a**)

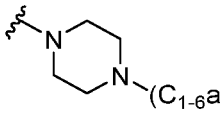
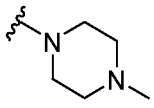
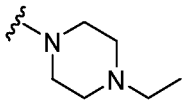
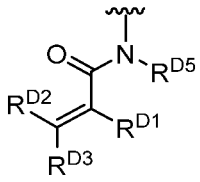
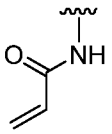
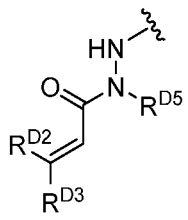
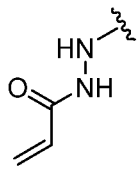


(**A3-b**)

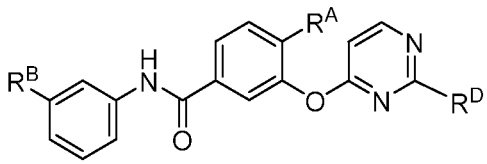


(**A3-c**)

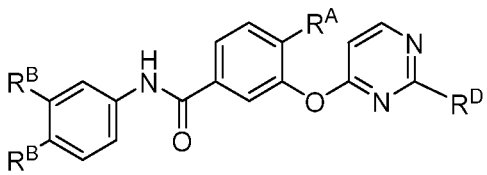
wherein R^D, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted –CH_2–(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is –CF_3. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one

R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are substituted or unsubstituted morpholine. In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  .

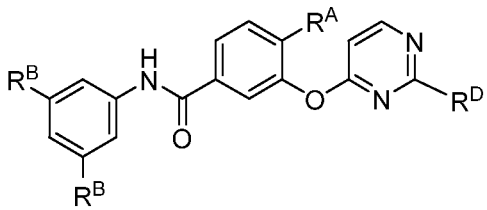
[00131] In certain embodiments, a compound of Formula (**A4**) is a compound of Formula (**A4-a**), (**A4-b**), or (**A4-c**):



(**A4**)

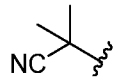
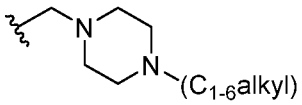
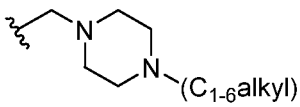
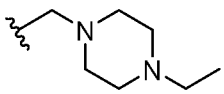
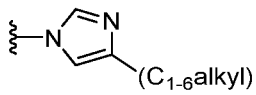
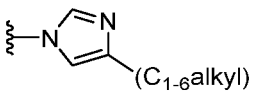
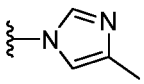
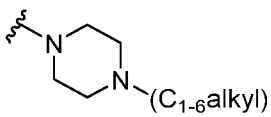
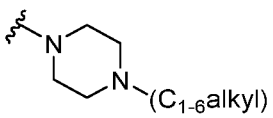
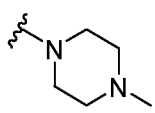
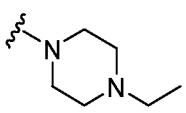


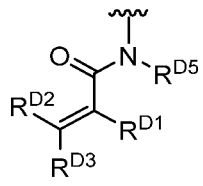
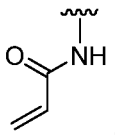
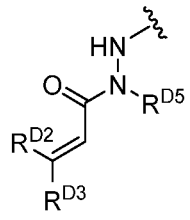
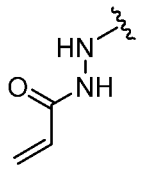
(**A4**)



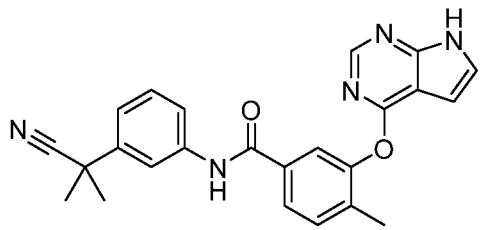
(**A4**)

wherein R^D, R^A, R^B, and l are defined herein. In certain embodiments R^A is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments, R^A is methyl. In certain embodiments, l is 1. In certain embodiments, l is 1; and R^B is *meta* to the point of attachment of the amide linker.

In certain embodiments, l is 2. In certain embodiments, l is 2; and the two R^B groups are *meta* to the point of attachment of the amide linker. In certain embodiments, l is 2; one R^B group is *meta* to the point of attachment of the amide linker; and the second R^B group is *para* to the point of attachment of the amide linker. In certain embodiments, one R^B group is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, one R^B group is C_{1-6}alkyl substituted with one –CN group. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted $-CH_2-$(piperazinyl). In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is haloalkyl. In certain embodiments, one R^B group is $-CF_3$. In certain embodiments, one R^B group is substituted or unsubstituted imidazoyl. In certain embodiments, one R^B group is  where the alkyl is optionally substituted. In certain embodiments, one R^B group is  where the alkyl is unsubstituted. In certain embodiments, one R^B group is  . In certain embodiments, one R^B group is substituted or unsubstituted piperazinyl. In certain embodiments, one R^B group is  where there alkyl is optionally substituted. In certain embodiments, one R^B group is  where there alkyl is unsubstituted. In certain embodiments, one R^B group is  or  . In certain embodiments, one R^B group is substituted or unsubstituted morpholine. In certain embodiments, two R^B groups are

substituted or unsubstituted morpholine. In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  . In certain embodiments, R^D is  .

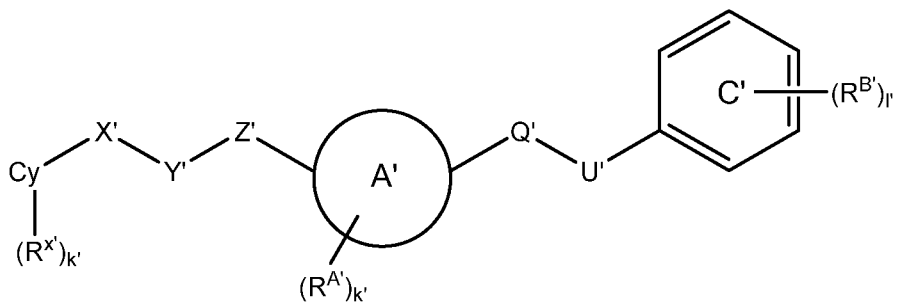
[00132] Another aspect of the invention relates to the compound of Formula (**I-11**):



(**I-11**),

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

[00133] In another aspect, provided are compounds of Formula (**V**):



(**V**)

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

each instance of each instance of $R^{A'}$, $R^{B'}$, and $R^{X'}$ are 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, optionally substituted heteroaryl, $-OR^{A1'}$, $-N(R^{A1'})_2$, $-SR^{A1'}$, $-CN$, $-C(=O)R^{A1'}$, $-C(=O)OR^{A1'}$, $-C(=O)SR^{A1'}$, $-C(=O)N(R^{A1'})_2$, $-C(=S)R^{A1'}$, $-C(=S)OR^{A1'}$, $-C(=S)SR^{A1'}$, $-C(=S)N(R^{A1'})_2$, $-C(=NR^{A1'})R^{A1'}$, –

$C(=NR^{A1'})OR^{A1'}$, $-C(=NR^{A1'})SR^{A1'}$, $-C(=NR^{A1'})N(R^{A1'})_2$, $-NO_2$, $-N_3$, $-N(R^{A1'})_3^+X^{'-}$, wherein $X^{'-}$ is a counterion, $-N(OR^{A1'})R^{A1'}$, $-NR^{A1'}C(=O)R^{A1'}$, $-NR^{A1'}C(=O)OR^{A1'}$, $-NR^{A1'}C(=O)SR^{A1'}$, $-NR^{A1'}C(=O)N(R^{A1'})_2$, $-NR^{A1'}C(=S)R^{A1'}$, $-NR^{A1'}C(=S)OR^{A1'}$, $-NR^{A1'}C(=S)SR^{A1'}$, $-NR^{A1'}C(=S)N(R^{A1'})_2$, $-NR^{A1'}C(=NR^{A1'})R^{A1'}$, $-NR^{A1'}C(=NR^{A1'})OR^{A1'}$, $-NR^{A1'}C(=NR^{A1'})SR^{A1'}$, $-NR^{A1'}C(=NR^{A1'})N(R^{A1'})_2$, $-NR^{A1'}S(=O)_2R^{A1'}$, $-NR^{A1'}S(=O)_2OR^{A1'}$, $-NR^{A1'}S(=O)_2SR^{A1'}$, $-NR^{A1'}S(=O)_2N(R^{A1'})_2$, $-NR^{A1'}S(=O)R^{A1'}$, $-NR^{A1'}S(=O)OR^{A1'}$, $-NR^{A1'}S(=O)SR^{A1'}$, $-NR^{A1'}S(=O)N(R^{A1'})_2$, $-NR^{A1'}P(=O)$, $-NR^{A1'}P(=O)_2$, $-NR^{A1'}P(=O)(R^{A1'})_2$, $-NR^{A1'}P(=O)R^{A1'}(OR^{A1'})$, $-NR^{A1'}P(=O)(OR^{A1'})_2$, $-OC(=O)R^{A1'}$, $-OC(=O)OR^{A1'}$, $-OC(=O)SR^{A1'}$, $-OC(=O)N(R^{A1'})_2$, $-OC(=NR^{A1'})R^{A1'}$, $-OC(=NR^{A1'})OR^{A1'}$, $-OC(=NR^{A1'})N(R^{A1'})_2$, $-OC(=S)R^{A1'}$, $-OC(=S)OR^{A1'}$, $-OC(=S)SR^{A1'}$, $-OC(=S)N(R^{A1'})_2$, $-ON(R^{A1'})_2$, $-OS(=O)R^{A1'}$, $-OS(=O)OR^{A1'}$, $-OS(=O)SR^{A1'}$, $-OS(=O)N(R^{A1'})_2$, $-OS(=O)_2R^{A1'}$, $-OS(=O)_2OR^{A1'}$, $-OS(=O)_2SR^{A1'}$, $-OS(=O)_2N(R^{A1'})_2$, $-OP(=O)_2$, $-OP(=O)(R^{A1'})_2$, $-OP(=O)R^{A1'}(OR^{A1'})$, $-OP(=O)(OR^{A1'})_2$, $-OP(=O)$, $-OP(R^{A1'})_2$, $-OPR^{A1'}(OR^{A1'})$, $-OP(OR^{A1'})_2$, $-OSi(R^{A1'})_3$, $-OSi(R^{A1'})_2OR^{A1'}$, $-OSi(R^{A1'})(OR^{A1'})_2$, $-OSi(OR^{A1'})_3$, $-SSR^{A1'}$, $-S(=O)R^{A1'}$, $-S(=O)OR^{A1'}$, $-S(=O)N(R^{A1'})_2$, $-S(=O)_2R^{A1'}$, $-S(=O)_2OR^{A1'}$, $-S(=O)_2N(R^{A1'})_2$, $-SC(=O)R^{A1'}$, $-SC(=O)OR^{A1'}$, $-SC(=O)SR^{A1'}$, $-SC(=O)N(R^{A1'})_2$, $-SC(=S)R^{A1'}$, $-SC(=S)OR^{A1'}$, $-SC(=S)SR^{A1'}$, $-SC(=S)N(R^{A1'})_2$, $-P(R^{A1'})_2$, $-PR^{A1'}(OR^{A1'})$, $-P(OR^{A1'})_2$, $-P(=O)$, $-P(=O)(R^{A1'})_2$, $-P(=O)(OR^{A1'})_2$, $-P(=O)R^{A1'}(OR^{A1'})$, $-P(=O)_2$, $-B(R^{A1'})_2$, $-B(OR^{A1'})_2$, $-BR^{A1'}(OR^{A1'})$, $-Si(R^{A1'})_3$, $-Si(R^{A1'})_2OR^{A1'}$, $-SiR^{A1'}(OR^{A1'})_2$, and $-Si(OR^{A1'})_3$, two $R^{A'}$ or $R^{B'}$ groups are joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring, or $R^{A'}$ or $R^{B'}$ forms an optional 5 to 8 membered ring with any one of X′, Y′, Z′, Q′, U′, or Cy; wherein each occurrence of $R^{A1'}$ is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two $R^{A1'}$ groups are joined to form an optionally substituted heterocyclic ring;

k′ and l′ are each independently 0, 1, 2, 3, 4, or 5;

X′, Y′, Z′ are each independently $-CH_2$, $-CHR^{A'}$, –CH, $-C(R^{A'})_2$, –C, –N, $-NR^{A'}$, –O, –S or –C=O, or bond and may optionally form a 5 to 8 membered ring with $R^{A'}$ or $R^{B'}$;

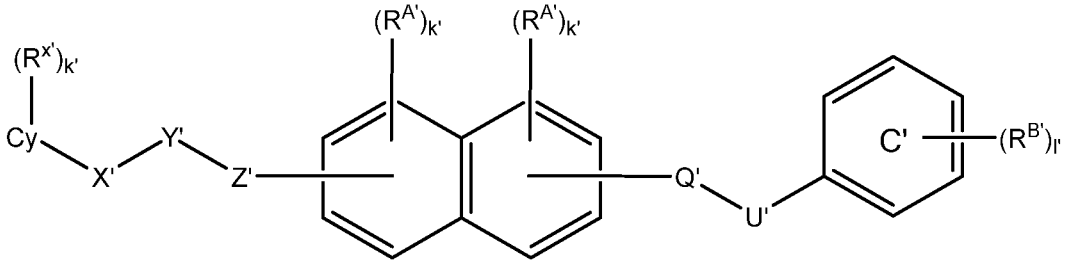
Q′ and U′ are each independently $-NR^{A'}$, –O, –C=O, $-NR^{A'}CO$, or bond;

Ring A′ is an optionally substituted aryl, or optionally substituted heteroaryl ring

Ring C′ is an optionally substituted aryl ring; and

Cy is an optionally substituted aryl ring, optionally substituted heteroaryl ring, bond, or hydrogen.

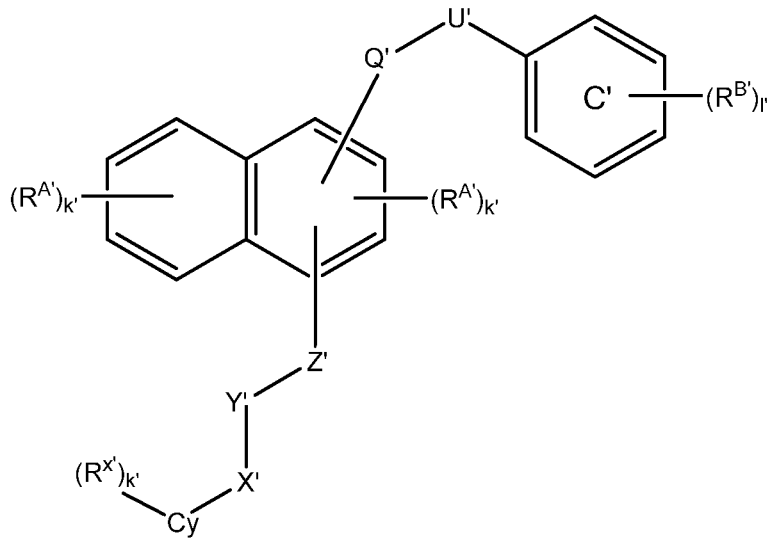
[00134] Compounds of Formula (**V**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is naphthyl, the invention provides compounds of Formula (**V-a**):



(**V-a**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

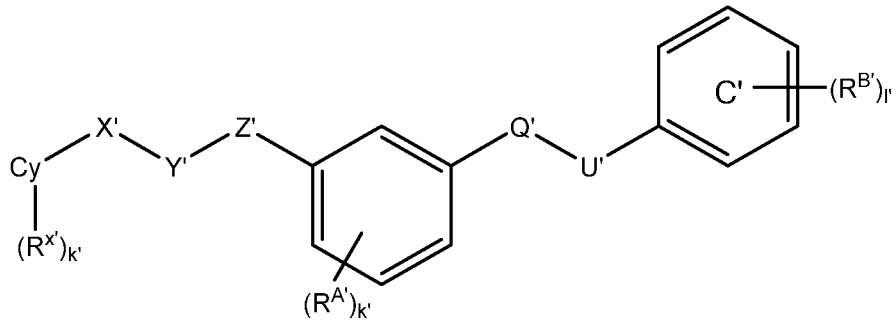
[00135] Compounds of Formula (**V**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, Ring A′ is naphthyl, the invention provides compounds of Formula (**V-b**):



(**V-b**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

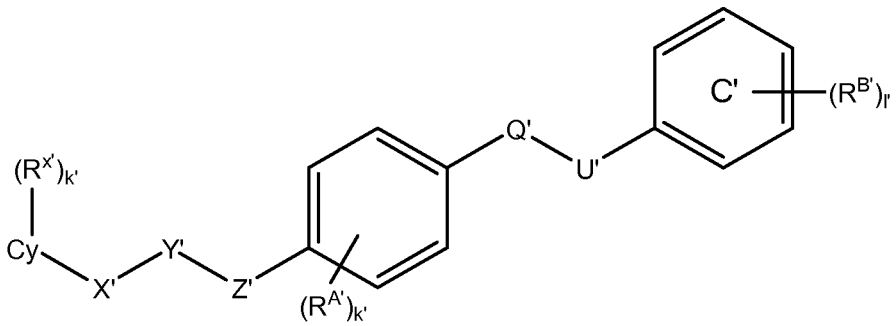
[00136] Compounds of Formula (**V**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, the invention provides compounds of Formula (**V-c**):



(**V-c**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

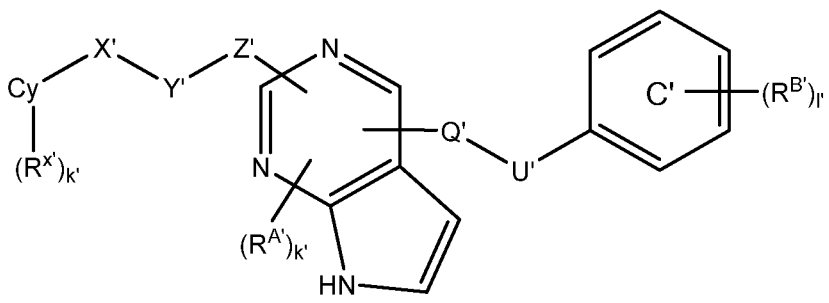
[00137] Compounds of Formula (**V**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, the invention provides compounds of Formula (**V-d**):



(**V-d**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

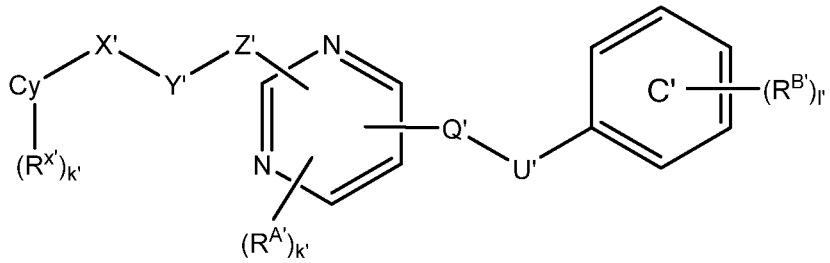
[00138] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is pyrrolopyrimidine, the invention provides compounds of Formula (**V-e**):



(**V-e**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

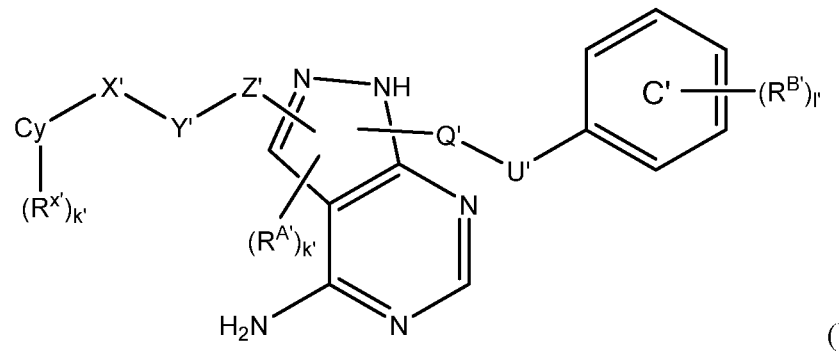
[00139] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a pyrimidine, the invention provides compounds of Formula (**V-e^{A}**):



(**V-e^{A}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

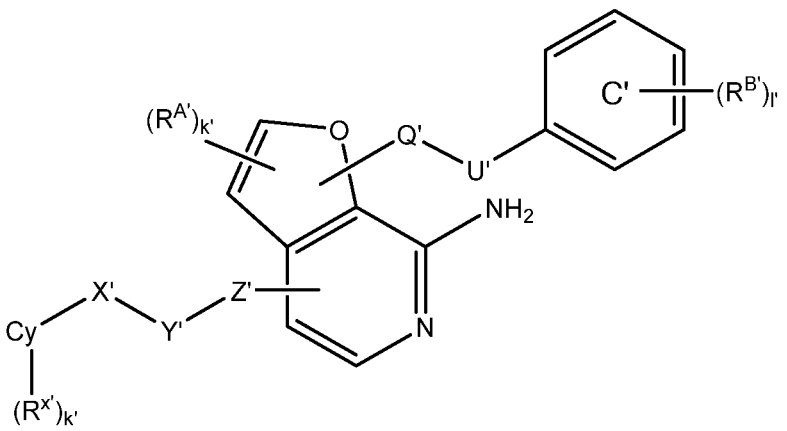
[00140] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a 1H-pyrazolo[3,4-d]pyrimidin-4-amine, the invention provides compounds of Formula (**V-e^{B}**):



(**V-e^{B}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

[00141] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a furo[2,3-c]pyridin-7-amine, the invention provides compounds of Formula (**V-e^{C}**):

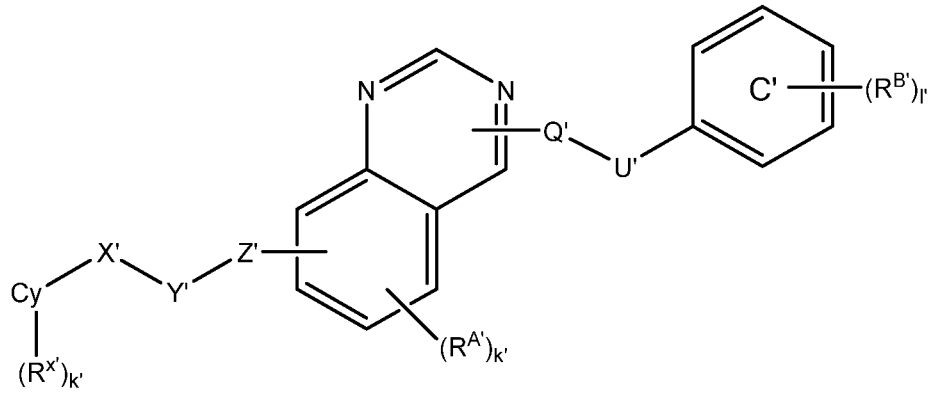


(**V-e^{C}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

[00142] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a

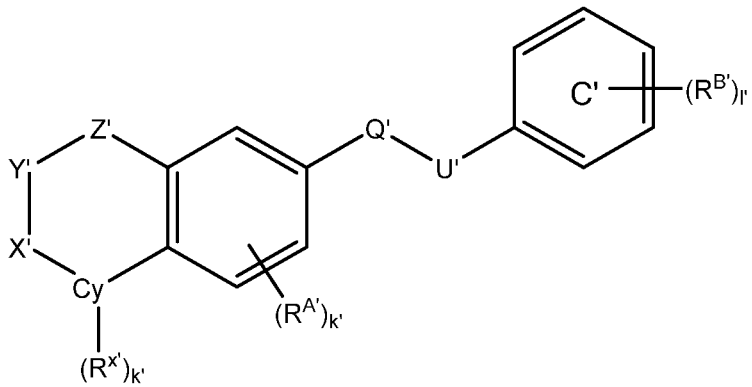
quinazoline, the invention provides compounds of Formula (**V-e^D**):



(**V-e^D**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

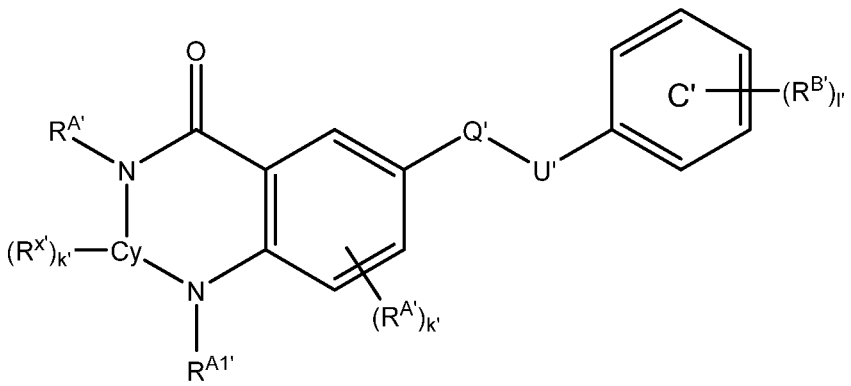
[00143] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, and at least one $R^{A'}$ group links to Cy forming an optional 5 to 8 membered ring, the invention provides compounds of Formula (**V-f**):



(**V-f**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

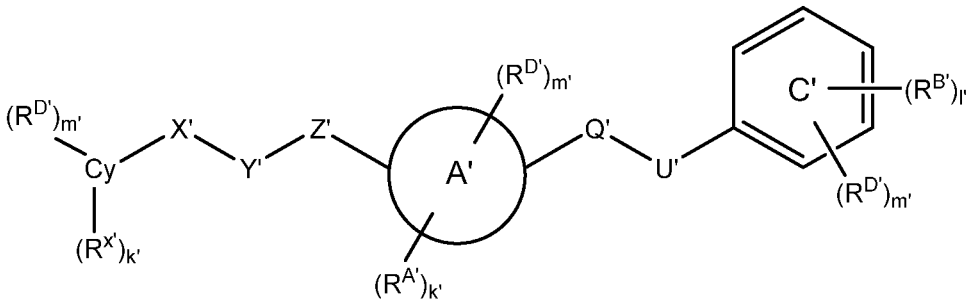
[00144] Compounds of Formula (**V**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, and at least one $R^{A'}$ group links to Cy forming an optional 5 to 8 membered ring, the invention provides compounds of Formula (**V-g**):



(**V-g**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

[00145] In another aspect, provided herein are compounds of Formula (**II**):



(**II**),

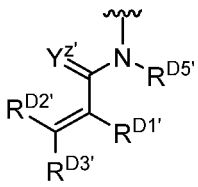
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof; wherein:

each instance of $R^{D'}$ is independently an optional electrophilic moiety that can be attached to Cy, Ring A′, or Ring C′;

each instance of m′ is independently 0 or 1; and

Ring A′, Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

[00146] In certain embodiments, $R^{D'}$ is an optional electrophilic moiety that can be attached to Cy, Ring A′, or Ring C′; and m′ is 0 or 1. In compounds of Formula (**II**), $R^{D'}$ is an optional electrophilic moiety that can be attached to Cy, Ring A′, or Ring C′. In certain embodiments, $R^{D'}$ is any one of Formulae (**i-1**)-(**i-17**):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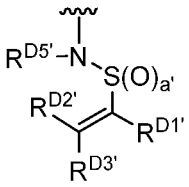
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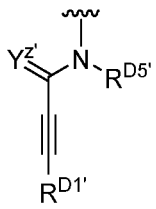
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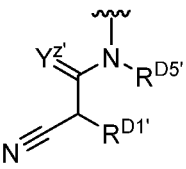
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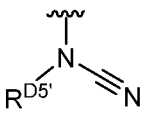
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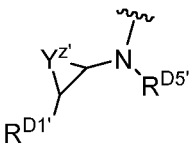
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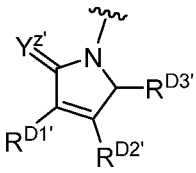
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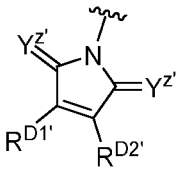
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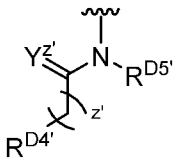
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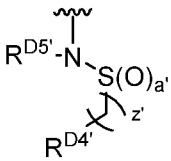
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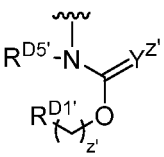
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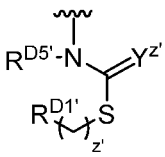
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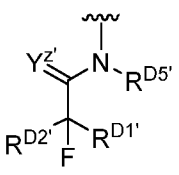
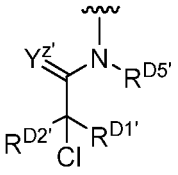
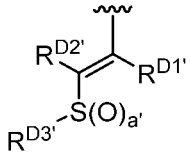
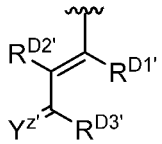

(**i-13**), 
(**i-14**), 
(**i-15**), 
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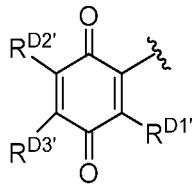

(**i-17**); wherein:

$R^{D1'}$ is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D1a'}$, $–N(R^{D1a'})_2$, $–SR^{D1a'}$, $–CH_2OR^{D1a'}$, $–CH_2N(R^{D1a'})_2$, $–CH_2SR^{D1a'}$, $–C(=O)R^{D1a'}$, $–C(=O)OR^{D1a'}$, $–C(=O)SR^{D1a'}$, $–C(=O)N(R^{D1a'})_2$, $–C(=S)R^{D1a'}$, $–C(=S)OR^{D1a'}$, $–C(=S)SR^{D1a'}$, $–C(=S)N(R^{D1a'})_2$, $–C(=NR^{D1a'})R^{D1a'}$, $–C(=NR^{D1a'})OR^{D1a'}$, $–C(=NR^{D1a'})SR^{D1a'}$, and $–C(=NR^{D1a'})N(R^{D1a'})_2$, wherein each occurrence of $R^{D1a'}$ 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 $R^{D1a'}$ groups are joined to form an optionally substituted heterocyclic ring;

$R^{D2'}$ is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D2a'}$, $–N(R^{D2a'})_2$, $–SR^{D2a'}$, $–CH_2OR^{D2a'}$, $–CH_2N(R^{D2a'})_2$, $–CH_2SR^{D2a'}$, $–C(=O)R^{D2a'}$, $–C(=O)OR^{D2a'}$, $–C(=O)SR^{D2a'}$, $–C(=O)N(R^{D2a'})_2$, $–C(=S)R^{D2a'}$, $–C(=S)OR^{D2a'}$, $–C(=S)SR^{D2a'}$, $–C(=S)N(R^{D2a'})_2$, $–C(=NR^{D2a'})R^{D2a'}$, $–C(=NR^{D2a'})OR^{D2a'}$, $–C(=NR^{D2a'})SR^{D2a'}$, and $–C(=NR^{D2a'})N(R^{D2a'})_2$, wherein each occurrence of $R^{D2a'}$ 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 $R^{D2a'}$ groups are joined to form an optionally substituted heterocyclic ring;

$R^{D3'}$ is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted

alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, –NO_2, –$OR^{D3a'}$, –$N(R^{D3a'})_2$, –$SR^{D3a'}$, –$CH_2OR^{D3a'}$, –$CH_2N(R^{D3a'})_2$, –$CH_2SR^{D3a'}$, –$C(=O)R^{D3a'}$, –$C(=O)OR^{D3a'}$, –$C(=O)SR^{D3a'}$, –$C(=O)N(R^{D3a'})_2$, –$C(=S)R^{D3a'}$, –$C(=S)OR^{D3a'}$, –$C(=S)SR^{D3a'}$, –$C(=S)N(R^{D3a'})_2$, –$C(=NR^{D3a'})R^{D3a'}$, –$C(=NR^{D3a'})OR^{D3a'}$, –$C(=NR^{D3a'})SR^{D3a'}$, and –$C(=NR^{D3a'})N(R^{D3a'})_2$, wherein each occurrence of $R^{D3a'}$ 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 $R^{D3a'}$ groups are joined to form an optionally substituted heterocyclic ring;

optionally $R^{D1'}$ and $R^{D3'}$, or $R^{D2'}$ and $R^{D3'}$, or $R^{D1'}$ and $R^{D2'}$ are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

$R^{D4'}$ is a leaving group;

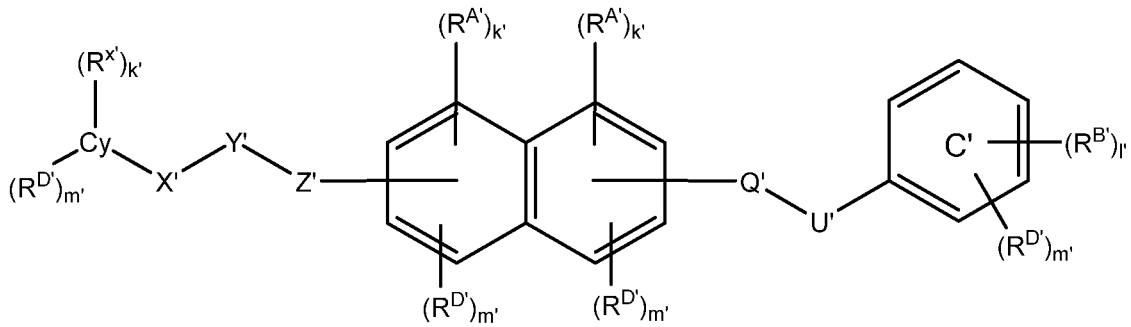
$R^{D5'}$ is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group;

$Y^{Z'}$ is –O, –S, or –$NR^{D6'}$, wherein $R^{D6'}$ is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group;

a′ is 1 or 2; and

z′ is 0, 1, 2, 3, 4, 5, or 6.

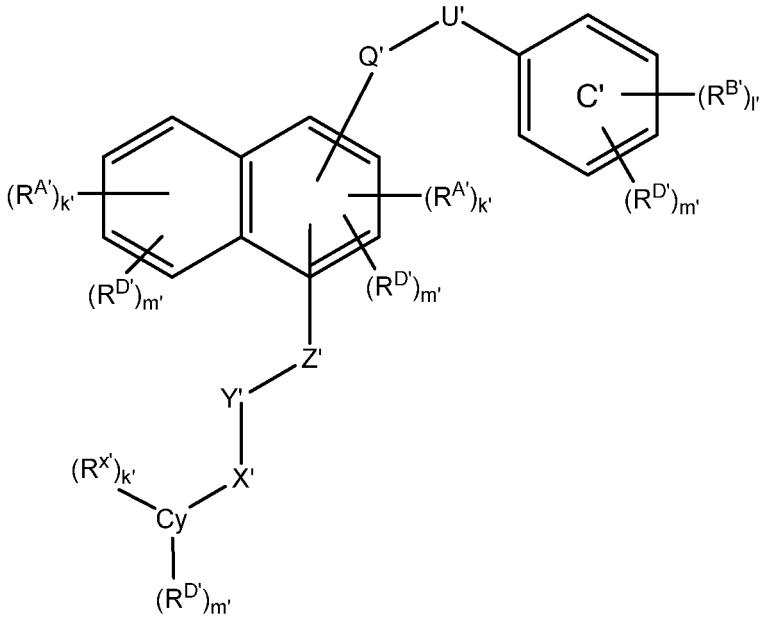
[00147] Compounds of Formula (**II**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is naphthyl, the invention provides compounds of Formula (**II-a**):



(**II-a**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

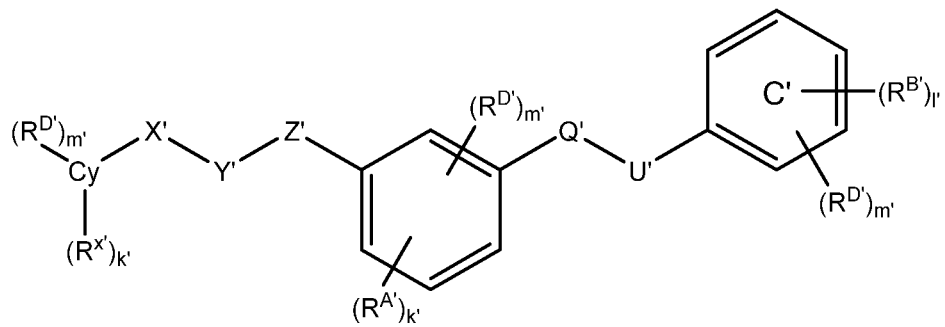
[00148] Compounds of Formula (**II**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is naphthyl, the invention provides compounds of Formula (**II-b**):



(**II-b**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

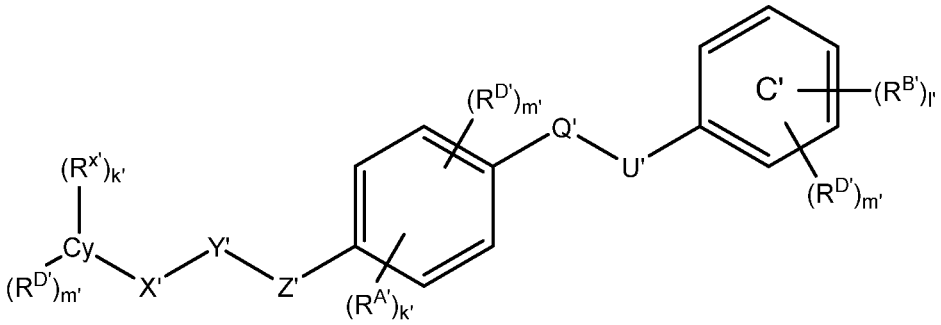
[00149] Compounds of Formula (**II**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, the invention provides compounds of Formula (**II-c**):



(**II-c**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

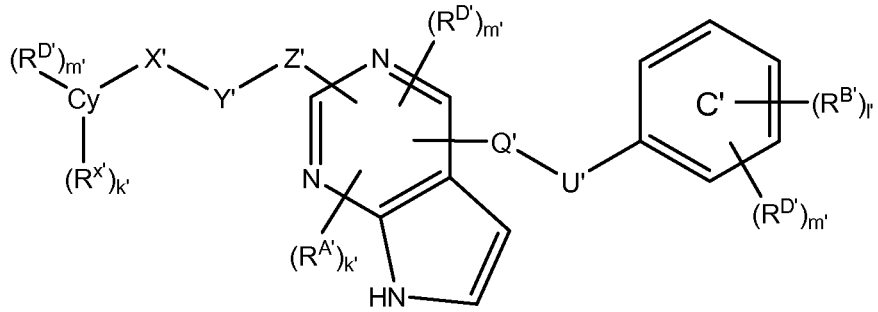
[00150] Compounds of Formula (**II**) include an aryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, the invention provides compounds of Formula (**II-d**):



(**II-d**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

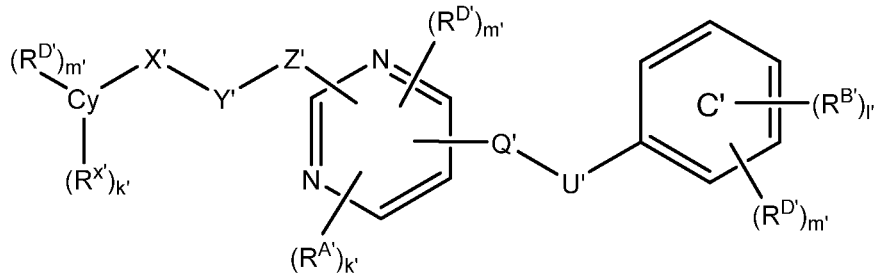
[00151] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is pyrrolopyrimidine, the invention provides compounds of Formula (**II-e**):



(**II-e**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

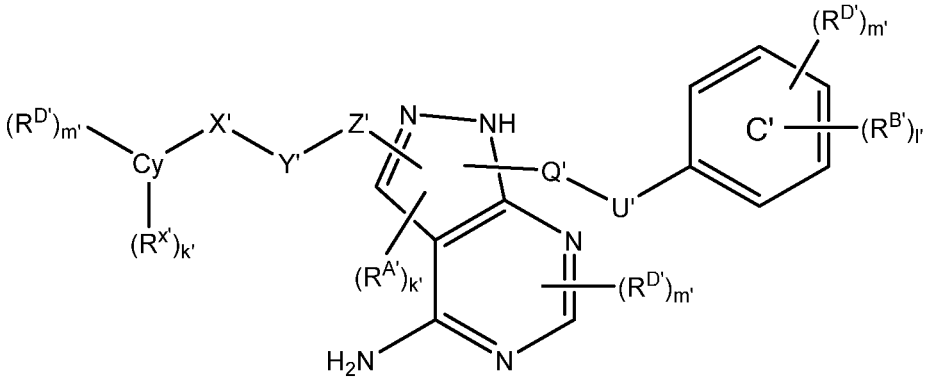
[00152] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is pyrimidine, the invention provides compounds of Formula (**II-e^{A}**):



(**II-e^{A}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

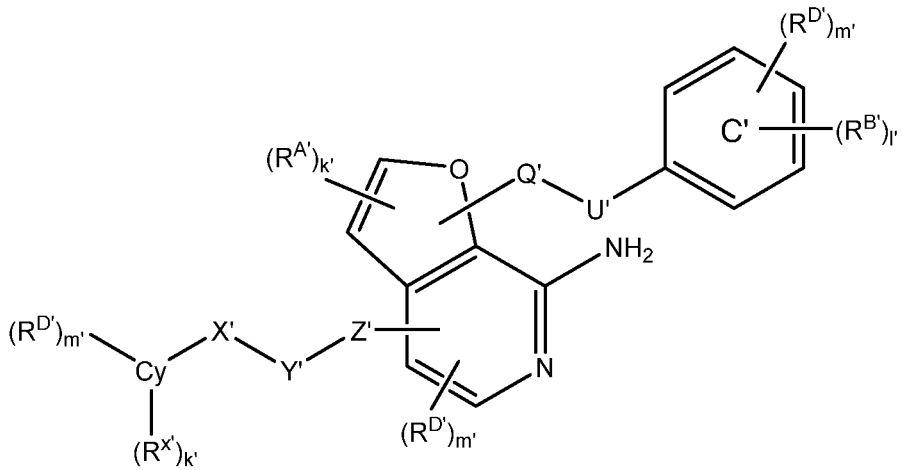
[00153] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is pyrimidine, the invention provides compounds of Formula (**II-e^{B}**):



(**II-e^{B}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

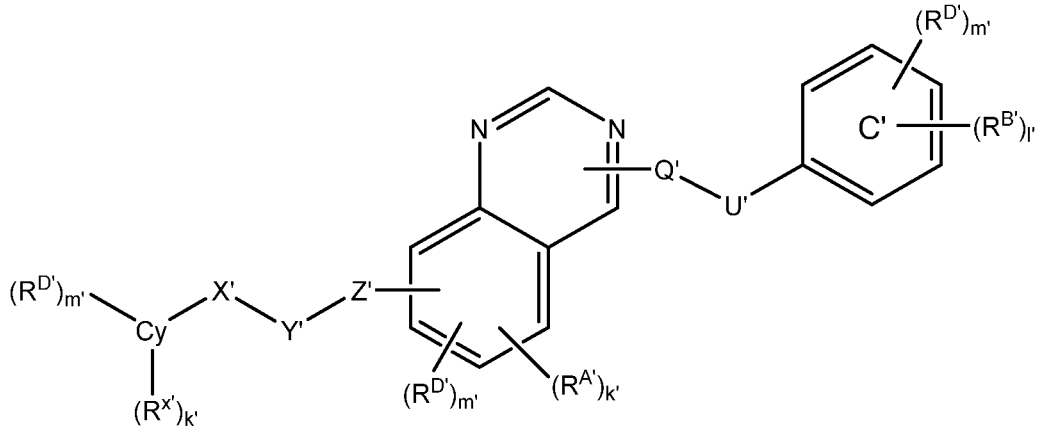
[00154] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a furo[2,3-c]pyridin-7-amine, the invention provides compounds of Formula (**II-e^{C}**):



(**II-e^{C}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

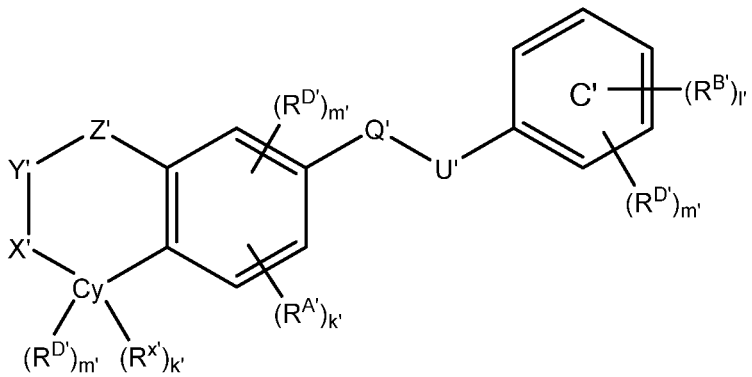
[00155] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is a quinazoline, the invention provides compounds of Formula (**II-e^{D}**):



(**II-e^{D}**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{X'}$, k′, and l′ are as defined herein.

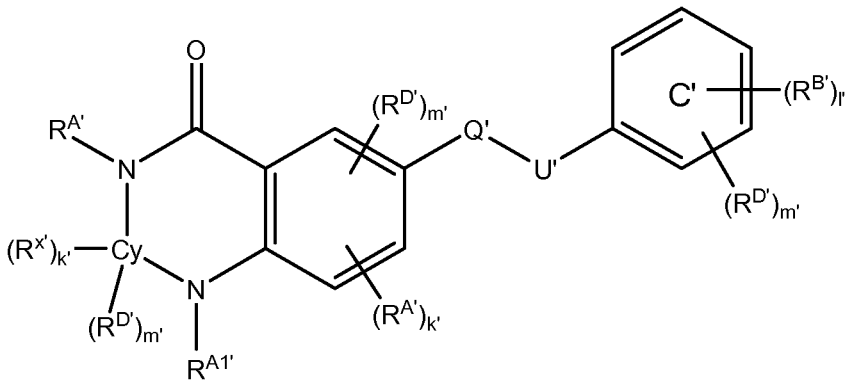
[00156] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, and at least one $R^{A'}$ group links to Cy forming an optional 5 to 8 membered ring, the invention provides compounds of Formula (**II-f**):



(**II-f**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

[00157] Compounds of Formula (**II**) include an heteroaryl group for Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, when Ring A′ is phenyl, and at least one $R^{A'}$ group links to Cy forming an optional 5 to 8 membered ring, the invention provides compounds of Formula (**II-g**):



(**II-g**)

wherein Ring C′, Cy, Q′, U′, X′, Y′, Z′, $R^{A'}$, $R^{B'}$, $R^{D'}$, $R^{X'}$, k′, l′, and m′ are as defined herein.

[00158] In compounds of Formula (**II**), $R^{D'}$ is a substituent on Ring A′, Ring C′, or Cy. In certain embodiments, $R^{D'}$ comprises a Michael acceptor moiety. This Michael acceptor moiety may react with a cysteine or other nucleophilic residue to allow covalent attachment of the compound to the target. In certain embodiments, the covalent attachment is irreversible. In other embodiments, the covalent attachment is reversible. In certain embodiments, $R^{D'}$ is of Formula (**i-1**). In certain embodiments, $R^{D'}$ is of Formula (**i-2**). In certain embodiments, $R^{D'}$ is of Formula (**i-3**). In certain embodiments, $R^{D'}$ is of Formula (**i-4**). In certain embodiments, $R^{D'}$ is of Formula (**i-5**). In certain embodiments, $R^{D'}$ is of Formula (**i-6**). In certain embodiments, $R^{D'}$ is of Formula (**i-7**). In certain embodiments, $R^{D'}$ is of Formula (**i-8**). In certain embodiments, $R^{D'}$ is of Formula (**i-9**). In certain embodiments, $R^{D'}$ is of Formula (**i-10**). In certain embodiments, $R^{D'}$ is of Formula (**i-11**). In certain embodiments, $R^{D'}$ is of Formula (**i-12**). In certain embodiments, $R^{D'}$ is of Formula (**i-13**). In certain embodiments, $R^{D'}$ is of Formula (**i-14**). In certain embodiments, $R^{D'}$ is of Formula (**i-15**). In certain embodiments, $R^{D'}$ is of Formula (**i-16**). In certain embodiments, $R^{D'}$ is of Formula (**i-17**).

[00159] In compounds of Formula (**II**), $R^{D'}$ may include a substituent $R^{D1'}$. In certain embodiments, $R^{D1'}$ is H. In certain embodiments, $R^{D1'}$ is halogen. In certain embodiments, $R^{D1'}$ is F. In certain embodiments, $R^{D1'}$ is Cl. In certain embodiments, $R^{D1'}$ is Br. In certain embodiments, $R^{D1'}$ is I (iodine). In certain embodiments, $R^{D1'}$ is substituted acyl. In certain embodiments, $R^{D1'}$ is unsubstituted acyl. In certain embodiments, $R^{D1'}$ is acetyl. In certain embodiments, $R^{D1'}$ is substituted alkyl. In certain embodiments, $R^{D1'}$ is unsubstituted alkyl. In

certain embodiments, $R^{D1'}$ is C_{1-6} alkyl. In certain embodiments, $R^{D1'}$ is methyl. In certain embodiments, $R^{D1'}$ is ethyl. In certain embodiments, $R^{D1'}$ is propyl. In certain embodiments, $R^{D1'}$ is butyl. In certain embodiments, $R^{D1'}$ is substituted alkenyl. In certain embodiments, $R^{D1'}$ is unsubstituted alkenyl. In certain embodiments, $R^{D1'}$ is substituted alkynyl. In certain embodiments, $R^{D1'}$ is unsubstituted alkynyl. In certain embodiments, $R^{D1'}$ is substituted carbocyclyl. In certain embodiments, $R^{D1'}$ is unsubstituted carbocyclyl. In certain embodiments, $R^{D1'}$ is substituted heterocyclyl. In certain embodiments, $R^{D1'}$ is unsubstituted heterocyclyl. In certain embodiments, $R^{D1'}$ is substituted aryl. In certain embodiments, $R^{D1'}$ is unsubstituted aryl. In certain embodiments, $R^{D1'}$ is substituted phenyl. In certain embodiments, $R^{D1'}$ is unsubstituted phenyl. In certain embodiments, $R^{D1'}$ is substituted heteroaryl. In certain embodiments, $R^{D1'}$ is unsubstituted heteroaryl. In certain embodiments, $R^{D1'}$ is substituted pyridyl. In certain embodiments, $R^{D1'}$ is unsubstituted pyridyl. In certain embodiments, $R^{D1'}$ is –CN. In certain embodiments, $R^{D1'}$ is $–NO_2$. In certain embodiments, $R^{D1'}$ is $–OR^{D1a'}$. In certain embodiments, $R^{D1'}$ is $–N(R^{D1a'})_2$. In certain embodiments, $R^{D1'}$ is $–SR^{D1a'}$. In certain embodiments, $R^{D1'}$ is $–CH_2OR^{D1a'}$. In certain embodiments, $R^{D1'}$ is $–CH_2N(R^{D1a'})_2$. In certain embodiments, $R^{D1'}$ is $–CH_2SR^{D1a'}$.

[00160] In certain embodiments, at least one $R^{D1a'}$ is H. In certain embodiments, at least one $R^{D1a'}$ is substituted acyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{D1a'}$ is acetyl. In certain embodiments, at least one $R^{D1a'}$ is substituted alkyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{D1a'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{D1a'}$ is methyl. In certain embodiments, at least one $R^{D1a'}$ is ethyl. In certain embodiments, at least one $R^{D1a'}$ is propyl. In certain embodiments, at least one $R^{D1a'}$ is butyl. In certain embodiments, at least one $R^{D1a'}$ is substituted alkenyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{D1a'}$ is substituted alkynyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{D1a'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{D1a'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{D1a'}$ is substituted aryl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{D1a'}$ is substituted phenyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{D1a'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{D1a'}$ is

substituted pyridyl. In certain embodiments, at least one $R^{D1a'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{D1a'}$ is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one $R^{D1a'}$ is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, $R^{D1a'}$ is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, $R^{D1a'}$ is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, $R^{D1a'}$ is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, $R^{D1a'}$ is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two $R^{D1a'}$ groups are joined to form a substituted heterocyclic ring. In certain embodiments, two $R^{D1a'}$ groups are joined to form an unsubstituted heterocyclic ring.

[00161] In compounds of Formula (**II**), $R^{D'}$ may include a substituent $R^{D2'}$. In certain embodiments, $R^{D2'}$ is H. In certain embodiments, $R^{D2'}$ is halogen. In certain embodiments, $R^{D2'}$ is F. In certain embodiments, $R^{D2'}$ is Cl. In certain embodiments, $R^{D2'}$ is Br. In certain embodiments, $R^{D2'}$ is I (iodine). In certain embodiments, $R^{D2'}$ is substituted acyl. In certain embodiments, $R^{D2'}$ is unsubstituted acyl. In certain embodiments, $R^{D2'}$ is acetyl. In certain embodiments, $R^{D2'}$ is substituted alkyl. In certain embodiments, $R^{D2'}$ is unsubstituted alkyl. In certain embodiments, $R^{D2'}$ is C_{1-6} alkyl. In certain embodiments, $R^{D2'}$ is methyl. In certain embodiments, $R^{D2'}$ is ethyl. In certain embodiments, $R^{D2'}$ is propyl. In certain embodiments, $R^{D2'}$ is butyl. In certain embodiments, $R^{D2'}$ is substituted alkenyl. In certain embodiments, $R^{D2'}$ is unsubstituted alkenyl. In certain embodiments, $R^{D2'}$ is substituted alkynyl. In certain embodiments, $R^{D2'}$ is unsubstituted alkynyl. In certain embodiments, $R^{D2'}$ is substituted carbocyclyl. In certain embodiments, $R^{D2'}$ is unsubstituted carbocyclyl. In certain embodiments, $R^{D2'}$ is substituted heterocyclyl. In certain embodiments, $R^{D2'}$ is unsubstituted heterocyclyl. In certain embodiments, $R^{D2'}$ is substituted aryl. In certain embodiments, $R^{D2'}$ is unsubstituted aryl. In certain embodiments, $R^{D2'}$ is substituted phenyl. In certain embodiments, $R^{D2'}$ is unsubstituted phenyl. In certain embodiments, $R^{D2'}$ is substituted heteroaryl. In certain embodiments, $R^{D2'}$ is unsubstituted heteroaryl. In certain embodiments, $R^{D2'}$ is substituted pyridyl. In certain embodiments, $R^{D2'}$ is unsubstituted pyridyl. In certain embodiments, $R^{D2'}$ is –CN. In certain embodiments, $R^{D2'}$ is $–NO_2$. In certain embodiments, $R^{D2'}$ is $–OR^{D2a'}$. In certain embodiments, $R^{D2'}$ is $–N(R^{D2a'})_2$. In certain embodiments, $R^{D2'}$ is $–SR^{D2a'}$. In certain embodiments, $R^{D2'}$ is $–CH_2OR^{D2a'}$. In certain embodiments, $R^{D2'}$ is $–CH_2N(R^{D2a'})_2$. In certain embodiments, $R^{D2'}$ is $–CH_2SR^{D2a'}$.

[00162] In certain embodiments, at least one $R^{D2a'}$ is H. In certain embodiments, at least one $R^{D2a'}$ is substituted acyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{D2a'}$ is acetyl. In certain embodiments, at least one $R^{D2a'}$ is substituted alkyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{D2a'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{D2a'}$ is methyl. In certain embodiments, at least one $R^{D2a'}$ is ethyl. In certain embodiments, at least one $R^{D2a'}$ is propyl. In certain embodiments, at least one $R^{D2a'}$ is butyl. In certain embodiments, at least one $R^{D2a'}$ is substituted alkenyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{D2a'}$ is substituted alkynyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{D2a'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{D2a'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{D2a'}$ is substituted aryl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{D2a'}$ is substituted phenyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{D2a'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{D2a'}$ is substituted pyridyl. In certain embodiments, at least one $R^{D2a'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{D2a'}$ is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one $R^{D2a'}$ is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, $R^{D2a'}$ is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, $R^{D2a'}$ is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, $R^{D2a'}$ is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, $R^{D2a'}$ is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two $R^{D2a'}$ groups are joined to form a substituted heterocyclic ring. In certain embodiments, two $R^{D2a'}$ groups are joined to form an unsubstituted heterocyclic ring.

[00163] In compounds of Formula (**II**), $R^{D'}$ may include a substituent $R^{D3'}$. In certain embodiments, $R^{D3'}$ is H. In certain embodiments, $R^{D3'}$ is halogen. In certain embodiments, $R^{D3'}$ is F. In certain embodiments, $R^{D3'}$ is Cl. In certain embodiments, $R^{D3'}$ is Br. In certain embodiments, $R^{D3'}$ is I (iodine). In certain embodiments, $R^{D3'}$ is substituted acyl. In certain

embodiments, $R^{D3'}$ is unsubstituted acyl. In certain embodiments, $R^{D3'}$ is acetyl. In certain embodiments, $R^{D3'}$ is substituted alkyl. In certain embodiments, $R^{D3'}$ is unsubstituted alkyl. In certain embodiments, $R^{D3'}$ is C_{1-6} alkyl. In certain embodiments, $R^{D3'}$ is methyl. In certain embodiments, $R^{D3'}$ is ethyl. In certain embodiments, $R^{D3'}$ is propyl. In certain embodiments, $R^{D3'}$ is butyl. In certain embodiments, $R^{D3'}$ is substituted alkenyl. In certain embodiments, $R^{D3'}$ is unsubstituted alkenyl. In certain embodiments, $R^{D3'}$ is substituted alkynyl. In certain embodiments, $R^{D3'}$ is unsubstituted alkynyl. In certain embodiments, $R^{D3'}$ is substituted carbocyclyl. In certain embodiments, $R^{D3'}$ is unsubstituted carbocyclyl. In certain embodiments, $R^{D3'}$ is substituted heterocyclyl. In certain embodiments, $R^{D3'}$ is unsubstituted heterocyclyl. In certain embodiments, $R^{D3'}$ is substituted aryl. In certain embodiments, $R^{D3'}$ is unsubstituted aryl. In certain embodiments, $R^{D3'}$ is substituted phenyl. In certain embodiments, $R^{D3'}$ is unsubstituted phenyl. In certain embodiments, $R^{D3'}$ is substituted heteroaryl. In certain embodiments, $R^{D3'}$ is unsubstituted heteroaryl. In certain embodiments, $R^{D3'}$ is substituted pyridyl. In certain embodiments, $R^{D3'}$ is unsubstituted pyridyl. In certain embodiments, $R^{D3'}$ is –CN. In certain embodiments, $R^{D3'}$ is $–NO_2$. In certain embodiments, $R^{D3'}$ is $–OR^{D3a'}$. In certain embodiments, $R^{D3'}$ is $–N(R^{D3a'})_2$. In certain embodiments, $R^{D3'}$ is $–SR^{D3a'}$. In certain embodiments, $R^{D3'}$ is $–CH_2OR^{D3a'}$. In certain embodiments, $R^{D3'}$ is $–CH_2N(R^{D3a'})_2$. In certain embodiments, $R^{D3'}$ is $–CH_2SR^{D3a'}$.

[00164] In certain embodiments, at least one $R^{D3a'}$ is H. In certain embodiments, at least one $R^{D3a'}$ is substituted acyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{D3a'}$ is acetyl. In certain embodiments, at least one $R^{D3a'}$ is substituted alkyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{D3a'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{D3a'}$ is methyl. In certain embodiments, at least one $R^{D3a'}$ is ethyl. In certain embodiments, at least one $R^{D3a'}$ is propyl. In certain embodiments, at least one $R^{D3a'}$ is butyl. In certain embodiments, at least one $R^{D3a'}$ is substituted alkenyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{D3a'}$ is substituted alkynyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{D3a'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{D3a'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{D3a'}$ is substituted aryl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{D3a'}$ is substituted phenyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted phenyl.

In certain embodiments, at least one $R^{D3a'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{D3a'}$ is substituted pyridyl. In certain embodiments, at least one $R^{D3a'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{D3a'}$ is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one $R^{D3a'}$ is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, $R^{D3a'}$ is an oxygen protecting group when attached to an oxygen atom. In certain embodiments, $R^{D3a'}$ is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, $R^{D3a'}$ is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, $R^{D3a'}$ is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom. In certain embodiments, two $R^{D3a'}$ groups are joined to form a substituted heterocyclic ring. In certain embodiments, two $R^{D3a'}$ groups are joined to form an unsubstituted heterocyclic ring.

[00165] In compounds of Formula (**II**), $R^{D'}$ may include a substituent $R^{D4'}$. In certain embodiments, $R^{D4'}$ is a leaving group. In certain embodiments, $R^{D4'}$ is halogen. In certain embodiments, $R^{D4'}$ is F. In certain embodiments, $R^{D4'}$ is Cl. In certain embodiments, $R^{D4'}$ is Br. In certain embodiments, $R^{D4'}$ is I (iodine). In certain embodiments, $R^{D4'}$ is $-OS(=O)_{w'}R^{D4a'}$. In certain embodiments, w′ is 1. In certain embodiments, w′ is 2. In certain embodiments, $R^{D4'}$ is –OMs. In certain embodiments, $R^{D4'}$ is –OTf. In certain embodiments, $R^{D4'}$ is –OTs. In certain embodiments, $R^{D4'}$ is –OBs. In certain embodiments, $R^{D4'}$ is 2-nitrobenzenesulfonyloxy.In certain embodiments, $R^{D4'}$ is $-OR^{D4a'}$. In certain embodiments, $R^{D4'}$ is –OMe. In certain embodiments, $R^{D4'}$ is $-OCF_3$. In certain embodiments, $R^{D4'}$ is –OPh. In certain embodiments, $R^{D4'}$ is $-OC(=O)R^{D4a'}$. In certain embodiments, $R^{D4'}$ is –OC(=O)Me. In certain embodiments, $R^{D4'}$ is $-OC(=O)CF_3$. In certain embodiments, $R^{D4'}$ is –OC(=O)Ph. In certain embodiments, $R^{D4'}$ is –OC(=O)Cl. In certain embodiments, $R^{D4'}$ is $-OC(=O)OR^{D4a'}$. In certain embodiments, $R^{D4'}$ is –OC(=O)OMe. In certain embodiments, $R^{D4'}$ is –OC(=O)O(*t*-Bu).

[00166] In certain embodiments, $R^{D4a'}$ is substituted alkyl. In certain embodiments, $R^{D4a'}$ is unsubstituted alkyl. In certain embodiments, $R^{D4a'}$ is C_{1-6} alkyl. In certain embodiments, $R^{D4a'}$ is methyl. In certain embodiments, $R^{D4a'}$ is ethyl. In certain embodiments, $R^{D4a'}$ is propyl. In certain embodiments, $R^{D4a'}$ is butyl. In certain embodiments, $R^{D4a'}$ is substituted alkenyl. In certain embodiments, $R^{D4a'}$ is unsubstituted alkenyl. In certain embodiments, $R^{D4a'}$ is vinyl. In certain embodiments, $R^{D4a'}$ is substituted alkynyl. In certain embodiments, $R^{D4a'}$ is

unsubstituted alkynyl. In certain embodiments, $R^{D4a\prime}$ is ethynyl. In certain embodiments, $R^{D4a\prime}$ is substituted carbocyclyl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted carbocyclyl. In certain embodiments, $R^{D4a\prime}$ is substituted heterocyclyl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted heterocyclyl. In certain embodiments, $R^{D4a\prime}$ is substituted aryl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted aryl. In certain embodiments, $R^{D4a\prime}$ is substituted phenyl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted phenyl. In certain embodiments, $R^{D4a\prime}$ is substituted heteroaryl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted heteroaryl. In certain embodiments, $R^{D4a\prime}$ is substituted pyridyl. In certain embodiments, $R^{D4a\prime}$ is unsubstituted pyridyl.

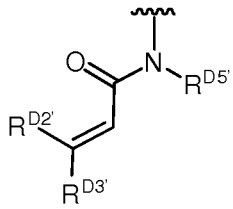
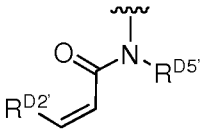
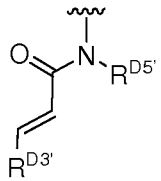
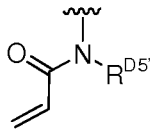
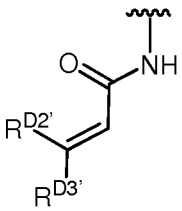
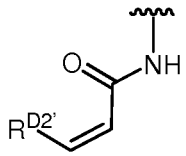
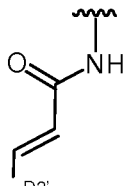
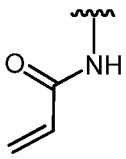
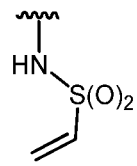
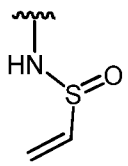
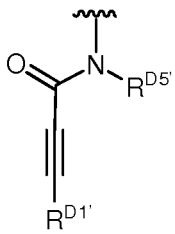
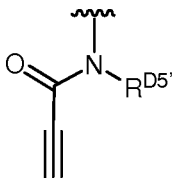
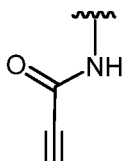
[00167] In compounds of Formula (**II**), $R^{D\prime}$ may include a substituent $R^{D5\prime}$. In certain embodiments, $R^{D5\prime}$ is H. In certain embodiments, $R^{D5\prime}$ is substituted alkyl. In certain embodiments, $R^{D5\prime}$ is unsubstituted alkyl. In certain embodiments, $R^{D5\prime}$ is C_{1-6} alkyl. In certain embodiments, $R^{D5\prime}$ is methyl. In certain embodiments, $R^{D5\prime}$ is ethyl. In certain embodiments, $R^{D5\prime}$ is propyl. In certain embodiments, $R^{D5\prime}$ is butyl. In certain embodiments, $R^{D5\prime}$ is a nitrogen protecting group. In certain embodiments, $R^{D5\prime}$ is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts.

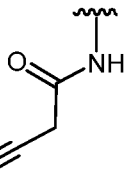
[00168] In certain embodiments, $R^{D1\prime}$ and $R^{D2\prime}$ are each hydrogen. In certain embodiments, $R^{D1\prime}$ and $R^{D3\prime}$ are each hydrogen. In certain embodiments, $R^{D2\prime}$ and $R^{D3\prime}$ are each hydrogen. In certain embodiments, $R^{D1\prime}$, $R^{D2\prime}$, and $R^{D3\prime}$ are each hydrogen. In certain embodiments, $R^{D1\prime}$, $R^{D2\prime}$, and $R^{D3\prime}$, and $R^{D5\prime}$ are each hydrogen.

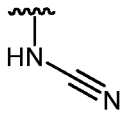
[00169] In certain embodiments, a′ is 1. In certain embodiments, a′ is 2.

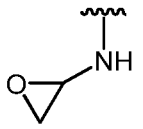
[00170] In certain embodiments, z′ is 0. In certain embodiments, z′ is 1. In certain embodiments, z′ is 2. In certain embodiments, z′ is 3. In certain embodiments, z′ is 4. In certain embodiments, z′ is 5. In certain embodiments, z′ is 6.

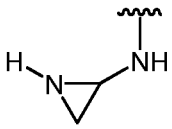
[00171] In certain embodiments, $Y^{Z\prime}$ is –O–. In certain embodiments, $Y^{Z\prime}$ is =O. In certain embodiments, $Y^{Z\prime}$ is –S–. In certain embodiments, $Y^{Z\prime}$ is =S. In certain embodiments, $Y^{Z\prime}$ is –$NR^{D6\prime}$–, wherein $R^{D6\prime}$ is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, $Y^{Z\prime}$ is –NH–. In certain embodiments, $Y^{Z\prime}$ is –NCH_3–. In certain embodiments, $Y^{Z\prime}$ is –N(BOC)–. In certain embodiments, $Y^{Z\prime}$ is –N(Fmoc)–. In certain embodiments, $Y^{Z\prime}$ is –N(Cbz)–. In certain embodiments, $Y^{Z\prime}$ is –N(Bn)–. In certain embodiments, $Y^{Z\prime}$ is =$NR^{D6\prime}$, wherein $R^{D6\prime}$ is hydrogen, C_{1-6} alkyl, or a nitrogen protecting group. In certain embodiments, $Y^{Z\prime}$ is =NH. In certain embodiments, $Y^{Z\prime}$ is =NCH_3. In certain embodiments, $Y^{Z\prime}$ is =NTs. In certain embodiments, $Y^{Z\prime}$ is =NBn. In certain embodiments, $Y^{Z\prime}$ is =$NCH(Ph)_2$.

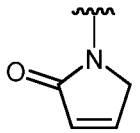
[00172] In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In certain embodiments, $R^{D\prime}$ is of the formula:  . In

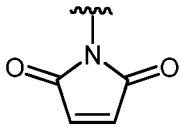


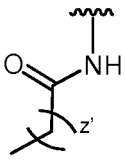


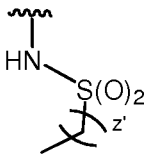


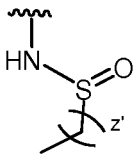


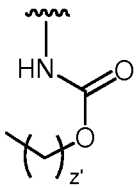


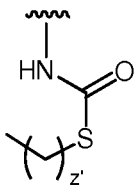


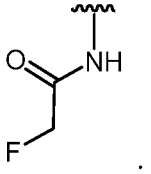


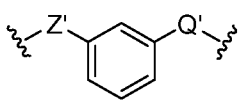






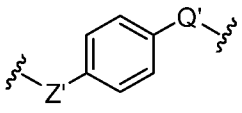
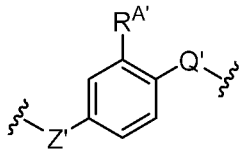


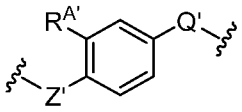
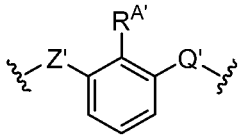
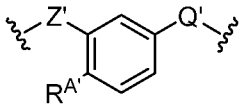
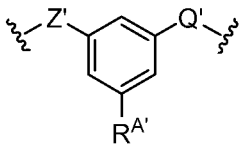
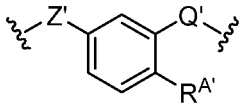


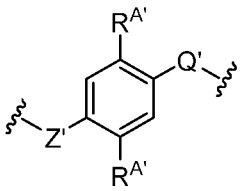
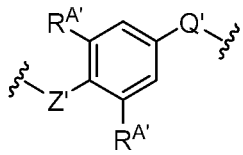
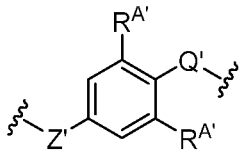
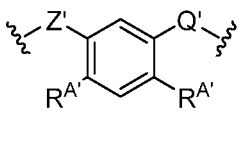
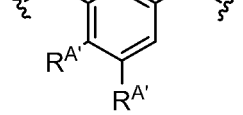


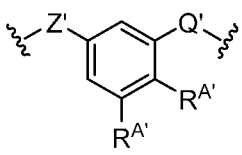
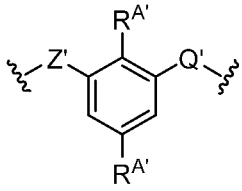
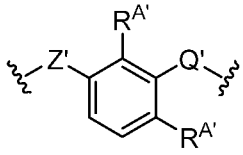
certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: . In certain embodiments, $R^{D'}$ is of the formula: .

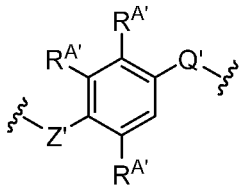
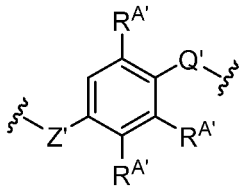
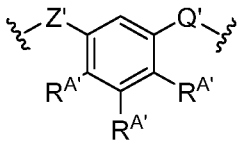
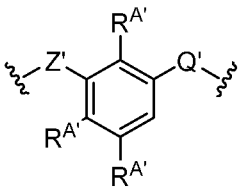
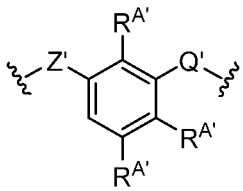
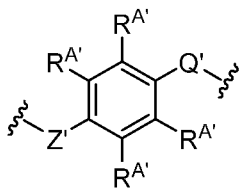
[00173] Compounds of Formula (**II**) or (**V**) include an aryl Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, k′ is 0. In certain embodiments, Ring A′ is of the formula: . In certain embodiments, Ring A′ is of the formula:

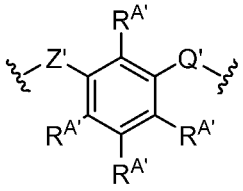

. In certain embodiments, k′ is 1. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, Ring A′ is of the formula:


. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, k′ is 2. In certain embodiments, Ring A′ is of the formula: 
. In certain embodiments, Ring A′ is of the formula:


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

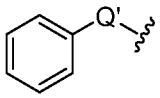

. In certain embodiments, Ring A′ is of the formula:

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

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

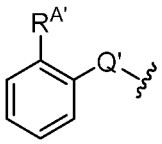
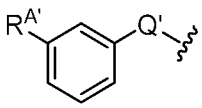
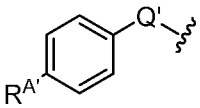
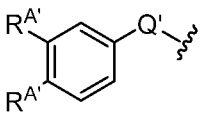
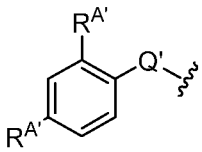
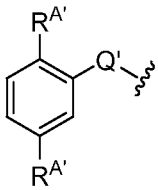
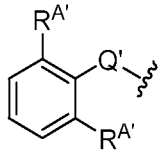
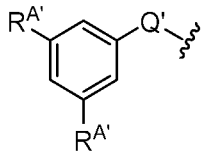
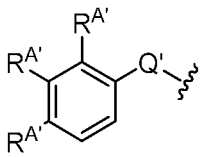
. In certain embodiments, k′ is 3. In certain embodiments, Ring A′ is of the formula:

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

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

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

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

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

. In certain embodiments, k′ is 4. In certain embodiments, Ring A′ is of the formula:
. In certain

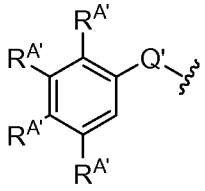


embodiments, Ring A′ is of the formula: .

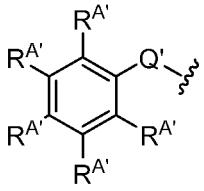
[00174] Compounds of Formula (**II**) or (**V**) include an aryl Ring A′ optionally substituted with one or more $R^{A'}$ groups. In certain embodiments, X′, Y′, and Z′ are bonds, and Cy is hydrogen. In certain embodiments, k′ is 0. In certain embodiments, Ring A′ is of the formula:



. In certain embodiments, k′ is 1. In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, k′ is 2. In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:  . In certain embodiments, Ring A′ is of the formula:



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



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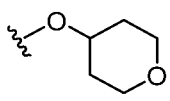
[00175] In compounds of Formula (**II**) or (**V**), Ring A′ may be substituted with one or more $R^{A'}$ groups. In certain embodiments, at least one $R^{A'}$ is H. In certain embodiments, at least two $R^{A'}$ groups are H. In certain embodiments, at least three $R^{A'}$ groups are H. In certain embodiments, at least four $R^{A'}$ groups are H. In certain embodiments, at least one $R^{A'}$ is halogen. In certain embodiments, at least one $R^{A'}$ is F. In certain embodiments, at least one $R^{A'}$ is Cl. In certain embodiments, at least one $R^{A'}$ is Br. In certain embodiments, at least one $R^{A'}$ is I (iodine). In certain embodiments, at least one $R^{A'}$ is substituted acyl. In certain embodiments, at least one $R^{A'}$ is $-C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-C(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{A'}$ is –C(=O)NHMe. In certain embodiments, at least one $R^{A'}$ is $-C(=O)NH_2$. In certain embodiments, at least one $R^{A'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{A'}$ is acetyl. In certain embodiments, at least one $R^{A'}$ is substituted alkyl. In certain embodiments, at least one $R^{A'}$ is substituted methyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{A'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{A'}$ is methyl. In certain embodiments, at least one $R^{A'}$ is ethyl. In certain embodiments, at least one $R^{A'}$ is propyl. In certain embodiments, at least one $R^{A'}$ is butyl. In certain embodiments, at least one $R^{A'}$ is substituted alkenyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{A'}$ is substituted alkynyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{A'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{A'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{A'}$ is

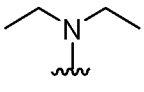


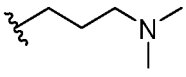
. In certain embodiments, at least one $R^{A'}$ is substituted aryl. In certain embodiments, at least one $R^{A'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{A'}$ is substituted phenyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{A'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{A'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{A'}$ is

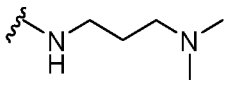
substituted pyridyl. In certain embodiments, at least one $R^{A'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{A'}$ is $-OR^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-O(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{A'}$ is –OMe. In certain embodiments, at least one $R^{A'}$ is –OH. In certain embodiments, at least one $R^{A'}$ is $-N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-NH_2$. In certain embodiments, at least one $R^{A'}$ is $-SR^{A1'}$. In certain embodiments, at least one $R^{A'}$ is –SH. In certain embodiments, at least one $R^{A'}$ is $-NR^{A1'}C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-NHC(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-NHC(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-NHC(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{A'}$ is –NHC(=O)NHMe. In certain embodiments, at least one $R^{A'}$ is $-NHC(=O)NH_2$. In certain embodiments, at least one $R^{A'}$ is $-NR^{A1'}C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-NR^{A1'}C(=O)NH_2$. In certain embodiments, at least one $R^{A'}$ is $-NR^{A1'}S(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-NHS(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{A'}$ is $-NHS(=O)_2(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{A'}$ is $-NHS(=O)_2Me$. In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2NH(t\text{-Bu})$. In certain embodiments, at least one $R^{A'}$ is $-S(=O)_2NH_2$.

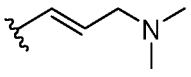
[00176] In compounds of Formula (**II**) or (**V**), Ring C′ may be substituted with one or more $R^{B'}$ groups. In certain embodiments, at least one $R^{B'}$ is H. In certain embodiments, at least two $R^{B'}$ groups are H. In certain embodiments, at least three $R^{B'}$ groups are H. In certain embodiments, at least four $R^{B'}$ groups are H. In certain embodiments, at least one $R^{B'}$ is halogen. In certain embodiments, at least one $R^{B'}$ is F. In certain embodiments, at least one $R^{B'}$ is Cl. In certain embodiments, at least one $R^{B'}$ is Br. In certain embodiments, at least one $R^{B'}$ is I (iodine). In certain embodiments, at least one $R^{B'}$ is substituted acyl. In certain embodiments, at least one $R^{B'}$ is $-C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{B'}$ is $-C(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{B'}$ is –C(=O)NHMe. In certain embodiments, at least one $R^{B'}$ is $-C(=O)NH_2$. In certain embodiments, at least one $R^{B'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{B'}$ is acetyl. In certain embodiments, at least one $R^{B'}$ is substituted alkyl. In certain embodiments, at least one $R^{B'}$ is substituted methyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{B'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{B'}$ is methyl. In certain embodiments, at least one $R^{B'}$ is

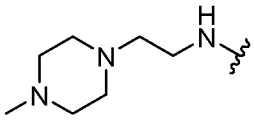
ethyl. In certain embodiments, at least one $R^{B'}$ is propyl. In certain embodiments, at least one $R^{B'}$ is butyl. In certain embodiments, at least one $R^{B'}$ is $-CF_3$. In certain embodiments, at least one $R^{B'}$ is substituted alkenyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{B'}$ is substituted alkynyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{B'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{B'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{B'}$ is substituted aryl. In certain embodiments, at least one $R^{B'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{B'}$ is substituted phenyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{B'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{B'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{B'}$ is substituted pyridyl. In certain embodiments, at least one $R^{B'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{B'}$ is $-O^{A1}$. In certain embodiments, at least one $R^{B'}$ is $-O(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{B'}$ is –OMe. In certain embodiments, at least one $R^{B'}$ is –OH. In certain embodiments, at least one $R^{B'}$ is $-N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-NH_2$. In certain embodiments, at least one $R^{B'}$ is $-SR^{A1'}$. In certain embodiments, at least one $R^{B'}$ is –SH. In certain embodiments, at least one $R^{B'}$ is $-NR^{A1'}C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-NHC(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-NHC(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{B'}$ is $-NHC(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{B'}$ is –NHC(=O)NHMe. In certain embodiments, at least one $R^{B'}$ is –$NHC(=O)NH_2$. In certain embodiments, at least one $R^{B'}$ is $-NR^{A1'}C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{B'}$ is $-NR^{A1'}C(=O)NH_2$. In certain embodiments, at least one $R^{B'}$ is $-NR^{A1'}S(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{B'}$ is $-NHS(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{B'}$ is $-NHS(=O)_2(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{B'}$ is $-NHS(=O)_2$Me. In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2NH(t$-Bu). In certain embodiments, at least one $R^{B'}$ is $-S(=O)_2NH_2$. In certain embodiments, at least one $R^{B'}$ is substituted imidazole. In certain embodiments, at least one $R^{B'}$ is substituted piperidine. In certain embodiments, at least one $R^{B'}$ substituted piperizine. In certain embodiments, at least one $R^{B'}$ substituted pyrrolidine. In certain embodiments, at least one $R^{B'}$ is substituted morpholine. In certain

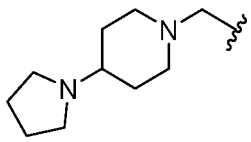


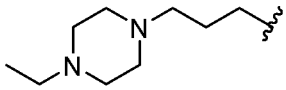


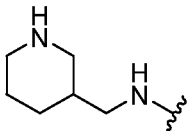


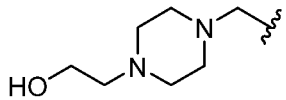


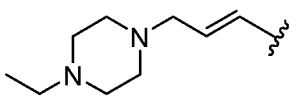


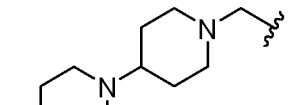


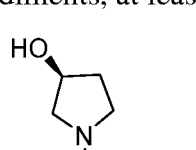


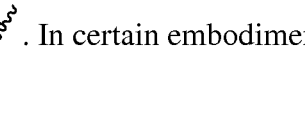


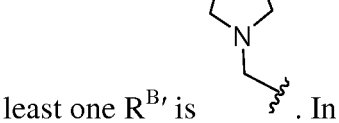


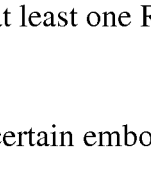


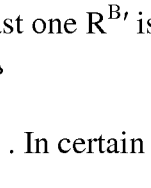


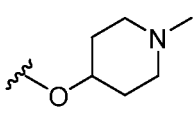




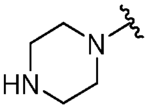
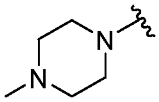
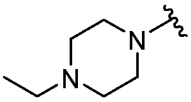
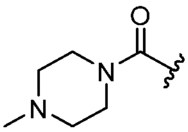
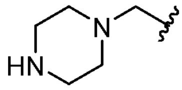
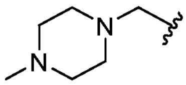
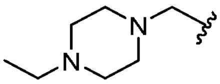
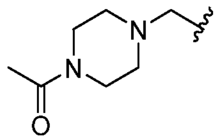
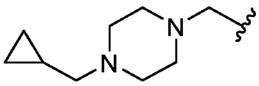
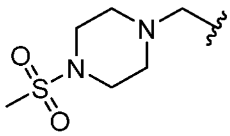
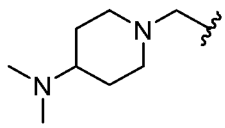
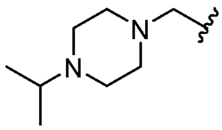
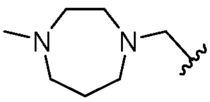
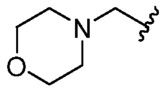
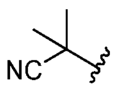
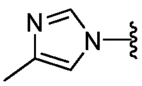
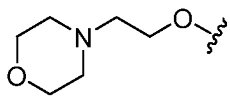
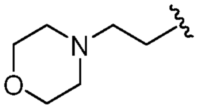
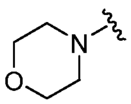
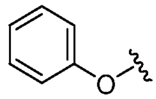


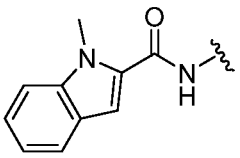
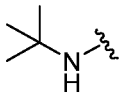
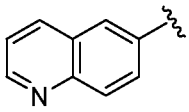






embodiments, at least one $R^{B'}$ is substituted diazapane. In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least one $R^{B'}$ is . In certain embodiments, at least

one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments,

at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  . In certain embodiments, at least one $R^{B'}$ is  .

[00177] In certain embodiments, two $R^{B'}$ groups are are joined to form a 1,3 dioxolane. In certain embodiments, two $R^{B'}$ groups are are joined to form a 1,3 dioxolane which is fused to aryl Ring C′, together comprising an optionally substituted benzodioxolane. In certain embodiments, two $R^{B'}$ groups are joined to form a 1,2,3-thiadiazole. In certain embodiments, two $R^{B'}$ groups are joined to form a 1,2,3-thiadiazole which is fused to aryl Ring C′, together comprising an optionally substituted. benzo[d][1,2,3]thiadiazole.

[00178] In certain embodiments, at least one $R^{A1'}$ is H. In certain embodiments, at least one $R^{A1'}$ is substituted acyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{A1'}$ is acetyl. In certain embodiments, at least one $R^{A1'}$ is substituted alkyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{A1'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{A1'}$ is methyl. In certain embodiments, at least one $R^{A1'}$ is ethyl. In certain embodiments, at least one $R^{A1'}$ is propyl. In certain embodiments, at least one $R^{A1'}$ is butyl. In certain embodiments, at least one $R^{A1'}$ is substituted alkenyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{A1'}$ is substituted alkynyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{A1'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{A1'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{A1'}$ is substituted aryl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{A1'}$ is substituted phenyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{A1'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{A1'}$ is substituted pyridyl. In certain embodiments, at least one $R^{A1'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{A1'}$ is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments, at least one $R^{A1'}$ is Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, or Ts when attached to a nitrogen atom. In certain embodiments, $R^{A1'}$ is an oxygen protecting

group when attached to an oxygen atom. In certain embodiments, $R^{A1'}$ is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl when attached to an oxygen atom. In certain embodiments, $R^{A1'}$ is a sulfur protecting group when attached to a sulfur atom. In certain embodiments, $R^{A1'}$ is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

[00179] In compounds of Formula (**II**) or (**V**), two $R^{A1'}$ groups may be joined to form an optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form a substituted carbocyclic ring. In certain embodiments, two $R^{A1'}$ groups are joined to form an unsubstituted carbocyclic ring. In certain embodiments, two $R^{A1'}$ groups are joined to form a substituted heterocyclic ring. In certain embodiments, two $R^{A1'}$ groups are joined to form an unsubstituted heterocyclic ring. In certain embodiments, two $R^{A1'}$ groups are joined to form a substituted aryl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form an unsubstituted aryl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form a substituted phenyl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form an unsubstituted phenyl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form a substituted heteroaryl ring. In certain embodiments, two $R^{A1'}$ groups are joined to form an unsubstituted heteroaryl ring.

[00180] In certain embodiments, $R^{A'}$ is $-OR^{A1'}$ and k′ is 1. In certain embodiments, $R^{A'}$ is $-O(C_{1-6}$ alkyl) and k′ is 1. In certain embodiments, $R^{A'}$ is –OMe and k′ is 1. In certain embodiments, $R^{A'}$ is –OH and k′ is 1.

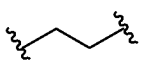
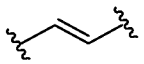
[00181] In certain embodiments, $R^{A'}$ is substituted C_{1-6} alkyl; and k′ is 1. In certain embodiments, $R^{A'}$ is unsubstituted C_{1-6} alkyl; and k′ is 1. In certain embodiments, $R^{A'}$ is methyl; and k′ is 1. In certain embodiments, $R^{A'}$ is $-CF_3$; and k′ is 1. In certain embodiments, $R^{A'}$ is ethyl; and k′ is 1. In certain embodiments, $R^{A'}$ is propyl; and k′ is 1. In certain embodiments, $R^{A'}$ is butyl; and k′ is 1. In certain embodiments, $R^{A'}$ is propyl; and k′ is 1. In certain embodiments, $R^{A'}$ is butyl; and k′ is 1.

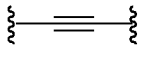
[00182] In certain embodiments, $R^{A'}$ is halogen; and k′ is 1. In certain embodiments, $R^{A'}$ is F; and k′ is 1. In certain embodiments, $R^{A'}$ is Cl; and k′ is 1. In certain embodiments, $R^{A'}$ is Br; and k′ is 1. In certain embodiments, $R^{A'}$ is I (iodine); and k′ is 1.

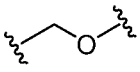
[00183] In certain embodiments, one instance of $R^{A'}$ is halogen, another instance of $R^{A'}$ is substituted C_{1-6} alkyl; and k′ is 2. In certain embodiments, one instance of $R^{A'}$ is F, another instance of $R^{A'}$ is substituted C_{1-6} alkyl; and k′ is 2. In certain embodiments, one instance of $R^{A'}$ is Cl, another instance of $R^{A'}$ is substituted C_{1-6} alkyl; and k′ is 2. In certain embodiments,

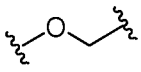
one instance of $R^{A\prime}$ is halogen, another instance of $R^{A\prime}$ is unsubstituted C_{1-6} alkyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is F, another instance of $R^{A\prime}$ is unsubstituted C_{1-6} alkyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is Cl, another instance of $R^{A\prime}$ is unsubstituted C_{1-6} alkyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is halogen, another instance of $R^{A\prime}$ is methyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is F, another instance of $R^{A\prime}$ is methyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is Cl, another instance of $R^{A\prime}$ is methyl; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is halogen, another instance of $R^{A\prime}$ is $–CF_3$; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is F, another instance of $R^{A\prime}$ is $–CF_3$; and k′ is 2. In certain embodiments, one instance of $R^{A\prime}$ is Cl, another instance of $R^{A\prime}$ is $–CF_3$; and k′ is 2.

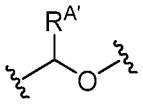
[00184] In compounds of Formula (**II**) or (**V**), linker X′, Y′, and Z′ are divalent linker moieties. In certain embodiments, X′ is a bond. In certain embodiments, X′ is a single bond. In certain embodiments, X′ is $–CH_2$. In certain embodiments, X′ is $–CHR^{A\prime}$. In certain embodiments, X′ is –CH. In certain embodiments, X′ is $–C(R^{A\prime})_2$. In certain embodiments, X′ is –C. In certain embodiments, X′ is –N. In certain embodiments, X′ is $–NR^{A\prime}$. In certain embodiments, X′ is –O. In certain embodiments, X′ is –C=O. In certain embodiments, X′ is –O. In certain embodiments, X′ is –S. In certain embodiments, X′ may optionally form a 5 to 8 membered ring with $R^{A\prime}$ or $R^{B\prime}$. In certain embodiments, Y′ is a bond. In certain embodiments, Y′ is a single bond. In certain embodiments, Y′ is $–CH_2$. In certain embodiments, Y′ is $–CHR^{A\prime}$. In certain embodiments, Y′ is –CH. In certain embodiments, Y′ is $–C(R^{A\prime})_2$. In certain embodiments, Y′ is –C. In certain embodiments, Y′ is –N. In certain embodiments, Y′ is $–NR^{A\prime}$. In certain embodiments, Y′ is –O. In certain embodiments, Y′ is –C=O. In certain embodiments, Y′ is –S. In certain embodiments, Y′ may optionally form a 5 to 8 membered ring with $R^{A\prime}$ or $R^{B\prime}$. In certain embodiments, Z′ is a bond. In certain embodiments, Z′ is a single bond. In certain embodiments, Z′ is $–CH_2$. In certain embodiments, Z′ is $–CHR^{A\prime}$. In certain embodiments, Z′ is –CH. In certain embodiments, Z′ is $–C(R^{A\prime})_2$. In certain embodiments, Z′ is –C. In certain embodiments, Z′ is –N. In certain embodiments, Z′ is $–NR^{A\prime}$. In certain embodiments, Z′ is –O. In certain embodiments, Z′ is –C=O. In certain embodiments, Z′ is –S. In certain embodiments, Z′ may optionally form a 5 to 8 membered ring with $R^{A\prime}$ or $R^{B\prime}$.

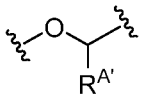
[00185] In compounds of Formula (**II**) or (**V**), linker X′, Y′, and Z′ can be taken together to represent specific linking groups. In certain embodiments, X′, Y′, and Z′ together represent  . In certain embodiments, X′, Y′, and Z′ together represent  . In certain

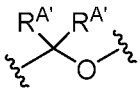


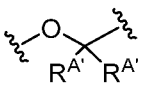


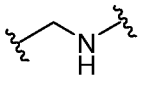


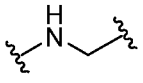


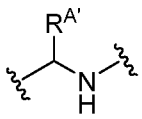


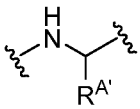


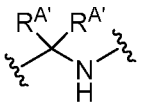


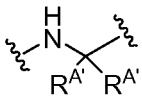


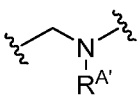


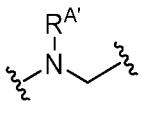


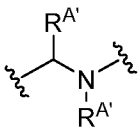


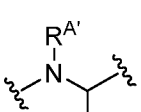


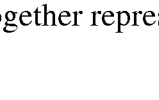


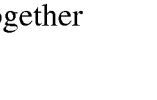




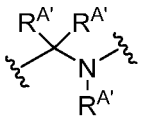
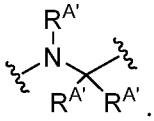


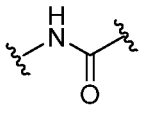


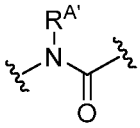


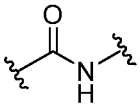


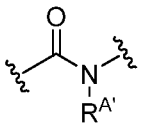
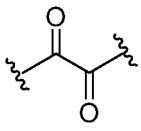
embodiments, X′, Y′, and Z′ together represent . In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together represent. In certain embodiments, X′, Y′, and Z′ together

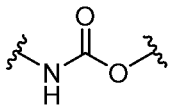
represent  . In certain embodiments, X′, Y′, and Z′ together represent  .

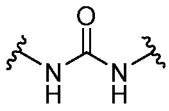
In certain embodiments, X′, Y′, and Z′ together represent  . In certain

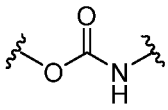
embodiments, X′, Y′, and Z′ together represent  . In certain embodiments, X′, Y′,

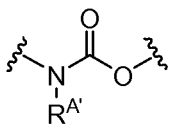
and Z′ together represent  . In certain embodiments, X′, Y′, and Z′ together

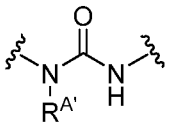
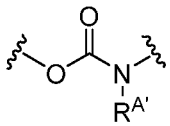
represent  . In certain embodiments, X′, Y′, and Z′ together represent  .

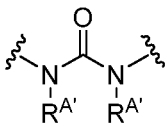
In certain embodiments, X′, Y′, and Z′ together represent  . In certain

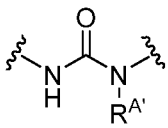
embodiments, X′, Y′, and Z′ together represent  . In certain embodiments, X′, Y′,

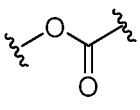
and Z′ together represent  . In certain embodiments, X′, Y′, and Z′ together

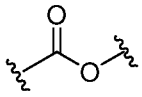
represent  . In certain embodiments, X′, Y′, and Z′ together represent

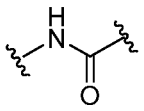
 . In certain embodiments, X′, Y′, and Z′ together represent  . In

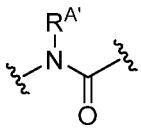
certain embodiments, X′, Y′, and Z′ together represent  . In certain embodiments,

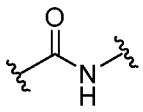
X′, Y′, and Z′ together represent  . In certain embodiments, X′, Y′, and Z′

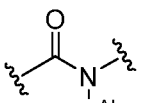
together represent  . In certain embodiments, X′, Y′, and Z′ together represent

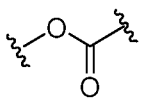


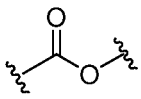


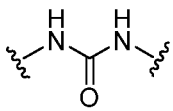


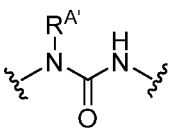


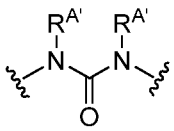


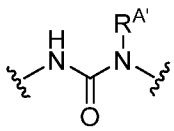


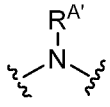








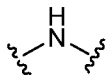




 . In certain embodiments, X′, Y′, and Z′ together represent a single bond.

[00186] In compounds of Formula (**II**) or (**V**), linker Q′ and U′ are divalent linker moieties. In certain embodiments, Q′ is –NR$^{A\prime}$. In certain embodiments, Q′ is –NH. In certain embodiments, Q′ is –C=O. In certain embodiments, Q′ is –NR$^{A\prime}$CO. In certain embodiments, Q′ is a bond. In certain embodiments, X′ may optionally form a 5 to 8 membered ring with R$^{A\prime}$ or R$^{B\prime}$. In certain embodiments, U′ is –NR$^{A\prime}$. In certain embodiments, U′ is –NH. In certain embodiments, U′ is –C=O. In certain embodiments, U′ is –NR$^{A\prime}$CO. In certain embodiments, U′ is a bond. In certain embodiments, U′ may optionally form a 5 to 8 membered ring with R$^{A\prime}$ or R$^{B\prime}$.

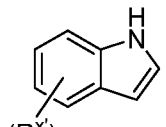
[00187] In compounds of Formula (**II**) or (**V**), linker Q′ and U′ can be taken together to represent specific linking groups. In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′ together represent . In certain embodiments, Q′ and U′

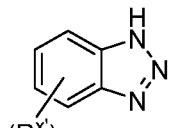
together represent  .

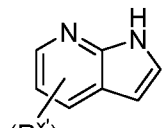
[00188] Cy of Formula (**II**) or (**V**) may be an optionally substituted aryl ring. In certain embodiments, Ring Cy is a substituted aryl ring. In certain embodiments, Cy is an unsubstituted aryl ring. In certain embodiments, Cy is a monocyclic aryl ring. In certain embodiments, Cy is substituted phenyl. In certain embodiments, Cy is unsubstituted phenyl. In certain embodiments, Cy is a bicyclic aryl ring. In certain embodiments, Cy is substituted naphthyl. In certain embodiments, Cy is unsubstituted naphthyl. In certain embodiments, Cy is an optionally substituted aryl ring fused with one or more optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl groups wherein the point of attachment is on the aryl ring.

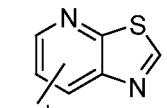
[00189] Cy of Formula (**II**) or (**V**) may also be an optionally substituted heteroaryl ring. In certain embodiments, Cy is a substituted heteroaryl ring. In certain embodiments, Cy is an unsubstituted heteroaryl ring. In certain embodiments, Cy is a monocyclic heteroaryl ring. In certain embodiments, Cy is a 5-membered monocyclic heteroaryl ring. In certain embodiments, Cy is a 5-membered monocyclic heteroaryl ring with one heteroatom selected from the group consisting of S, N, and O. In certain embodiments, Cy is a 5-membered monocyclic heteroaryl ring with two heteroatoms selected from the group consisting of S, N, and O. In certain embodiments, Cy is a 5-membered monocyclic heteroaryl ring with three heteroatoms selected from the group consisting of S, N, and O. In certain embodiments, Cy is substituted pyrrolyl. In certain embodiments, Cy is unsubstituted pyrrolyl. In certain embodiments, Cy is substituted furanyl. In certain embodiments, Cy is unsubstituted furanyl. In certain embodiments, Cy is substituted thienyl. In certain embodiments, Cy is unsubstituted thienyl. In certain embodiments, Cy is substituted pyrazolyl. In certain embodiments, Cy is unsubstituted pyrazolyl. In certain embodiments, Cy is substituted imidazolyl. In certain embodiments, Cy is unsubstituted imidazolyl. In certain embodiments, Cy is substituted oxazolyl. In certain embodiments, Cy is unsubstituted oxazolyl. In certain embodiments, Cy is substituted isoxazolyl. In certain embodiments, Cy is unsubstituted isoxazolyl. In certain embodiments, Cy is substituted thiazolyl. In certain embodiments, Cy is unsubstituted thiazolyl. In certain embodiments, Cy is substituted isothiazolyl. In certain embodiments, Cy is unsubstituted isothiazolyl. In certain embodiments, Cy is substituted triazolyl. In certain embodiments, Cy is unsubstituted triazolyl. In certain embodiments, Cy is substituted oxadiazolyl. In certain embodiments, Cy is unsubstituted oxadiazolyl. In certain embodiments, Cy is substituted thiadiazolyl. In certain embodiments, Cy is unsubstituted

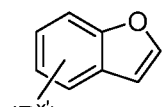
thiadiazolyl. In certain embodiments, Cy is a 6-membered monocyclic heteroaryl ring. In certain embodiments, Cy is a 6-membered monocyclic heteroaryl ring with one heteroatom selected from the group consisting of S, N, and O. In certain embodiments, Cy is a 6-membered monocyclic heteroaryl ring with two heteroatoms selected from the group consisting of S, N, and O. In certain embodiments, Cy is a 6-membered monocyclic heteroaryl ring with three heteroatoms selected from the group consisting of S, N, and O. In certain embodiments, Cy is substituted pyridyl. In certain embodiments, Cy is unsubstituted pyridyl. In certain embodiments, Cy is substituted pyridazinyl. In certain embodiments, Cy is unsubstituted pyridazinyl. In certain embodiments, Cy is substituted pyrimidinyl. In certain embodiments, Cy is unsubstituted pyrimidinyl. In certain embodiments, Cy is substituted pyrazinyl. In certain embodiments, Cy is unsubstituted pyrazinyl. In certain embodiments, Cy is substituted triazinyl. In certain embodiments, Cy is unsubstituted triazinyl. In certain embodiments, Cy is an optionally substituted heteroaryl ring fused with one or more optionally substituted carbocyclic, optionally substituted heterocyclic, optionally substituted aryl, or optionally substituted heteroaryl groups wherein the point of attachment is on any one of the heteroaryl ring, or carbocyclic, heterocyclic, aryl, or heteroaryl groups, as valency permits. In certain embodiments, Cy is a bicyclic heteroaryl ring. In certain embodiments, Cy is an optionally substituted heteroaryl ring fused with an optionally substituted phenyl ring. In certain embodiments, Cy is substituted indolyl. In certain embodiments, Cy is unsubstituted indolyl. In certain embodiments, Cy is substituted isoindolyl. In certain embodiments, Cy is unsubstituted isoindolyl. In certain embodiments, Cy is substituted indazolyl. In certain embodiments, Cy is unsubstituted indazolyl. In certain embodiments, Cy is substituted benzothienyl. In certain embodiments, Cy is unsubstituted benzothienyl. In certain embodiments, Cy is substituted isobenzothienyl. In certain embodiments, Cy is unsubstituted isobenzothienyl. In certain embodiments, Cy is substituted benzofuranyl. In certain embodiments, Cy is unsubstituted benzofuranyl. In certain embodiments, Cy is substituted benzoisofuranyl. In certain embodiments, Cy is unsubstituted benzoisofuranyl. In certain embodiments, Cy is substituted benzimidazolyl. In certain embodiments, Cy is unsubstituted benzimidazolyl. In certain embodiments, Cy is substituted benzoxazolyl. In certain embodiments, Cy is unsubstituted benzoxazolyl. In certain embodiments, Cy is substituted benzisoxazolyl. In certain embodiments, Cy is unsubstituted benzisoxazolyl. In certain embodiments, Cy is substituted benzothiazolyl. In certain embodiments, Cy is unsubstituted benzothiazolyl. In certain embodiments, Cy is substituted benzisothiazolyl. In certain embodiments, Cy is unsubstituted benzisothiazolyl. In certain embodiments, Cy is substituted

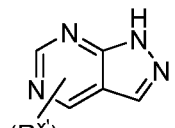


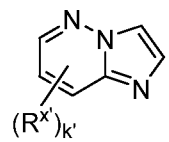




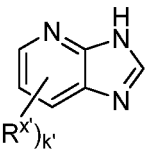


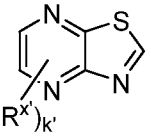


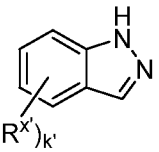


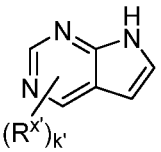


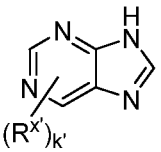
benzotriazolyl. In certain embodiments, Cy is unsubstituted benzotriazolyl. In certain embodiments, Cy is substituted benzoxadiazolyl. In certain embodiments, Cy is unsubstituted benzoxadiazolyl. In certain embodiments, Cy is substituted quinolinyl. In certain embodiments, Cy is unsubstituted quinolinyl. In certain embodiments, Cy is substituted isoquinolinyl. In certain embodiments, Cy is unsubstituted isoquinolinyl. In certain embodiments, Cy is substituted cinnolinyl. In certain embodiments, Cy is unsubstituted cinnolinyl. In certain embodiments, Cy is substituted quinoxalinyl. In certain embodiments, Cy is unsubstituted quinoxalinyl. In certain embodiments, Cy is substituted phthalazinyl. In certain embodiments, Cy is unsubstituted phthalazinyl. In certain embodiments, Cy is substituted quinazolinyl. In certain embodiments, Cy is unsubstituted quinazolinyl. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position.

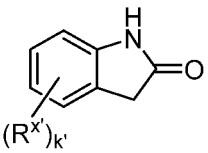
In certain embodiments, Cy is  wherein X′ may link to any freely valent position.

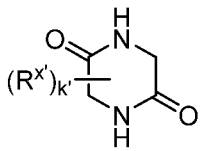
In certain embodiments, Cy is  wherein X′ may link to any freely valent position.

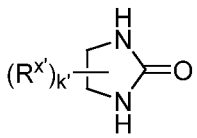
In certain embodiments, Cy is  wherein X′ may link to any freely valent

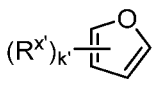
position. In certain embodiments, Cy is  wherein X′ may link to any freely valent

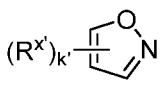
position. In certain embodiments, Cy is  wherein X′ may link to any freely valent

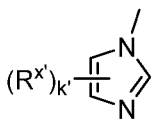
position. In certain embodiments, Cy is  wherein X′ may link to any freely

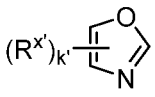
valent position. In certain embodiments, Cy is  wherein X′ may link to any

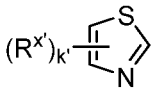
freely valent position. In certain embodiments, Cy is  wherein X′ may link to

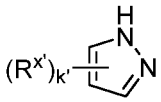
any freely valent position. In certain embodiments, Cy is  wherein X′ may link to

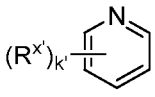
any freely valent position. In certain embodiments, Cy is  wherein X′ may link to

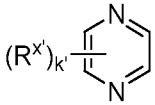
any freely valent position. In certain embodiments, Cy is  wherein X′ may link to

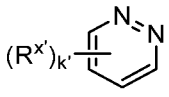


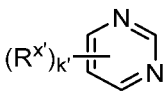


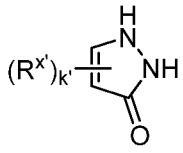


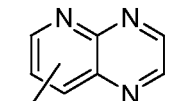


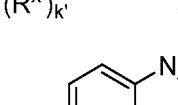


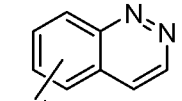


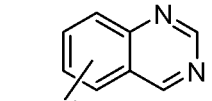






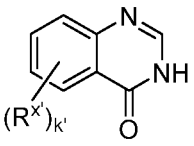
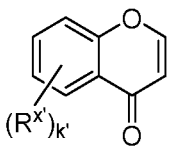
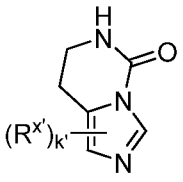
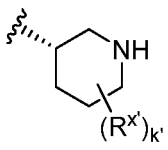
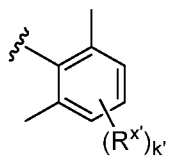




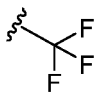
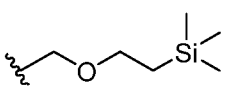
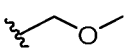


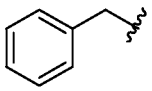
any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments, Cy is

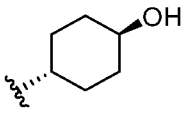
wherein X′ may link to any freely valent position. In certain embodiments, Cy is wherein X′ may link to any freely valent position. In certain embodiments,

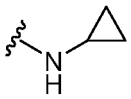
Cy is  wherein X′ may link to any freely valent position. In certain embodiments, Cy is  wherein X′ may link to any freely valent position. In certain embodiments, Cy is  wherein X′ may link to any freely valent position. In certain embodiments, Cy is  wherein X′ may link to any freely valent position. In certain embodiments, Cy is  wherein X′ may link to any freely valent position.

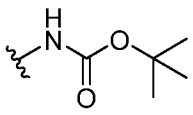
[00190] In compounds of Formula (**II**) or (**V**), Cy may be substituted with one or more $R^{X'}$ groups. In certain embodiments, at least one $R^{X'}$ is H. In certain embodiments, at least two $R^{X'}$ groups are H. In certain embodiments, at least three $R^{X'}$ groups are H. In certain embodiments, at least four $R^{X'}$ groups are H. In certain embodiments, at least one $R^{X'}$ is halogen. In certain embodiments, at least one $R^{X'}$ is F. In certain embodiments, at least one $R^{X'}$ is Cl. In certain embodiments, at least one $R^{X'}$ is Br. In certain embodiments, at least one $R^{X'}$ is I (iodine). In certain embodiments, at least one $R^{X'}$ is substituted acyl. In certain embodiments, at least one $R^{X'}$ is $-C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-C(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{X'}$ is –C(=O)NHMe. In certain embodiments, at least one $R^{X'}$ is $-C(=O)NH_2$. In certain embodiments, at least one $R^{X'}$ is unsubstituted acyl. In certain embodiments, at least one $R^{X'}$ is acetyl. In certain embodiments, at least one $R^{X'}$ is substituted alkyl. In certain embodiments, at least one $R^{X'}$ is substituted methyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted alkyl. In certain embodiments, at least one $R^{X'}$ is C_{1-6} alkyl. In certain embodiments, at least one $R^{X'}$ is methyl. In certain embodiments, at least one $R^{X'}$ is ethyl. In certain embodiments, at least one $R^{X'}$ is propyl. In certain

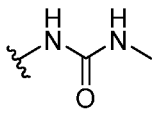
embodiments, at least one $R^{X'}$ is butyl. In certain embodiments, at least one $R^{X'}$ is substituted alkenyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted alkenyl. In certain embodiments, at least one $R^{X'}$ is substituted alkynyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted alkynyl. In certain embodiments, at least one $R^{X'}$ is substituted carbocyclyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted carbocyclyl. In certain embodiments, at least one $R^{X'}$ is substituted heterocyclyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted heterocyclyl. In certain embodiments, at least one $R^{X'}$ is substituted aryl. In certain embodiments, at least one $R^{X'}$ is unsubstituted aryl. In certain embodiments, at least one $R^{X'}$ is substituted phenyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted phenyl. In certain embodiments, at least one $R^{X'}$ is substituted heteroaryl. In certain embodiments, at least one $R^{X'}$ is unsubstituted heteroaryl. In certain embodiments, at least one $R^{X'}$ is substituted pyridyl. In certain embodiments, at least one $R^{X'}$ is unsubstituted pyridyl. In certain embodiments, at least one $R^{X'}$ is $-OR^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-O(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{X'}$ is –OMe. In certain embodiments, at least one $R^{X'}$ is –OH. In certain embodiments, at least one $R^{X'}$ is $-N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-NH_2$. In certain embodiments, at least one $R^{X'}$ is $-SR^{A1'}$. In certain embodiments, at least one $R^{X'}$ is –SH. In certain embodiments, at least one $R^{X'}$ is $-NR^{A1'}C(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-NHC(=O)N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-NHC(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-NHC(=O)NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{X'}$ is –NHC(=O)NHMe. In certain embodiments, at least one $R^{X'}$ is $-NHC(=O)NH_2$. In certain embodiments, at least one $R^{X'}$ is $-NR^{A1'}C(=O)NHR^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-NR^{A1'}C(=O)NH_2$. In certain embodiments, at least one $R^{X'}$ is $-NR^{A1'}S(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-NHS(=O)_2R^{A1'}$. In certain embodiments, at least one $R^{X'}$ is $-NHS(=O)_2(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{X'}$ is $-NHS(=O)_2$Me. In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2N(R^{A1'})_2$. In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2N(C_{1-6}$ alkyl)$_2$. In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2NH(C_{1-6}$ alkyl). In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2NH(t$-Bu). In certain embodiments, at least one $R^{X'}$ is $-S(=O)_2NH_2$. In certain embodiments, at least one $R^{X'}$ is  . In certain embodiments, at least one $R^{X'}$ is  . In certain embodiments, at least one $R^{X'}$ is  . In

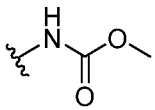


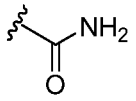


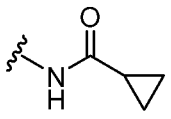


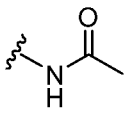


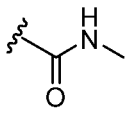


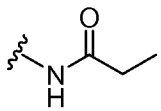


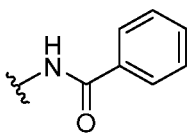


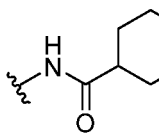


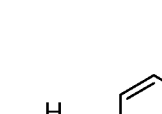


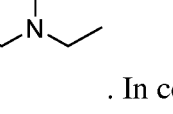


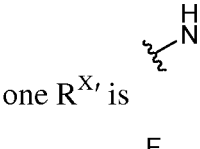


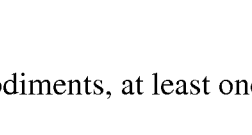


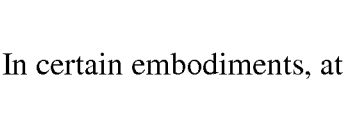




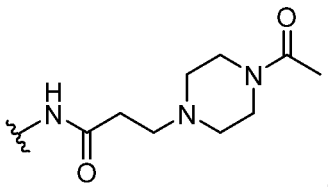




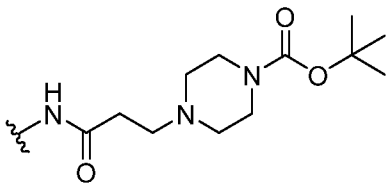




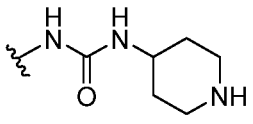
certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is . In certain embodiments, at least one $R^{X'}$ is



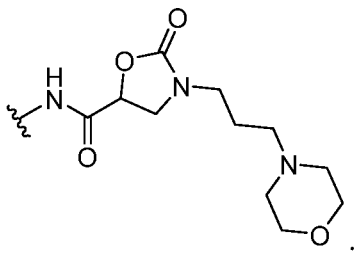
. In certain embodiments, at least one $R^{X'}$ is



. In certain embodiments, at least one $R^{X'}$ is

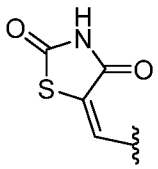


. In certain embodiments, at least one $R^{X'}$ is

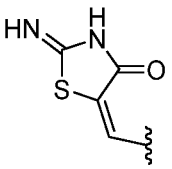


.

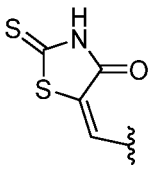
In certain embodiments, at least one $R^{X'}$ is



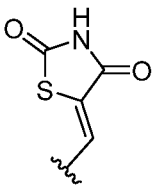
. In certain embodiments, at least one $R^{X'}$ is



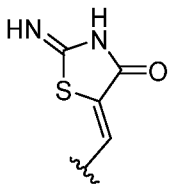
. In certain embodiments, at least one $R^{X'}$ is



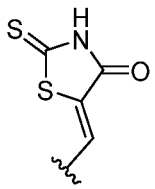
. In certain embodiments, at least one $R^{X'}$ is



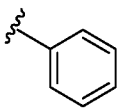
. In certain embodiments, at least one $R^{X'}$ is



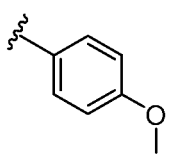
. In certain embodiments, at least one $R^{X'}$ is



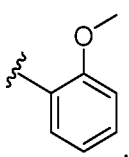
. In certain embodiments, at least one $R^{X'}$ is



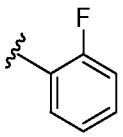
. In certain embodiments, at least one $R^{X'}$ is

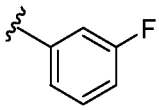


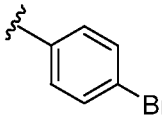
. In certain embodiments, at least one $R^{X'}$ is

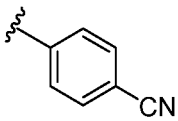


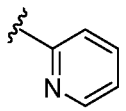
. In certain embodiments,

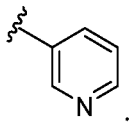


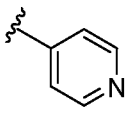


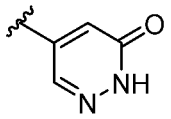


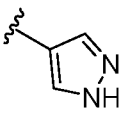


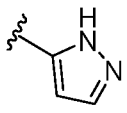


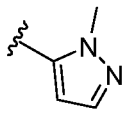


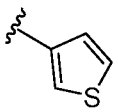


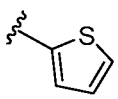


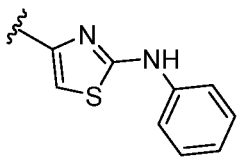


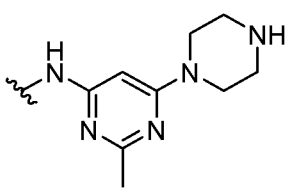


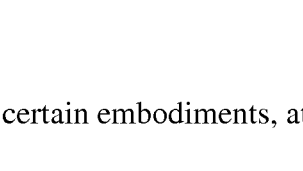


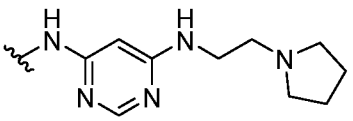












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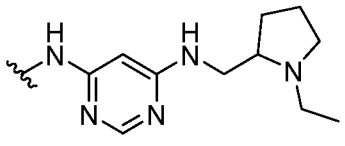

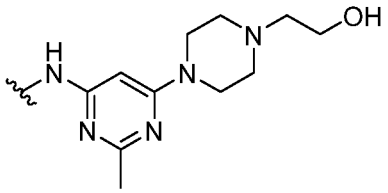

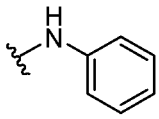

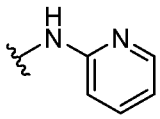

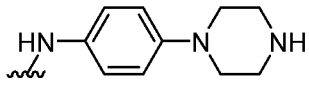

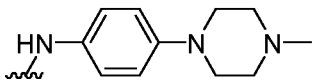

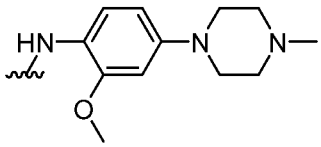

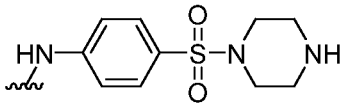

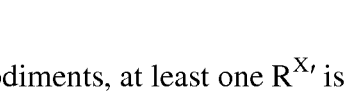

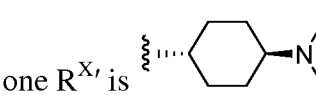

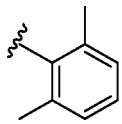

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[00191] In certain embodiment, a compound of the invention is a compound of Formula (**A**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiment, a compound of the invention is a compound of Formula (**A**), or a pharmaceutically acceptable salt thereof. In certain embodiment, a compound of the invention is a compound of Formula (**I-11**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiment, a compound of the invention is a compound of Formula (**I-11**), or a

pharmaceutically acceptable salt thereof. In certain embodiment, a compound of the invention 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 embodiment, a compound of the invention is a compound of Formula (**II**), or a pharmaceutically acceptable salt thereof. In certain embodiment, a compound of the invention is a compound of Formula (**V**), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof. In certain embodiment, a compound of the invention is a compound of Formula (**V**), or a pharmaceutically acceptable salt thereof.

[00192] In certain embodiments, compounds of the present invention include those which:

- 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 hematopoietic progenitor kinase 1 (HPK1, also known as mitogen-activated protein kinase kinase kinase kinase 1 or MAP4K1),
- 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 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.

[00193] As used herein "kinase" refers to a large class of enzymes which catalyze the transfer of the γ-phosphate from ATP to the hydroxyl group on the side chain of Ser/Thr or Tyr in proteins and peptides and are intimately involved in the control of various important cell functions, perhaps most notably: signal transduction, differentiation and proliferation. There are estimated to be about 2,000 distinct protein kinases in the human body and although each of these phosphorylates particular protein/peptide substrates, they all bind the same second substrate ATP in a highly conserved pocket. About 50% of the known oncogene products are protein tyrosine kinases PTKs and their kinase activity has been shown to lead to cell transformation.

[00194] In certain embodiments, the kinase to be inhibited is involved in the myeloid differentiation primary response gene (88) (MYD88) signaling pathway. For example, the kinase is Transforming growth factor b-activated kinase-1 (TAK1) or Hemopoietic cell

kinase (HCK). In certain embodiments, the compound of the invention inhibits TAK1, HCK, or both TAK1 and HCK.

[00195] Myeloid differentiation primary response gene (88) (MYD88) L265P is a widely expressed somatic mutation in WM patients that supports NF- NFκB signaling through stimulation of BTK, IRAK1/4, TAK1. 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 and TAK1 activation.

[00196] 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 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.

[00197] Hemopoietic cell kinase (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. USA.* **1994**, *91*(17), 8152–55). 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.

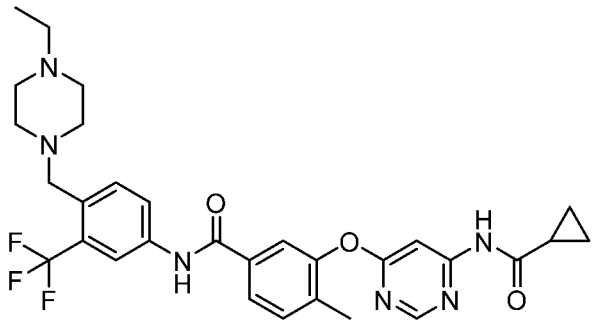
[00198] Hematopoietic progenitor kinase 1 (HPK1) is a hematopoietic cell-restricted member of the Ste20 serine/threonine kinase super family. HPK1 is also known as mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1). HPK1 is a tissue-specific upstream activator of the MEKK/JNK/SAPK signaling pathway. HPK1 diminishes T cell receptor (TCR) signaling activity and T cell proliferation by phosphorylating the adaptor protein SLP-76. Cytosolic HPK1 is recruited to the TCR complex, and its kinase activity is induced upon the engagement of the TCR. Overexpression of HPK1 suppresses TCR-induced activation of AP-1-dependent gene transcription in a kinase-dependent manner, suggesting that the kinase activity of HPK1 is required to inhibit the Erk MAPK pathway. This blockage of the Erk MAPK pathway is thought to be the inhibitory mechanism that negatively regulates TCR-induced IL-2 gene transcription (*Immunol. Res.* **2012**, *54*(1-3), 262-65). In certain embodiments, the compounds of the invention, such as the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**) (*e.g.*, compounds of Formula (**A-1**)-(**A-18**)), inhibit HPK1.

[00199] In certain embodiments, the compounds of the invention are selective inhibitors of TAK1, HCK, or HPK1. The term "selective inhibitor" as used herein is understood to mean that in contrast to many kinase inhibitors of the prior art, the compounds do not act on a variety of kinases but act specifically on TAK1, HCK, or HPK1. In certain embodiments, the compounds of the invention inhibit one or more kinases in additon to TAK1, HCK, or HPK1 such as BTK or the SRC family of kinases. In certain embodiments of the invention, the specificity of the inhibitors is given by the IC_{50} value. In some embodiments, the IC_{50} value for a selective inhibitor is < 100 μM for TAK1, HCK, or HPK1, but >100 μM for other kinases.

[00200] The IC_{50} value is defined as the concentration of inhibitor required to inhibit 50% of the kinase activity. In certain embodiments, the compounds of the invention may exhibit IC_{50} values < 100 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 50 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 40 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 30 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 20 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 10 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 7.5 μM. In certain embodiments, the compounds exhibit IC_{50} values < 5 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 2.5 μM. In certain embodiments, the compounds exhibit IC_{50} values < 1 μM. In certain embodiments, the compounds exhibit IC_{50} values < 0.75 μM. In certain embodiments, the compounds exhibit IC_{50} values < 0.5 μM. In certain embodiments, the compounds exhibit IC_{50} values < 0.25 μM.

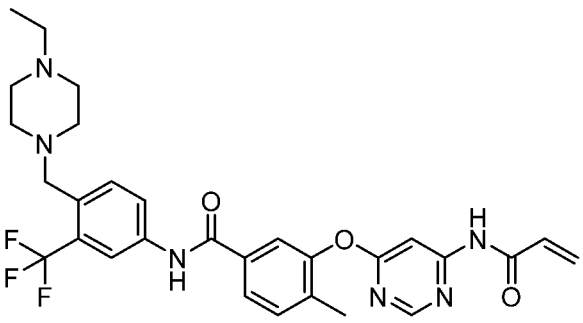
In certain embodiments, the compounds exhibit IC_{50} values < 0.1 μM. In certain other embodiments, the compounds exhibit IC_{50} values < 75 nM. In certain other embodiments, the compounds exhibit IC_{50} values < 50 nM. In certain other embodiments, the compounds exhibit IC_{50} values < 25 nM. In certain other embodiments, the compounds exhibit IC_{50} values < 10 nM. In other embodiments, the compounds exhibit IC_{50} values < 7.5 nM. In other embodiments, the compounds exhibit IC_{50} values < 5 nM.

[00201] In certain embodiments, the compounds of the invention (*e.g.*, the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**)) inhibit HCK selectively. In certain embodiments, the compounds of the invention (*e.g.*, the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**)) inhibit TAK1 selectively. A non-limiting example of a selective TAK1 inhibitor is:



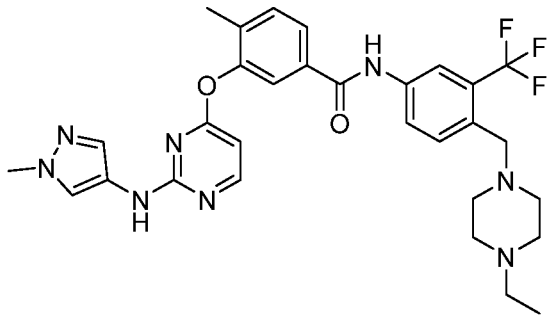
(**A-3**).

[00202] In certain embodiments, the compounds of the invention (*e.g.*, the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**)) inhibit both TAK1 and HCK. A non-limiting example of a dual TAK1/HCK inhibitor is:



(**A-17**).

[00203] In certain embodiments, the compounds of the invention (*e.g.*, the compounds of Formula (**A**), (**I-11**), (**II**), or (**V**)) inhibit HPK1 selectively. A non-limiting example of a selective HPK1 inhibitor is:



(**A-14**).

[00204] Also, provided are methods to treat B cell neoplasms using compounds of the ivention in combination with inhibitors of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase 4 (IRAK4), bone marrow on X chromosome kinase (BMX), phosphoinositide 3-kinase (PI3K), transforming growth factor b-activated kinase-1 (TAK1), and/or a Src family kinase. In certain embodiments, one or more compounds of the invention are used in combination with an inhibitor of the phosphoinositide 3-kinase delta isoform (PI3Kδ). In certain embodiments, combinations of 2, 3, 4, 5, 6,7, 8, 9, 10, or more of the agents described herein are used for treating WM. In certain embodiments, the agents described herein are used in combination with inhibitors of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase 4 (IRAK4), bone marrow on X chromosome kinase (BMX), phosphoinositide 3-kinase (PI3K), transforming growth factor b-activated kinase-1 (TAK1), and/or a Src family kinase.

[00205] Bruton's tyrosine kinase (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;

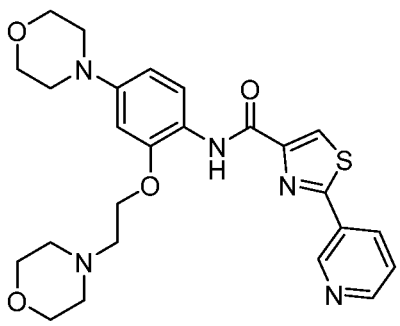
Iwaki *et al.*, *J. Biol. Chem.*, **2005**, *280*(48), 40261-40270; Vassilev *et al.*, *J. Biol. Chem.*, **1999**, *274*(3),1646-1656; and Quek *et al.*, *Curr. Biol.*, **1998**, *8*(20),1137-1140. Activated Btk interacts with MyD88 and TRIF, promoting the activation of MyD88-dependent and TRIF-dependent pathways (*Nature Immunology*, **2011**, *12*, 416–424).

[00206] BTK inhibitors are well-known in the art, and include, for example, ibrutinib and benzonaphthyridinones (see U.S. provisional patent application 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.

[00207] IRAK1 and 4 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.

[00208] IRAK1 and IRAK4 inhibitors are well-known in the art, and include, for example, those disclosed in WO 2003/030902, WO 2012/007375, G.M. Buckely *et al.*, *Biorg. Med. Chem. Lett.*, **2008**, *18*, 3211-3214, and G.M. Buckely *et al.*, *Biorg. Med. Chem. Lett.*, **2008**, *18*, 3656-3660, WO2013/074986, and U.S. provisional patent application, U.S.S.N. 61/727,640, filed November 16, 2012.

[00209] In certain embodiments, the IRAK4 inhibitor is of formula:



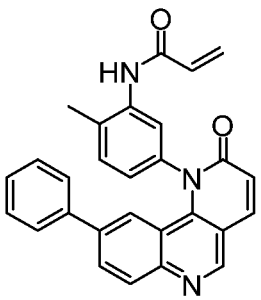
JH-IV-96-01
IRAK4 IC50 = 20nm

or an analog thereof.

"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, the contents of both of which are incorporated herein by reference. In certain embodiments, the BMX inhibitor is of formula:



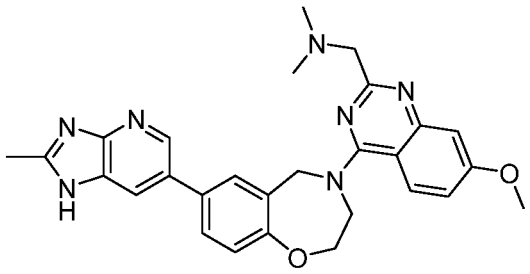
BMX IC_{50} = 16 nM

or an analog thereof.

[00210] 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 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. Of particular interest is the PI3K delta isoform, which is expressed in white blood cells and is mainly involved in the signaling, development, and survival of B cells.

[00211] PI3K inhibitors are well-known in the art, and include, for example, those disclosed in International PCT PublicationsWO 2013/088404, WO 2012/068096, and WO 2013/052699, which are incorporated herein by reference.

[00212] In certain embodiments, the PI3K inhibitor is



PI3Kα IC_{50} = 3 nM

or its analogs.

[00213] Compounds of the invention may be combined with other kinase inhibitors to treat WM or other B cell neoplasms. In certain embodiments, a compound of the invention is administered with an inhibitor of Bruton's tyrosine kinase (BTK) to treat WM or other B cell neoplasm. In certain embodiments, a compound of the invention is administered with an inhibitor of interleukin-1 receptor-associated kinase 1 (IRAK1) to treat WM or otherB cell neoplasm. In certain embodiments, a compound of the invention is administered with an inhibitor of phosphoinositide 3-kinase (PI3K) to treat WM or other B cell neoplasm. In certain embodiments, a compound of of the invention is administered with an inhibitor of the phosphoinositide 3-kinase delta isoform (PI3Kδ) to treat WM or other B cell neoplasm. In certain embodiments, a compound of of the invention is administered with two of any inhibitors of BTK, IRAK1, or PI3K to treat WM or other B cell neoplasm. In certain embodiments, a compound of the invention is administered with more than two of any inhibitors of BTK, IRAK1, or PI3K to treat WM or other B cell neoplasm.

[00214] The BTK inhibitors, the IRAK1 inhibitors, the IRAK4 inhibitors, and/or the PI3K inhibitors can be administered to the subject simultaneously or sequentially.

[00215] A "subject" or "patient" to which administration is contemplated includes, any animal. In some embodiments, a subject includes but is not limited to, humans, commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys) and experimental animals (*e.g.,* mice, rats, non-human primates). A subject in need of treatment is a subject identified as having a B cell neoplasm, *i.e.*, the subject has been diagnosed by a physician (*e.g.*, using methods well known in the art) as having a B cell neoplasm. In certain

embodiments, the subject in need of treatment is a subject suspected of having or developing a B cell neoplasm, such as a subject presenting one or more symptoms indicative of a B cell neoplasm. The term "subject in need of treatment" further includes people who once had a B cell neoplasm but whose signs and/or symptoms have been ameliorated (*i.e.,* their cancer is in remission). The one or more symptoms or clinical features of B cell neoplasms include, but are not limited to, asymptomatic localized or generalized peripheral lymphadenopathy, plasmacytic difference, bone marrow involvement, autoimmune thrombocytopenia, peripheral blood villous lymphocytes, end organ damage (hypercalcemia, renal insufficiency, bone lesions), recurrent infections, elevated creatine, hyperuricemia, and hypoalbunemia.

[00216] In certain embodiments, the subject is diagnosed as having Waldenström's macroglobulinemia (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 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. Non-limiting examples of the biological sample include bone marrow, lymph node, spleen, or blood.

[00217] The terms "administer," "administering," or "administration," as used he rein refers to implanting, absorbing, ingesting, injecting, or inhaling an inventive compound, or a pharmaceutical composition thereof.

[00218] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a B cell neoplasm. In certain embodiments, treatment may be administered after one or more signs or symptoms have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the B cell neoplasm. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[00219] An "effective amount" of compounds of the invention refers to an amount

sufficient to elicit the desired biological response, *i.e.*, treating the B cell neoplasm. As will be appreciated by those of ordinary skill in this art, the effective amount of compounds of the invention may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount includes, but is not limited to, that amount necessary to slow, reduce, inhibit, ameliorate or reverse one or more signs and/or symptoms associated with a B cell neoplasm. In the treatment of Waldenström's macroglobulinemia, this may refer to a reduction in the levels of IgM serum paraprotein, reduction in anemia, reduction in hyper-viscosity, reduction in neuropathy, reduction in coagulopathies, reduction in splenomegaly, reduction in hepatomegaly, and reduction in adenopathy.

[00220] An effective amount of a compound may vary from about 0.001 mg/kg to about 1000 mg/kg in one or more dose administrations, for one or several days (depending on the mode of administration). In certain embodiments, the effective amount varies from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, from about 1.0 mg/kg to about 100 mg/kg, and from about 10.0 mg/kg to about 150 mg/kg.

[00221] One or more additional pharmaceutical agents, such as anti-cancer agents (*e.g.*, chemotherapeutics), anti-inflammatory agents, steroids, immunosuppressants, radiation therapy, or other agents, can be used in combination with the compounds of of the invention in the treatment of a B cell neoplasm. The one or more additional pharmaceutical agents can be administered to the subject simultaneously or sequentially.

[00222] Exemplary chemotherapeutic agents include alkylating agents such as nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosuoureas, and triazenes; antimetabolites such as folic acid analogs, pyrimidine analogs, in particular fluorouracil and cytosine arabinoside, and purine analogs; natural products such as vinca alkaloids epi-podophyllotoxins, antibiotics, enzymes, and biological response modifiers; and miscellaneous products such as platinum coordination complexes, anthracenedione, substituted urea such as hydroxyurea, methyl hydrazine derivatives, and adrenocorticoid suppressant.

[00223] Exemplary chemotherapeutic agents also include anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, paclitaxel, colchicine, cytochalasin B, emetine, maytansine, amsacrine, cisplatin, carboplatin, mitomycin, altretamine, cyclophosphamide, lomustine, and carmustine.

[00224] In yet another aspect, the present invention provides pharmaceutical compositions

comprising an effective amount of a compound of of the invention, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs, and optionally a pharmaceutically acceptable excipient, for use in the treatment of a B cell neoplasm. In certain embodiments, provided by the invention are the compounds of of the invention, and pharmaceutically acceptable salts and compositions thereof, for use in the treatment of a B cell neoplasm. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is an amount useful for the treatment and/or prevention of a B cell neoplasm. In certain embodiments, the B cell neoplasm is, but is not limited to, Hodgkin's lymphomas and most non-Hodgkins lymphomas, such as, diffuse large B cell lymphoma, Follicular lymphoma, Mucosa-Associated Lymphatic Tissue lymphoma (MALT), small cell lymphocytic lymphoma (overlaps with Chronic lymphocytic leukemia), Mantle cell lymphoma (MCL), Burkitt lymphoma, Mediastinal large B cell lymphoma, Waldenström's macroglobulinemia, Nodal marginal zone B cell lymphoma (NMZL), Splenic marginal zone lymphoma (SMZL), Intravascular large B-cell lymphoma, Primary effusion lymphoma and Lymphomatoid granulomatosis. An effective amount of a compound may vary from about 0.001 mg/kg to about 1000 mg/kg in one or more dose administrations, for one or several days (depending on the mode of administration). In certain embodiments, the effective amount varies from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 0.1 mg/kg to about 500 mg/kg, from about 1.0 mg/kg to about 250 mg/kg, and from about 10.0 mg/kg to about 150 mg/kg.

[00225] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound of of the invention (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.

[00226] 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. As used herein, a "unit dose" is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage, such as, for example, one-half or one-third of such a dosage.

[00227] The pharmaceutical preparations of the present invention may include or be diluted

into a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable carrier" as used herein means one or more compatible fillers, diluents or other such substances, which are suitable for administration to a human or other mammal, such as a dog, cat, rat, mouse, or horse. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The carriers are capable of being commingled with the preparations of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy or stability. Carriers suitable for oral, subcutaneous, intravenous, intramuscular, *etc.* formulations can be found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa.

[00228] 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).

[00229] 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. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00230] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1

mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00231] In certain embodiments, the compound of the invention is administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00232] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

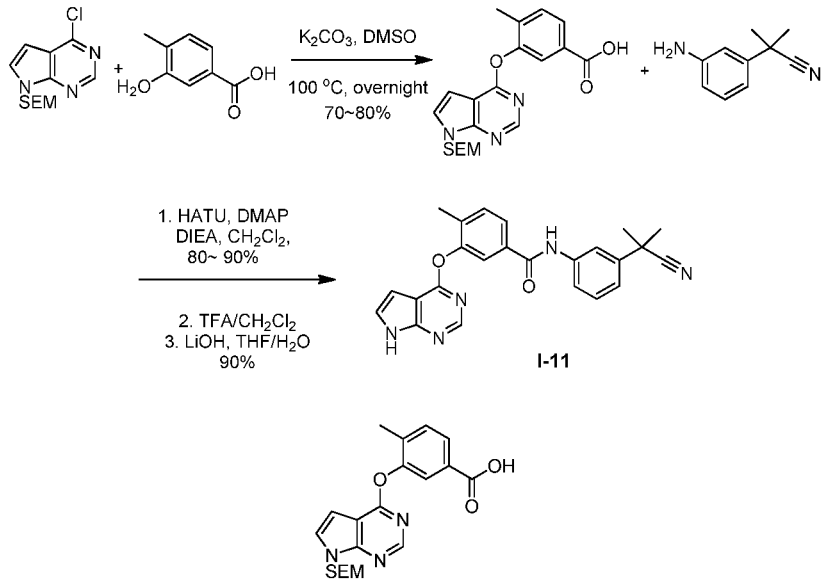
[00233] The present invention is further illustrated by the following Example, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

EXAMPLES

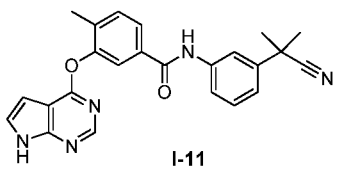
[00234] In order that the invention described herein may be more fully understood, the following examples are set forth. The synthetic and biological examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

Example 1. Preparation of the Compounds

Preparation of I-11



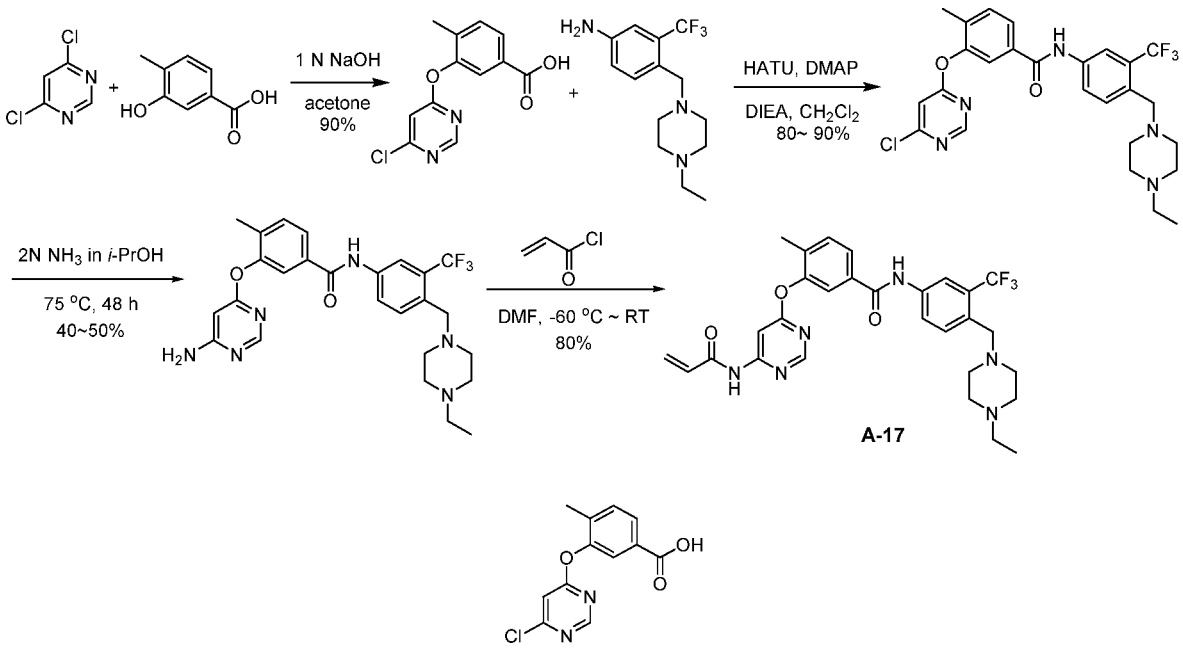
4-methyl-3-((7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)benzoic acid: 4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-d]pyrimidine (284 mg, 1.0 mmol), 3-hydroxy-4-methylbenzoic acid (152 mg, 1.0 mmol) and K_2CO_3 (414 mg, 3.0 mmol) were combined in DMSO (5 mL) and stirred overnight at 100 °C. The reaction mixture was then cooled to room temperature. The mixture was acidified with 1N HCl solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography to yield 296 mg of product as a colorless oil. MS (ESI) m/z 400 $(M+H)^+$.



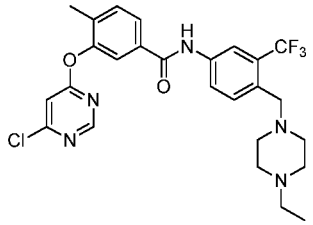
3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-N-(3-(2-cyanopropan-2-yl)phenyl)-4-methylbenzamide (**I-11**): To a solution of 4-methyl-3-((7-((2-(trimethylsilyl)ethoxy)methyl)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)benzoic acid (200 mg, 0.5 mmol), HATU (230 mg, 0.6 mmol), DMAP (73 mg, 0.6 mmol) and *i*Pr_2NEt (220 uL, 1.25 mmol) in CH_2Cl_2 (3 mL) was added 2-(3-aminophenyl)-2-methylpropanenitrile (80 mg, 0.5 mmol) and the resulting mixture was stirred at room temperature for 24 hours. The solution was filtered to remove solids, concentrated and purified with column chromatography (dichloromethane : methanol = 10:1) to afford 455 mg of product as a colorless oil. To the solution of the obtained oil in

CH_2Cl_2 (5 mL) was added TFA (0.5 mL) and the resulting mixture was stirred at room temperature for 5 hours. The solution was concentrated and dried with vacuum, then dissolved in THF (4 mL) and 1 N NaOH solution (4 mL). The reaction mixture was stirred for 24 h and extracted with ethyl acetate. The combined organic phase was washed with brine and dried with Na_2SO_4, then filtered and concentrated, and purified by reverse phase HPLC to give 185 mg (90%) of title compound as a white solid.

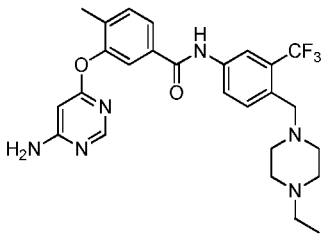
Preparation of A-17



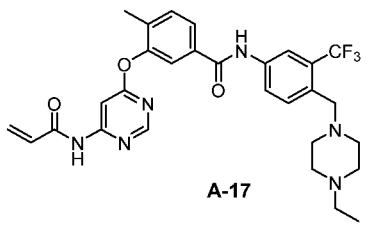
[00235] 3-((6-chloropyrimidin-4-yl)oxy)-4-methylbenzoic acid: Sodium hydroxide (2 ml of a 1N solution) was added to a solution of 4,6-dichloropyrimidine (150 mg, 1.0 mmol) and 3-hydroxy-4-methylbenzoic acid (152 mg, 1.0 mmol) in acetone (2 mL) and the reaction mixture as stirred at room temperature for 1 hour at which point LC-MS analysis indicated complete consumption of starting material. The reaction mixture was extracted with ethyl acetate. The combined organic phase was washed with brine and dried with Na_2SO_4, then filtered and concentrated, and purified by column chromatography to yield 250 mg of product as a white solid. MS (ESI) m/z 265 $(M+H)^+$.



[00236] 3-((6-chloropyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide: To a solution of 3-((6-chloropyrimidin-4-yl)oxy)-4-methylbenzoic acid (210 mg, 0.8 mmol), HATU (365 mg, 0.96 mmol), DMAP (117 mg, 0.96 mmol) and *i*Pr_2NEt (350uL, 2.0 mmol) in CH_2Cl_2 (4 mL) was added 4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)aniline (230 mg, 0.8 mmol) and the resulting mixture was stirred at room temperature for 24 hours. The solution was filtered to remove solids, concentrated and purified column chromatography to yield 360 mg (84%) of product as a pale yellow oil. MS (ESI) m/z 534 $(M+H)^+$.



[00237] 3-((6-aminopyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide: 10 mL of a 2N solution of NH_3 in *i*-PrOH was added to 3-((6-chloropyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide (270 mg, 0.5 mmol) and the reaction mixture was stirred for 48 hours at 75 °C then cooled to room temperature and concentrated. The crude product was purified by column chromatography to yield 120 mg of product as a colorless oil. MS (ESI) m/z 515 $(M+H)^+$.



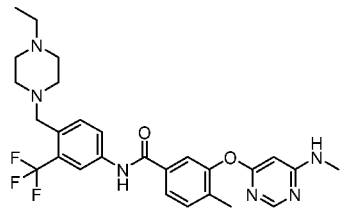
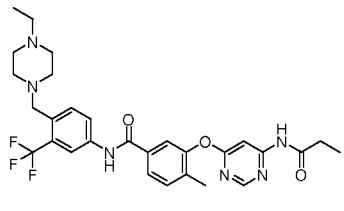
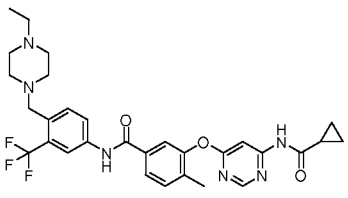
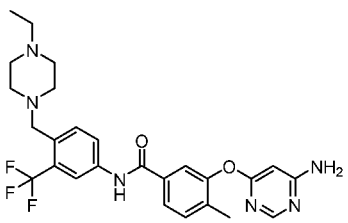
A-17

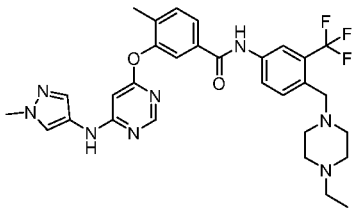
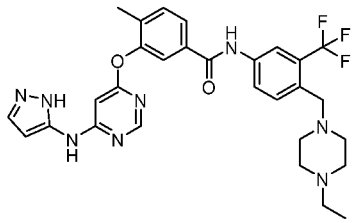
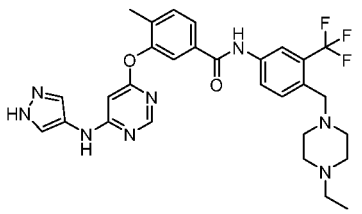
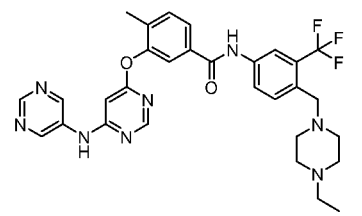
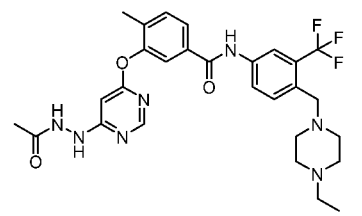
[00238] 3-((6-acrylamidopyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide (**A-17**): To a solution of 3-((6-aminopyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide (51 mg, 0.1 mmol) in DMF cooled in a dry ice/SOLVENT bath was added

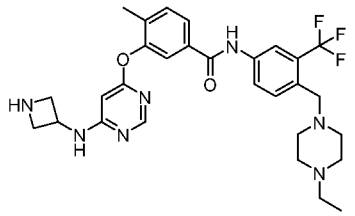
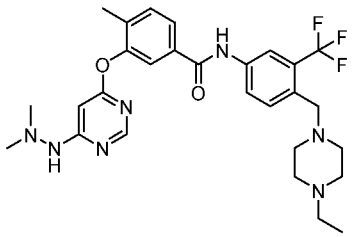
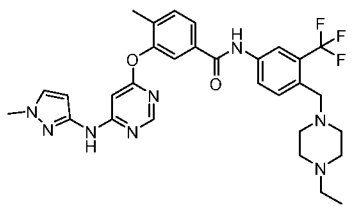
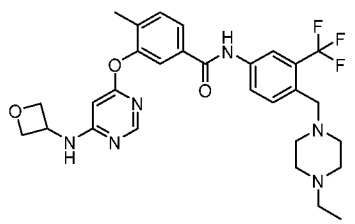
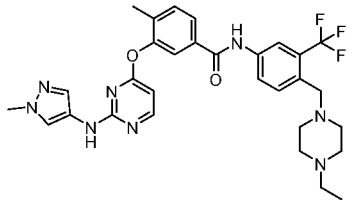
acryloyl chloride (8.9 uL, 0.11 mmol). The cooling bath was removed allowing the mixture to warm to room temperature and continue stirring for an half hour. The solution was then diluted in DMSO and purified by reverse phase HPLC to afford 45 mg (80%) of **A-17** as a white solid.

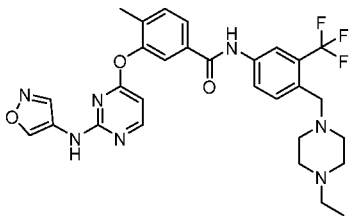
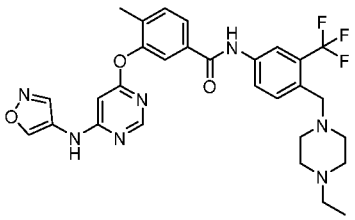
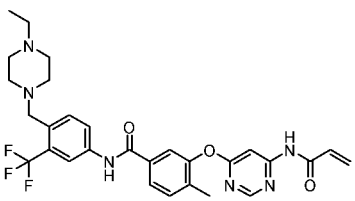
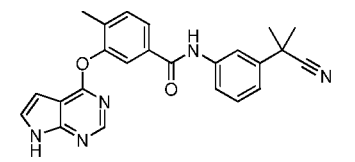
[00239] Compounds (**A-1**)-(**A-16**) and (**A-18**) were prepared similarly to **A-17**.

[00240] Characterization data for all final compounds is in the table below.

ID #	Structure	Name	^{1}H NMR and or MS (m/z)
A-1		N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-(methylamino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (400 MHz, DMSO) δ 10.39 (s,1H), 8.11 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.33 (bs, 1H), 3.60 (s, 2H), 3.38 (m, 2H), 2.97-2.79 (m, 6H), 2.71 (bs, 3H), 2.37-2.22 (m, 2H), 2.09 (s, 3H), 1.12 (t, *J* = 6.8 Hz, 3H). MS (ESI) *m/z* 529 $(M+H)^+$.
A-2		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-propionamidopyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.89 (s, 1H), 10.42 (s, 1H), 9.36 (br, 1H), 8.42 (s, 1H), 8.13 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.71 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.57 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 3.61 (s, 2H), 3.38 (m, 2H), 3.07 (m, 2H), 2.92 (m, 2H), 2.85 (m, 2H), 2.37 (q, *J* = 7.2 Hz, 2H), 2.32 (m, 2H), 2.10 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 571 $(M+H)^+$.
A-3		3-((6-(cyclopropanecarboxamido)pyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, DMSO) δ 11.25 (s, 1H), 10.36 (s, 1H), 8.43 (s, 1H), 8.11 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.70 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 3.49 (s, 2H), 2.32 (m, 8H), 2.24 (m, 2H), 2.09 (s, 3H), 1.97 (m, 1H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.79 (m, 4H). MS (ESI) *m/z* 583 $(M+H)^+$.
A-4		3-((6-aminopyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 8.06 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.43 (d, *J* = 7.2 Hz, 1H), 5.78 (s, 1H), 3.70 (s, 2H), 3.47 (m, 2H), 3.15 (q, *J* = 7.2 Hz, 2H), 3.01 (m, 4H), 2.42 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 515 $(M+H)^+$.

ID #	Structure	Name	^{1}H NMR and or MS (m/z)
A-5		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-((1-methyl-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, DMSO) δ 10.36 (s, 1H), 9.37 (br, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.84 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.36 (s, 1H), 5.94 (s ,1H), 3.74 (s, 3H), 3.50 (s, 2H), 2.18-2.42 (m, 10H), 2.12 (s, 3H), 0.92 (m, 3H). MS (ESI) *m/z* 595 $(M+H)^+$.
A-6		3-((6-((1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.45 (s, 1H), 9.92 (s, 1H), 9.33 (br, 1H), 8.24 (s, 1H), 8.18 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.74 (s, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 3.66 (s, 2H), 3.44 (m, 2H), 3.12 (m, 2H), 2.97 (m, 2H), 2.91 (m, 2H), 2.37 (m, 2H), 2.17 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 581 $(M+H)^+$.
A-7		3-((6-((1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, DMSO) δ 12.63 (br, 1H), 10.44 (s, 1H), 9.42 (br, 1H), 8.26 (br, 1H), 8.19 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.90 (br, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.53 (br, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 1H), 3.60 (s ,2H), 2.25-2.86 (m, 10H), 2.19 (s, 3H), 1.05 (m, 3H). MS (ESI) *m/z* 581 $(M+H)^+$.
A-8		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-(pyrimidin-5-ylamino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.49 (s, 1H), 10.02 (s, 1H), 9.44 (br, 1H), 9.08 (s, 2H), 8.82 (s, 1H), 8.42 (s, 1H), 8.19 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 6.27 (s, 1H), 3.66 (s, 2H), 3.44 (m, 2H), 3.13 (m, 2H), 2.98 (m, 2H), 2.91 (m, 2H), 2.38 (m, 2H), 2.20 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 593 $(M+H)^+$.
A-9		3-((6-(2-acetylhydrazinyl)pyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, DMSO) δ 10.43 (s, 1H), 9.88 (s, 1H), 9.20 (s, 1H), 8.19 (s, 1H), 8.17 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 5.99 (s, 1H), 3.56 (s ,2H), 3.32 (m, 4H), 2.29-2.48 (m, 4H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.17 (s, 3H), 1.92 (s, 3H), 0.97 (*J* = 7.2 Hz, 3H). MS (ESI) *m/z* 572 $(M+H)^+$.

ID #	Structure	Name	^{1}H NMR and or MS (m/z)
A-10		3-((6-(azetidin-3-ylamino)pyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.56 (s, 1H), 10.05 (s, 1H), 9.47 (br, 1H), 8.76 (s, 1H), 8.20 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 4.60 (m, 1H), 4.38 (m, 2H), 3.68 (s, 2H), 3.57 (m, 2H), 3.46 (m, 2H), 3.12 (m, 2H), 2.98 (m, 2H), 2.92 (m, 2H), 2.39 (m, 2H), 2.21 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 570 $(M+H)^+$.
A-11		3-((6-(2,2-dimethylhydrazinyl)pyrimidin-4-yl)oxy)-N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.58 (s, 1H), 9.48 (br, 1H), 8.95 (s, 1H), 8.20 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.79 (s, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 6.84 (br, 2H), 3.71 (s, 6H), 3.68 (s, 2H), 3.46 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.92 (m, 2H), 2.39 (m, 2H), 2.21 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 558 $(M+H)^+$.
A-12		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-((1-methyl-1*H*-pyrazol-3-yl)amino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.47 (s, 1H), 9.94 (s, 1H), 9.36 (br, 1H), 8.26 (s, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.58 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 6.16 (br, 1H), 3.75 (s, 3H), 3.68 (s, 2H), 3.45 (m, 2H), 3.14 (m, 2H), 2.99 (m, 2H), 2.94 (m, 2H), 2.37 (m, 2H), 2.19 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 595 $(M+H)^+$.
A-13		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((6-(oxetan-3-ylamino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.46 (s, 1H), 9.32 (br, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 8.15 (br, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.03 (d, *J* = 6.6 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.72 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 5.88 (br, 1H), 4.15 (m, 2H), 3.70 (m, 2H), 3.68 (s, 2H), 3.46 (m, 2H), 3.14 (m, 2H), 2.99 (m, 2H), 2.93 (m, 2H), 2.38 (m, 2H), 2.17 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 571 $(M+H)^+$.
A-14		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methyl-3-((2-((1-methyl-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)benzamide	^{1}H NMR (600 MHz, DMSO) δ 10.45 (s, 1H), 9.60 (br, 1H), 8.33 (s, 1H), 8.17 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.98 (m, 1H), 7.88 (m, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.61 (m, 1H), 7.05 (m, 1H), 6.73 (m, 1H), 6.46 (m ,1H), 3.55 (s, 3H), 3.49 (br, 2H), 2.20-2.58 (m, 10H), 2.18 (s, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 595 $(M+H)^+$.

ID #	Structure	Name	^{1}H NMR and or MS (m/z)
A-15		*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-((2-(isoxazol-4-ylamino)pyrimidin-4-yl)oxy)-4-methylbenzamide	^{1}H NMR (600 MHz, TFA salt, DMSO) δ 10.51 (s, 1H), 9.90 (m, 1H), 9.31 (br, 1H), 8.44 (d, *J* = 5.4 Hz, 1H), 8.32 (m, 1H), 8.20 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.97 (m, 1H), 7.87 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.61 (s, 1H), 6.62 (s, 1H), 3.69 (s, 2H), 3.46 (m, 2H), 3.15 (m, 2H), 2.99 (m, 2H), 2.94 (m, 2H), 2.39 (m, 2H), 2.19 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 582 $(M+H)^+$.
A-16		N-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-((6-(isoxazol-4-ylamino)pyrimidin-4-yl)oxy)-4-methylbenzamide	MS (ESI) m/z 582 (M+H)+.
A-17		3-((6-acrylamidopyrimidin-4-yl)oxy)-*N*-(4-((4-ethylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-4-methylbenzamide	^{1}H NMR (600 MHz, DMSO) δ 11.16 (s, 1H), 10.37 (s, 1H), 8.46 (s, 1H), 8.11 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 6.54 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.30 (d, *J* = 16.8 Hz, 1H), 5.81 (d, *J* = 10.8 Hz, 1H), 3.49 (s, 2H), 2.32 (m, 8H), 2.23 (q, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 569 $(M+H)^+$.
I-11		3-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)-N-(3-(2-cyanopropan-2-yl)phenyl)-4-methylbenzamide	^{1}H NMR (400 MHz, DMSO) δ 10.23 (s,1H), 8.22 (s, 1H), 7.86 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.0, 1H), 7.43 (d, *J* = 3.2 Hz, 1H), 7.33 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 2.10 (s, 3H), 1.61 (s, 6H). MS (ESI) *m/z* 412 $(M+H)^+$.

Example 2. Biological assays of the Compounds

In vitro activity assays

[00241] The *in vitro* activity of the compounds described herein in inhibiting TAK1, HCK and other kinases were obtained using an Invitrogen Select Screening assay as known in the art. The IC50 values determined from this assay are shown below.

Cell proliferation analysis

[00242] CellTiter-Glo® Luminescent cell viability assay (Promega) was used to assess cell survival following treatment with the compounds described. Cells were seeded into 384 well plates with the EL406 Combination Washer Dispenser (BioTek Instruments, Inc.) and the

compounds were injected into the cells culture media with the JANUS Automated Workstation (PerkinElmer Inc.). Cells were treated with a series diluted inhibitors (20~0.04 μM) for 72 hours at 37° C. Luminescent measurement is performed using the 2104 Envision® Multilabel Reader (PerkinElmer Inc.).

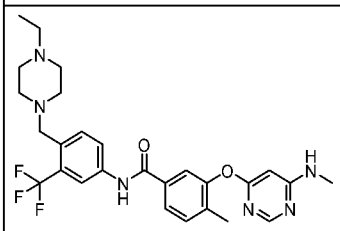
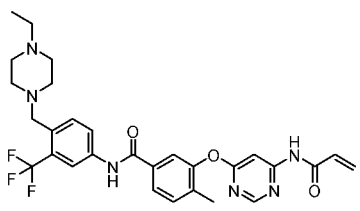
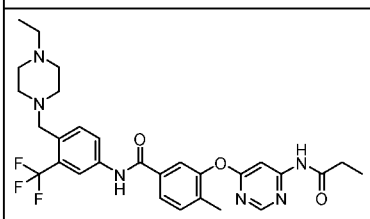
Apoptosis analysis for primary patient bone marrow tumor cells

[00243] WM cells were treated with and without the compounds described herein. Cells were incubated at 37° C with 0.01~4 uM of the compounds described herein. Apoptosis analysis was performed using Annexin V/Propidium iodide staining with the Apoptosis Detection Kit I (BD Pharmingen). 1×106/well cells were treated in 24 well plates for ~ 24 hours with inhibitors or corresponding controls. A minimum of 10,000 events were acquired using a BD™ FACSCanto II flow cytometer and analyzed with BD FACS DIVA Software.

Results

[00244] A number of compounds described herein show inhibitory activity against TAK1, HCK, BTK and other kinases. Shown in Table 1 and 1a are exemplary *in vitro* IC_{50} data of these compounds. Table 2 and 2a shows the *in vitro* EC_{50} values of these compounds.

Table 1.

Structure	Compound ID	BTK IC_{50} (nM)	HCK IC_{50} (nM) Inv	TAK1 IC_{50} (nM)	GCK IC_{50} (nM)
	(A-1)	–	275	364	31
	(A-17)	3380	28	45	17
	(A-2)	–	253	100	28

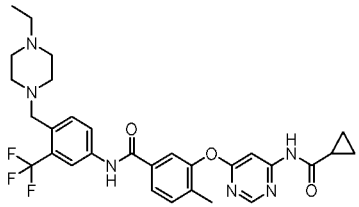
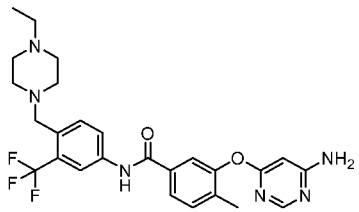
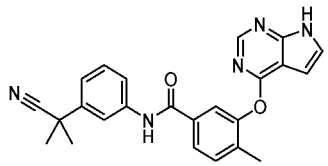
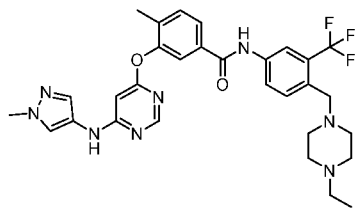
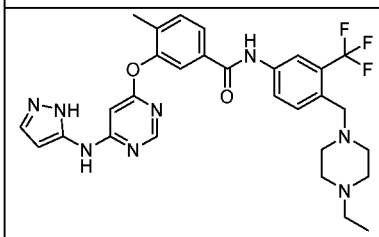
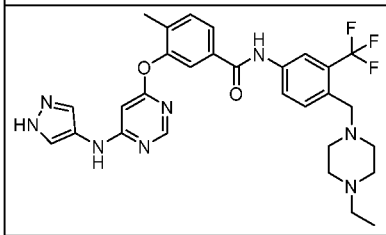
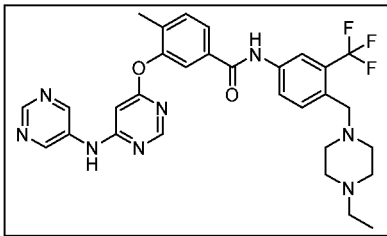
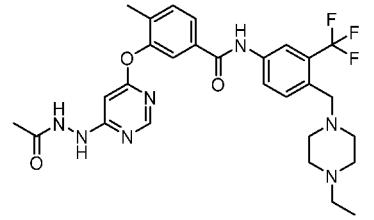
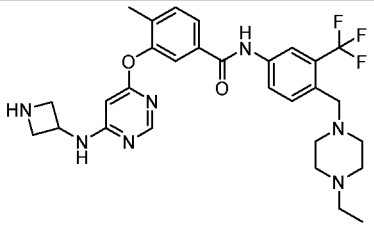
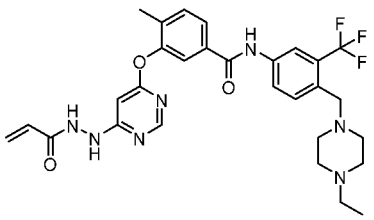
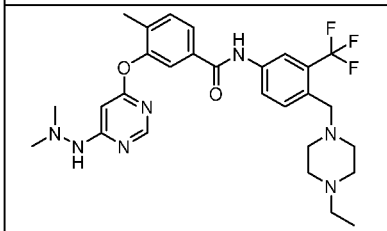
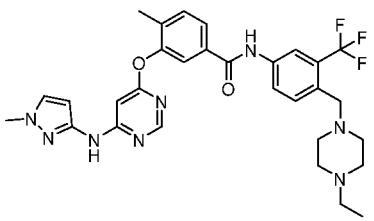
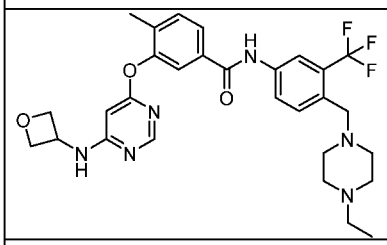
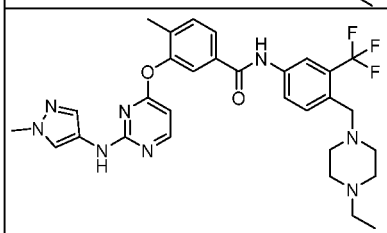
Structure	Compound ID	BTK IC_{50} (nM)	HCK IC_{50} (nM) Inv	TAK1 IC_{50} (nM)	GCK IC_{50} (nM)
	(A-3)	–	185	92	–
	(A-4)	–	382	591	–
	(I-11)	–	–	–	–

Table 1a.

Structure	Cpd. ID	BTK IC_{50} (nM)	HCK IC_{50} (nM) Inv	TAK1 IC_{50} (nM)
	(A-5)	> 10000	61.8	100
	(A-6)	–	38.4	63.5
	(A-7)	–	33.8	71.7

	**(A-8)**	–	889	487
	**(A-9)**	–	> 10000	7310
	**(A-10)**	–	> 10000	> 10000
	**(A-18)**	–	6980	1750
	**(A-11)**	–	> 10000	> 10000
	**(A-12)**	–	18	76.2
	**(A-13)**	–	392	400
	**(A-14)**	–	27.4	53.8

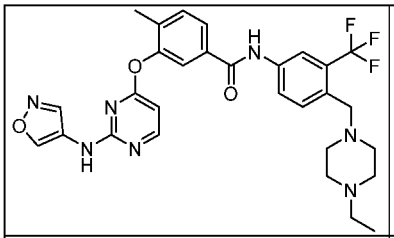
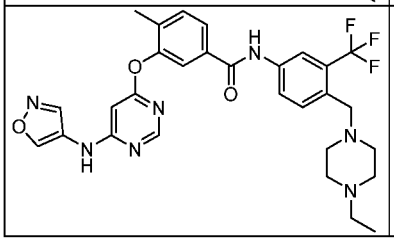
	(A-15)	–	116	136
	(A-16)	–	–	–

Table 2.

Cpd. ID	BCWM.1 EC_{50} (nM)	MWCL-1 EC_{50} (nM)	RPCIWM-1 EC_{50} (nM)	OCI-Ly3 EC_{50} (nM)	Ramos EC_{50} (nM)	OCI-Ly19 EC_{50} (nM)	Mec1 EC_{50} (nM)
(A-1)	1720	3990	–	11500	9480	4980	–
(A-2)	42	1350	–	2960	5340	1750	–
(A-3)	50	910	–	480	2680	600	–
(A-4)	3010	1150	–	31900	21100	9430	14300
(A-17)	8	202	–	247	389	188	–

Table 2a.

Cpd. ID	BCWM.1 EC_{50} (nM)	MWCL-1 EC_{50} (nM)	TMD8 EC_{50} (nM)	OCI-Ly7 EC_{50} (nM)	OCI-Ly3 EC_{50} (nM)	Ramos EC_{50} (nM)	OCI-Ly19 EC_{50} (nM)
(A-5)	51 72	73 242	132	655	4710	3000 6060	173 417
(A-6)	86	118	–	–	4770	3080	302
(A-7)	48	71	–	–	4000	3020	192
(A-8)	980	2660	–	–	> 10000	6180	1700
(A-9)	10800 6460	18700 > 20000	–	–	19600 > 20000	> 20000	> 20000

Cpd. ID	BCWM.1 EC_{50} (nM)	MWCL-1 EC_{50} (nM)	TMD8 EC_{50} (nM)	OCI-Ly7 EC_{50} (nM)	OCI-Ly3 EC_{50} (nM)	Ramos EC_{50} (nM)	OCI-Ly19 EC_{50} (nM)
(A-10)	8250 > 20000	24800 > 20000	–	–	8370 > 20000	> 20000	> 20000
(A-11)	19700	> 20000	–	–	> 20000	> 20000	> 20000
(A-12)	38 71	75 71	–	–	156 472	2960	209
(A-13)	361 964	1760 2860	–	–	1200 1730	3260	2280
(A-14)	33	128	45	173	–	2090	179
(A-15)	185	718	392	786	–	4680	307
(A-16)	610	1710	856	1030	–	1310	777
(A-18)	1980 3750	4090 6740	–	–	1860 5030	7240	2780
(I-11)	4950	1440	3460	1120	9690	3890	–

Kinome Scan

[00245] Compounds (**A-2**) and (**A-17**) were run in the Kinome Scan™ (DiscoverRx) assay to determine the inhibition against a broad panel of known kinases.

Results

[00246] *Table 3* shows the KinomeScan (an active site-directed competition binding assay to measure interactions between test compounds and individual kinases) data of each compound, **II-1** and **I-13**. Lower values indicate a greater inhibition for a given kinase by the test compound. As is shown, **II-1** and **I-13** inhibited several other kinases include LOK, DDR1, JNK2, ZAK, IKK-alpha, BLK, p38-alpha, ABL1, LYN, and STK36 along with the key target HCK.

Table 3.

Kinases	A-2 (1 μM)	A-17 (1 μM)
TAOK1	**0.45**	**0.05**

Kinases	A-2 (1 μM)	A-17 (1 μM)
LOK	**0.05**	**0.1**
TAOK3	**0.45**	**0.1**
DDR1	**0.35**	**0.25**
HCK	**1.5**	**0.3**
JNK2	**0.15**	**0.3**
ZAK	**1.6**	**0.4**
IKK-alpha	**13**	**0.55**
BLK	**0.65**	**0.6**
p38-alpha	**0**	**0.75**
ABL1-nonphosphorylated	**1**	**0.8**
LYN	**3.6**	**0.8**
STK36	**1**	**0.9**
LCK	**1.6**	**1**
FLT3	**1.8**	**1.2**
MKK7	**11**	**1.2**
MAP4K2	**2.8**	**1.4**
p38-beta	**1.8**	**2.1**
PDGFRB	**5.1**	**2.5**
CSF1R	**3.2**	**2.6**
RET(M918T)	**7.4**	**2.8**
ABL2	**2.9**	**2.9**
ABL1(E255K)-phosphorylated	**3.3**	**3**
CDC2L1	**0.45**	**3.2**
EPHA8	**5.4**	**3.6**
RET	**9.9**	**3.6**
CDC2L2	**0.4**	**3.8**
KIT(L576P)	**2.2**	**3.9**
CDK8	**12**	**4**
MAP4K4	**6.4**	**4**
KIT(V559D)	**3.4**	**4.2**
MINK	**18**	**4.6**
MAP3K3	**21**	**4.8**
TAOK2	**0.15**	**4.8**
JAK3(JH1domain-catalytic)	47	**4.9**
JNK1	**6.8**	**5**
KIT	**5.6**	**5.1**
FES	**4.1**	**5.2**
CDKL2	**1.4**	**5.5**
TIE1	**5.5**	**5.5**
ULK3	71	**6**
HPK1	**30**	**6.2**

Kinases	A-2 (1 μM)	A-17 (1 μM)
CDK11	**1.6**	**6.6**
CDKL3	**1.6**	**6.8**
FGR	**13**	**7.7**
TNIK	**20**	**9**
CDC2L5	**19**	**10**
MST3	36	**10**
ABL1(M351T)-phosphorylated	6	**11**
DDR2	3	**11**
FGFR1	21	**12**
FLT3(N841I)	14	**12**
HIPK2	29	**12**
NLK	29	**12**
SRC	5.9	**12**
HIPK3	13	**13**
MAP4K5	29	**14**
p38-gamma	6.6	**14**
RSK2(Kin.Dom.2-C-terminal)	97	**15**
KIT(A829P)	32	**16**
KIT(V559D,T670I)	11	**16**
OSR1	79	**16**
TNK1	33	**16**
EPHB2	69	**17**
YSK1	21	**17**
EGFR(L747-E749del, A750P)	21	**18**
EPHA3	32	**18**
FRK	19	**18**
MST4	38	**18**
PCTK1	45	**18**
RET(V804M)	26	**18**
TIE2	13	**18**
PCTK2	10	**20**
ULK1	100	**20**
FGFR4	32	**21**
BRAF(V600E)	23	**22**
HIPK1	32	**22**
EGFR(L747-S752del, P753S)	19	**23**
FLT3(D835Y)	23	**23**
JNK3	15	**23**
p38-delta	15	**23**
FLT3(D835H)	23	**24**
CAMK1	38	**26**

Kinases	A-2 (1 μM)	A-17 (1 μM)
CTK	40	**26**
FLT1	38	**26**
MYO3A	59	**26**
SGK3	97	**26**
YES	24	**27**
FGFR2	34	**28**
NEK4	59	**30**
SBK1	89	**31**
ABL1(F317L)-phosphorylated	3.9	**33**
AURKA	95	**33**
MEK3	84	**33**
CAMK1D	73	**34**
HIPK4	14	**34**
ZAP70	69	**35**
MUSK	43	37
ASK2	65	38
EGFR(E746-A750del)	28	38
FLT4	54	38
STK39	23	38
TTK	39	38
FLT3(R834Q)	64	39
PAK3	61	39
SLK	17	39
ABL1(T315I)-phosphorylated	37	40
CDK3	58	40
CSK	69	40
PFTK1	27	40
BRAF	42	41
FER	30	42
IKK-beta	48	42
PIK3CA(Q546K)	85	42
ABL1(T315I)-nonphosphorylated	0	44
MYLK2	63	44
PRKCD	39	44
ROCK1	97	44
CDKL1	45	45
TYK2(JH1domain-catalytic)	90	45
GRK7	68	46
PLK4	78	46
ROCK2	100	46
CDK2	43	47

Kinases	A-2 (1 μM)	A-17 (1 μM)
MAST1	59	47
ABL1(F317I)-nonphosphorylated	0	48
EIF2AK1	62	48
AURKB	77	50
MEK6	77	50
ERBB2	46	51
ERN1	58	51
RET(V804L)	62	51
RPS6KA5(Kin.Dom.1-N-terminal)	78	51
KIT(V559D,V654A)	50	52
PCTK3	32	52
EGFR(L747-T751del,Sins)	18	53
EPHA2	40	53
EGFR(L861Q)	56	54
MAP3K15	100	54
SGK	100	54
FYN	52	55
PDGFRA	25	55
PIK3CA(C420R)	100	55
SRMS	66	55
CDK5	67	56
IRAK1	97	56
PIK3C2G	81	56
PKNB(M.tuberculosis)	100	56
QSK	69	56
YSK4	89	57
CIT	56	58
EGFR(T790M)	83	58
JAK2(JH1domain-catalytic)	74	58
MAP3K1	60	58
PIK3CA(E545A)	89	58
PIK3CG	94	58
NDR1	87	59
PFPK5(P.falciparum)	100	59
SRPK1	70	59
DYRK2	99	60
EGFR	55	60
GSK3A	40	60
ABL1(F317L)-nonphosphorylated	0	61
CLK1	85	61
PRKCQ	55	61

Kinases	A-2 (1 μM)	A-17 (1 μM)
PAK1	96	62
STK35	80	62
ABL1(F317I)-phosphorylated	7.9	63
CAMK1G	61	64
CAMK4	100	64
CDKL5	93	64
CDK7	33	66
PLK3	100	66
PRKD1	87	66
IRAK4	99	67
PIK3CA(E545K)	88	67
EGFR(S752-I759del)	37	68
INSRR	71	68
PFTAIRE2	100	68
MYLK	100	69
PIK3CA(I800L)	83	70
SYK	21	70
AURKC	100	71
CASK	60	71
CDK9	46	71
CSNK1A1	83	71
EPHB6	92	71
PIK3CA	100	71
BMPR1B	99	72
FLT3-autoinhibited	68	72
PIK3CA(E542K)	87	72
PRKCI	65	73
ANKK1	100	74
EPHA4	64	75
EGFR(G719C)	60	76
EPHA5	86	76
JAK1(JH1domain-catalytic)	86	76
MST2	82	76
PRKCH	94	76
ARK5	96	77
CLK4	66	77
FGFR3	80	77
GAK	77	77
MEK1	100	77
MYO3B	76	77
WNK3	95	77

Kinases	A-2 (1 μM)	A-17 (1 μM)
DCAMKL1	77	78
EPHA6	68	78
FGFR3(G697C)	81	78
KIT(D816H)	82	78
RIPK5	90	78
SNRK	68	78
ERBB4	88	79
EGFR(L858R)	83	80
IKK-epsilon	100	80
TLK1	100	80
TRKC	100	80
ERK2	100	81
PRKD2	73	81
ACVRL1	83	82
BMPR2	86	82
NEK10	100	82
PAK2	78	82
S6K1	54	82
SIK	73	82
GSK3B	83	83
HUNK	100	83
MERTK	100	83
NIK	62	83
PIP5K2B	100	83
RIOK1	100	83
VRK2	96	83
CAMK2D	92	84
PAK6	100	84
TBK1	95	84
GCN2(Kin.Dom.2,S808G)	84	85
PKN1	100	85
SGK2	100	85
TGFBR2	100	85
WNK1	100	85
ALK	92	86
DCAMKL3	97	86
MEK2	83	86
PIM1	100	86
PRKCE	92	86
TAK1	3.2	86
YANK2	100	86

Kinases	A-2 (1 μM)	A-17 (1 μM)
AXL	68	87
MKNK2	72	87
NEK6	91	87
PIP5K1A	100	87
ADCK3	100	88
CLK2	100	88
ERK8	100	88
PIK3CB	66	88
PIM3	93	88
RAF1	75	88
AKT1	82	89
BUB1	80	89
MAP4K3	100	89
BTK	65	90
ICK	65	90
PAK7	100	90
PIK3CD	100	90
RIOK3	83	90
BMX	79	91
CDK4-cyclinD1	94	91
SNARK	100	91
TRKA	90	91
ALK(L1196M)	90	92
LATS2	100	92
PRKG2	74	92
NEK2	98	93
TRKB	85	93
AAK1	94	94
EGFR(L858R,T790M)	80	94
ERK3	93	94
LRRK2(G2019S)	100	94
PAK4	95	94
PIK3CA(H1047L)	97	94
RIPK4	88	94
RPS6KA4(Kin.Dom.1-N-terminal)	96	94
TESK1	81	94
CSF1R-autoinhibited	96	95
LIMK2	94	95
LRRK2	95	95
PIK3CA(M1043I)	83	95
RPS6KA4(Kin.Dom.2-C-terminal)	100	95

Kinases	A-2 (1 μM)	A-17 (1 μM)
TNNI3K	64	95
HASPIN	84	96
MAP3K4	80	96
PRP4	94	96
YANK1	73	96
ABL1(Y253F)-phosphorylated	4.8	97
EGFR(G719S)	65	97
MLK1	91	97
NEK1	93	97
PIK4CB	98	97
BIKE	92	98
RSK2(Kin.Dom.1-N-terminal)	100	98
SRPK2	100	98
STK16	100	98
AMPK-alpha2	95	99
CAMKK2	79	99
EPHB4	87	99
RSK4(Kin.Dom.1-N-terminal)	92	99
ABL1(Q252H)-phosphorylated	11	100
ACVR1	100	100
ACVR1B	100	100
ACVR2A	100	100
ACVR2B	95	100
ADCK4	100	100
AKT2	90	100
AKT3	100	100
ALK(C1156Y)	49	100
AMPK-alpha1	85	100
ASK1	96	100
BMPR1A	100	100
BRK	100	100
BRSK1	100	100
BRSK2	100	100
CAMK2A	92	100
CAMK2B	100	100
CAMK2G	86	100
CAMKK1	100	100
CDK4-cyclinD3	100	100
CHEK1	100	100
CHEK2	100	100
CLK3	100	100

Kinases	A-2 (1 μM)	A-17 (1 μM)
CSNK1A1L	99	100
CSNK1D	100	100
CSNK1E	100	100
CSNK1G1	100	100
CSNK1G2	100	100
CSNK1G3	93	100
CSNK2A1	100	100
CSNK2A2	100	100
DAPK1	100	100
DAPK2	93	100
DAPK3	100	100
DCAMKL2	74	100
DLK	100	100
DMPK	100	100
DMPK2	88	100
DRAK1	100	100
DRAK2	85	100
DYRK1A	92	100
DYRK1B	77	100
EPHA1	90	100
EPHA7	75	100
EPHB1	78	100
EPHB3	100	100
ERBB3	100	100
ERK1	100	100
ERK4	96	100
ERK5	98	100
FAK	100	100
GRK1	77	100
GRK4	100	100
IGF1R	100	100
INSR	100	100
IRAK3	100	100
ITK	95	100
JAK1(JH2domain-pseudokinase)	90	100
KIT(D816V)	96	100
KIT-autoinhibited	65	100
LATS1	100	100
LIMK1	100	100
LKB1	100	100
LTK	100	100

Kinases	A-2 (1 μM)	A-17 (1 μM)
LZK	100	100
MAK	93	100
MAP3K2	90	100
MAPKAPK2	100	100
MAPKAPK5	94	100
MARK1	83	100
MARK2	100	100
MARK3	94	100
MARK4	92	100
MEK4	82	100
MEK5	37	100
MELK	89	100
MET	100	100
MET(M1250T)	89	100
MET(Y1235D)	100	100
MKNK1	94	100
MLCK	100	100
MLK2	100	100
MLK3	62	100
MRCKA	100	100
MRCKB	100	100
MST1	80	100
MST1R	100	100
MTOR	86	100
MYLK4	100	100
NDR2	100	100
NEK11	100	100
NEK3	65	100
NEK5	85	100
NEK7	100	100
NEK9	100	100
NIM1	100	100
PDPK1	69	100
PHKG1	100	100
PHKG2	100	100
PIK3C2B	100	100
PIK3CA(H1047Y)	79	100
PIM2	71	100
PIP5K1C	50	100
PIP5K2C	82	100
PKAC-alpha	72	100

Kinases	A-2 (1 μM)	A-17 (1 μM)
PKAC-beta	100	100
PKMYT1	100	100
PKN2	89	100
PLK1	100	100
PLK2	100	100
PRKD3	100	100
PRKG1	100	100
PRKR	100	100
PRKX	100	100
PYK2	97	100
RIOK2	100	100
RIPK1	54	100
RIPK2	86	100
ROS1	75	100
RPS6KA5(Kin.Dom.2-C-terminal)	100	100
RSK1(Kin.Dom.1-N-terminal)	100	100
RSK1(Kin.Dom.2-C-terminal)	100	100
RSK3(Kin.Dom.1-N-terminal)	100	100
RSK3(Kin.Dom.2-C-terminal)	100	100
RSK4(Kin.Dom.2-C-terminal)	100	100
SgK110	100	100
SIK2	100	100
SRPK3	100	100
STK33	97	100
TEC	82	100
TGFBR1	100	100
TLK2	100	100
TNK2	100	100
TRPM6	58	100
TSSK1B	83	100
TXK	89	100
TYK2(JH2domain-pseudokinase)	87	100
TYRO3	92	100
ULK2	81	100
VEGFR2	28	100
WEE1	100	100
WEE2	100	100
YANK3	88	100

Kinative

[00247] The kinase selectivity of compounds (**A-5**) and (**A-14**) were evaluated using a

chemical proteomic approach named KiNativ which detects 260 kinases in A375 cells (ActivX Biosciences). To probe the intracellular targets of the compounds, A375 cells were incubated with the inhibitor at 1 μM final concentration and then looked for protection of labeling by an ATP-biotin probe that non-specifically labels conserved lysines on kinases and other nucleotide-dependent enzymes.

Results

[00248] *Table 4* shows that compound (**A-5**) inhibits a number of kinases at 1 μM, including Abl (>90%), FYN (71.2%), LYN (87.8%), and ZAK (75.7%). *Table 5* shows that compound (**A-14**) inhibits a number of kinases at 1 μM, including Abl (>90%), FYN (88.2%), LYN (85.7%), and ZAK (75.8%).

Table 4.

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
ABL, ARG	UniRef100_P00519, UniRef100_P42684	LMTGDTYTAHAGAKFPIK	1	Activation Loop	95.5
ACK	UniRef100_Q07912	TVSVAVKCLKPDVLSQPEA MDDFIR	2	Lys1	4.9
AGK	UniRef100_Q53H12	ATVFLNPAACKGK	3	ATP	-31.4
AMPKa1, AMPKa2	UniRef100_P54646, UniRef100_Q13131	DLKPENVLLDAHMNAK	4	Lys2	16.3
ARAF	UniRef100_P10398	DLKSNNIFLHEGLTVK	5	Lys2	12.2
ATR	UniRef100_Q13535	FYIMMCKPK	6	ATP	23.0
AurA	UniRef100_O14965	FILALKVLFK	7	Lys1	-16.0
AurB	UniRef100_Q96GD4	SHFIVALKVLFK	8	Lys1	-51.1
BARK1	UniRef100_P25098	DLKPANILLDEHGHVR	9	Lys2	-13.4
BRAF	UniRef100_P15056	DLKSNNIFLHEDLTVK	10	Lys2	18.9
BTK	UniRef100_Q06187	YVLDDEYTSSVGSKFPVR	11	Activation Loop	-18.8
CaMK1a	UniRef100_Q14012	LVAIKCIAK	12	Lys1	12.4
CaMK1d	UniRef100_Q8IU85	LFAVKCIPK	13	Lys1	-6.0
CaMK2d	UniRef100_Q13557	IPTGQEYAAKIINTKK	14	Lys1	-8.1
CaMK2g	UniRef100_Q13555	TSTQEYAAKIINTK	15	Lys1	-23.1
CaMK4	UniRef100_Q16566	DLKPENLLYATPAPDAPLK	16	Lys2	5.9

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
CaMKK2	UniRef100_Q96RR4	DIKPSNLLVGEDGHIK	17	Lys2	6.2
CASK	UniRef100_O14936, UniRef100_C9JGY0	ETGQQFAVKIVDVAK	18	Lys1	-28.1
CDC2	UniRef100_P06493	DLKPQNLLIDDKGTIK	19	Lys2	-2.3
CDK11, CDK8	UniRef100_P49336, UniRef100_Q9BWU1	DLKPANILVMGEGPER	20	Lys2	50.0
CDK2	UniRef100_P24941	DLKPQNLLINTEGAIK	21	Lys2	-3.5
CDK4	UniRef100_P11802	DLKPENILVTSGGTVK	22	Lys2	17.4
CDK5	UniRef100_Q00535	DLKPQNLLINR	23	Lys2	-27.3
CDK6	UniRef100_Q00534	DLKPQNILVTSSGQIK	24	Lys2	13.1
CDK7	UniRef100_P50613	DLKPNNLLLDENGVLK	25	Lys2	3.9
CDK9	UniRef100_P50750	DMKAANVLITR	26	Lys2	-16.2
CHK1	UniRef100_B5BTY6, UniRef100_O14757	DIKPENLLLDER	27	Lys2	-5.0
CHK2	UniRef100_O96017	DLKPENVLLSSQEEDCLIK	28	Lys2	-7.8
CK1a	UniRef100_P48729, UniRef100_B4E1D9	DIKPDNFLMGIGR	29	Lys2	-0.6
CK1g2	UniRef100_P78368	DVKPENFLVGRPGTK	30	Lys2	-9.1
CK2a2	UniRef100_P19784	DVKPHNVMIDHQQK	31	Lys2	-18.2
CLK3	UniRef100_P49761	YEIVGNLGEGTFGKVVECL DHAR	32	ATP Loop	-52.8
CSK	UniRef100_P41240	VSDFGLTKEASSTQDTGKL PVK	33	Activation Loop	15.3
DGKA	UniRef100_P23743	IDPVPNTHPLLVFVNPKSG GK	34	ATP	-4.8
DGKH	UniRef100_Q86XP1	ATFSFCVSPLLVFVNSKSG DNQGVK	35	ATP	-6.3
DGKQ	UniRef100_P52824	GRLLTALVLPDLLHAKLPP DSCPLLVFVNPKSGGLK	36	ATP	11.0
DNAPK	UniRef100_P78527	KGGSWIQEINVAEK	37	ATP	-61.5
DNAPK	UniRef100_P78527	EHPFLVKGGEDLR	38	ATP	-64.6
eEF2K	UniRef100_O00418	YIKYNSNSGFVR	39	ATP	-30.5

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
EphB1	UniRef100_P54762	YLQDDTSDPTYTSSLGGKI PVR	40	Activation Loop	-1.7
EphB2	UniRef100_P29323	FLEDDTSDPTYTSALGGKI PIR	41	Activation Loop	-12.8
Erk1	UniRef100_P27361	DLKPSNLLINTTCDLK	42	Lys2	-9.0
Erk2	UniRef100_P28482	DLKPSNLLLNTTCDLK	43	Lys2	-3.8
Erk5	UniRef100_Q13164	DLKPSNLLVNENCELK	44	Lys2	25.9
FER	UniRef100_P16591	TSVAVKTCKEDLPQELK	45	Lys1	91.4
FES	UniRef100_P07332	LRADNTLVAVKSCR	46	Lys1	89.1
FGR	UniRef100_P09769	LIKDDEYNPCQGSKFPIK	47	Activation Loop	31.9
FRAP	UniRef100_P42345	IQSIAPSLQVITSKQRPR	48	ATP	-7.5
FRK	UniRef100_P42685	HEIKLPVK	49	Activation Loop	91.1
FYN, SRC, YES	UniRef100_P12931, UniRef100_P07947, UniRef100_P06241	QGAKFPIKWTAPEAALYG R	50	Activation Loop	71.2
GCK	UniRef100_Q12851	DIKGANLLLTLQGDVK	51	Lys2	94.9
GCN2	UniRef100_Q9P2K8	DLKPVNIFLDSDDHVK	52	Lys2	20.8
GSK3A	UniRef100_P49840	DIKPQNLLVDPDTAVLK	53	Lys2	36.0
GSK3B	UniRef100_P49841	DIKPQNLLLDPDTAVLK	54	Lys2	0.5
HPK1	UniRef100_Q92918	DIKGANILINDAGEVR	55	Lys2	68.1
IKKa	UniRef100_O15111	DLKPENIVLQDVGGK	56	Lys2	-17.0
IKKb	UniRef100_O14920	DLKPENIVLQQGEQR	57	Lys2	-12.6
IKKe	UniRef100_Q14164	SGELVAVKVFNTTSYLRPR	58	Lys1	-9.9
ILK	UniRef100_Q13418	WQGNDIVVKVLK	59	Lys1	5.2
IRAK1	UniRef100_P51617	AIQFLHQDSPSLIHGDIKSS NVLLDER	60	Lys2	-3.5

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
IRAK4	UniRef100_Q9NWZ3	DIKSANILLDEAFTAK	61	Lys2	1.9
IRE1	UniRef100_O75460	DLKPHNILISMPNAHGK	62	Lys2	-2.2
ITPK1	UniRef100_Q13572	ESIFFNSHNVSKPESSSVLTELDKIEGVFERPSDEVIR	63	ATP	1.2
JAK1	UniRef100_P23458	QLASALSYLEDKDLVHGNVCTKNLLLAR	64	Protein Kinase Domain	4.3
JAK1 domain2	UniRef100_P23458	IGDFGLTKAIETDKEYYTVK	65	Activation Loop	-6.2
JAK3 domain2	UniRef100_P52333	IADFGLAKLLPLDKDYYVVR	66	Activation Loop	7.7
JNK1, JNK2, JNK3	UniRef100_P45983, UniRef100_P53779, UniRef100_P45984	DLKPSNIVVK	67	Lys2	77.2
KHS1	UniRef100_Q9Y4K4	NVHTGELAAVKIIK	68	Lys1	15.8
KSR1	UniRef100_Q8IVT5	SKNVFYDNGKVVITDFGLFGISGVVR	69	Activation Loop	-22.0
KSR1, KSR2	UniRef100_Q6VAB6, UniRef100_Q8IVT5	SKNVFYDNGK	70	Activation Loop	-10.0
LATS1	UniRef100_O95835	ALYATKTLR	71	Lys1	5.4
LATS2	UniRef100_Q9NRM7	DIKPDNILIDLDGHIK	72	Lys2	-1.9
LCK	UniRef100_P06239	EGAKFPIKWTAPEAINYGTFTIK	73	Activation Loop	92.3
LKB1	UniRef100_Q15831	DIKPGNLLLTTGGTLK	74	Lys2	-6.0
LOK	UniRef100_O94804	DLKAGNVLMTLEGDIR	75	Lys2	19.9
LRRK2	UniRef100_Q5S007	DLKPHNVLLFTLYPNAAIIAK	76	Lys2	-15.9
LYN	UniRef100_P07948	VAVKTLKPGTMSVQAFLEEANLMK	77	Lys1	87.8
MAP2K1	UniRef100_Q02750	IMHRDVKPSNILVNSR	78	Lys2	11.4
MAP2K1, MAP2K2	UniRef100_P36507, UniRef100_Q02750	DVKPSNILVNSR	79	Lys2	-16.3
MAP2K3	UniRef100_P46734	DVKPSNVLINK	80	Lys2	-1.0
MAP2K4	UniRef100_P45985	DIKPSNILLDR	81	Lys2	-14.1
MAP2K5	UniRef100_Q13163	DVKPSNMLVNTR	82	Lys2	20.5

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
MAP2K6	UniRef100_P52564	DVKPSNVLINALGQVK	83	Lys2	0.5
MAP2K7	UniRef100_O14733	DVKPSNILLDER	84	Lys2	-38.2
MAP3K1	UniRef100_Q13233	DVKGANLLIDSTGQR	85	Lys2	26.9
MAP3K2	UniRef100_Q9Y2U5	ELAVKQVQFDPDSPETSK EVNALECEIQLLK	86	Lys1	4.2
MAP3K2, MAP3K3	UniRef100_Q9Y2U5, UniRef100_Q99759	DIKGANILR	87	Lys2	3.2
MAP3K3	UniRef100_Q99759	ELASKQVQFDPDSPETSKE VSALECEIQLLK	88	Lys1	3.7
MAP3K4	UniRef100_Q9Y6R4	DIKGANIFLTSSGLIK	89	Lys2	19.2
MAP3K5	UniRef100_Q99683	DIKGDNVLINTYSGVLK	90	Lys2	-30.4
MAP3K6	UniRef100_O95382	DIKGDNVLINTFSGLLK	91	Lys2	-25.0
MARK2, MARK3	UniRef100_P27448, UniRef100_Q7KZI7	DLKAENLLLDADMNIK	92	Lys2	4.6
MARK3	UniRef100_P27448	EVAIKIIDKTQLNPTSLQK	93	Lys1	-26.1
MARK3, MARK4	UniRef100_Q96L34, UniRef100_P27448	EVAIKIIDK	94	Lys1	-16.2
MARK4	UniRef100_Q96L34	DLKAENLLLDAEANIK	95	Lys2	2.9
MAST1, MAST2	UniRef100_Q6P0Q8, UniRef100_Q9Y2H9	DLKPDNLLITSMGHIK	96	Lys2	35.6
MAST3	UniRef100_O60307	DLKPDNLLITSLGHIK	97	Lys2	-8.1
MASTL	UniRef100_Q96GX5	GAFGKVYLGQK	98	ATP Loop	12.8
MASTL	UniRef100_Q96GX5	LYAVKVVK	99	Lys1	3.3
MELK	UniRef100_Q14680	DLKPENLLFDEYHK	100	Lys2	-19.6
MER	UniRef100_Q12866	NCMLRDDMTVCVADFGL SKK	101	Activation Loop	49.8
MER, TYRO3	UniRef100_Q06418, UniRef100_Q12866	KIYSGDYYR	102	Activation Loop	1.6
MET	UniRef100_P08581	DMYDKEYYSVHNK	103	Activation Loop	-21.0
MLK3	UniRef100_Q16584	DLKSNNILLLQPIESDDME HK	104	Lys2	20.7
MLK4	UniRef100_Q5TCX8	DLKSSNILLLEK	105	Lys2	-1.7

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
MLKL	UniRef100_Q8NB16	APVAIKVFK	106	Lys1	-14.9
MPSK1	UniRef100_O75716	DLKPTNILLGDEGQPVLM DLGSMNQACIHVEGSR	107	Lys2	16.1
MSK1 domain1	UniRef100_O75582	DIKLENILLDSNGHVVLTD FGLSK	108	Lys2	5.7
MSK2 domain1	UniRef100_O75676	DLKLENVLLDSEGHIVLTD FGLSK	109	Lys2	-64.9
MST1	UniRef100_Q13043	ETGQIVAIKQVPVESDLQE IIK	110	Lys1	-4.7
MST2	UniRef100_Q13188	ESGQVVAIKQVPVESDLQ EIIK	111	Lys1	-6.2
MST3	UniRef100_Q9Y6E0	DIKAANVLLSEHGEVK	112	Lys2	-3.7
MST4	UniRef100_Q9P289	TQQVVAIKIIDLEEAEDEIE DIQQEITVLSQCDSSYVTK	113	Lys1	6.2
MST4, YSK1	UniRef100_O00506, UniRef100_Q9P289	DIKAANVLLSEQGDVK	114	Lys2	4.6
MYO3A, MYO3B	UniRef100_Q8NEV4, UniRef100_Q8WXR4	DVKGNNILLTTEGGVK	115	Lys2	-15.3
NDR1	UniRef100_Q15208	DIKPDNLLLDSK	116	Lys2	9.3
NDR2	UniRef100_Q9Y2H1	DIKPDNLLLDAK	117	Lys2	-10.9
NEK1	UniRef100_Q96PY6	DIKSQNIFLTK	118	Lys2	-3.0
NEK2	UniRef100_P51955	DLKPANVFLDGK	119	Lys2	-22.7
NEK3	UniRef100_P51956	SKNIFLTQNGK	120	Activation Loop	13.1
NEK4	UniRef100_P51957	DLKTQNVFLTR	121	Lys2	1.5
NEK6, NEK7	UniRef100_Q8TDX7, UniRef100_Q9HC98	DIKPANVFITATGVVK	122	Lys2	-12.5
NEK7	UniRef100_Q8TDX7	AACLLDGVPVALKK	123	Lys1	-7.2
NEK8	UniRef100_Q86SG6	DLKTQNILLDK	124	Lys2	-11.4
NEK9	UniRef100_Q8TD19	DIKTLNIFLTK	125	Lys2	-1.2
OSR1	UniRef100_C9JIG9, UniRef100_O95747	DVKAGNILLGEDGSVQIA DFGVSAFLATGGDITR	126	Lys2	-11.1
p38a	UniRef100_Q16539	DLKPSNLAVNEDCELK	127	Lys2	61.4
p38a	UniRef100_Q16539	QELNKTIWEVPER	128	Protein Kinase Domain	92.2

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
p38b	UniRef100_Q15759	QELNKTVWEVPQR	129	Protein Kinase Domain	51.4
p38d, p38g	UniRef100_O15264, UniRef100_P53778	DLKPGNLAVNEDCELK	130	Lys2	62.5
p70S6K	UniRef100_P23443	DLKPENIMLNHQGHVK	131	Lys2	-2.3
p70S6Kb	UniRef100_Q9UBS0	DLKPENIMLSSQGHIK	132	Lys2	8.2
PAN3	UniRef100_Q58A45	VMDPTKILITGK	133	ATP	12.1
PCTAIRE1	UniRef100_Q00536	SKLTDNLVALKEIR	134	Lys1	-3.5
PCTAIRE2, PCTAIRE3	UniRef100_Q00537, UniRef100_Q07002	SKLTENLVALKEIR	135	Lys1	11.7
PDK1	UniRef100_O15530	EYAIKILEK	136	Lys1	18.8
PEK	UniRef100_Q9NZJ5	DLKPSNIFFTMDDVVK	137	Lys2	9.4
PFTAIRE1	UniRef100_O94921	LVALKVIR	138	Lys1	4.3
PHKg1	UniRef100_Q16816	DLKPENILLDDNMNIK	139	Protein Kinase Domain	-49.0
PHKg2	UniRef100_P15735	ATGHEFAVKIMEVTAER	140	Lys1	15.2
PI4KA, PI4KAP2	UniRef100_A4QPH2, UniRef100_P42356	SGTPMQSAAKAPYLAK	141	ATP	19.3
PI4KB	UniRef100_Q9UBF8	VPHTQAVVLNSKDK	142	ATP	-0.2
PIK3C2B	UniRef100_O00750	VIFKCGDDLRQDMLTLQ MIR	143	ATP	24.0
PIK3C3	UniRef100_Q8NEB9	TEDGGKYPVIFKHGDDLR	144	ATP	-5.1
PIK3CB	UniRef100_Q9BTS4, UniRef100_P42338	VFGEDSVGVIFKNGDDLR QDMLTLQMLR	145	ATP	27.8
PIK3CD	UniRef100_O00329	VNWLAHNVSKDNRQ	146	ATP	2.2
PIK3CG	UniRef100_P48736	KKPLWLEFK	147	ATP	-21.1
PIP4K2A	UniRef100_P48426	AKELPTLKDNDFINEGQK	148	ATP	-26.7
PIP4K2B	UniRef100_P78356	AKDLPTFKDNDFLNEGQK	149	ATP	-44.7

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
PIP4K2C	UniRef100_Q8TBX8	TLVIKEVSSEDIADMHSNL SNYHQYIVK	150	ATP	5.2
PIP5K3	UniRef100_Q9Y2I7	GGKSGAAFYATEDDRFILK	151	ATP	0.9
PITSLRE	UniRef100_P21127	DLKTSNLLLSHAGILK	152	Lys2	-10.4
PKCa, PKCb	UniRef100_P17252, UniRef100_P05771, UniRef100_B5BU22	DLKLDNVMLDSEGHIK	153	Lys2	2.3
PKD2	UniRef100_Q9BZL6	DVAVKVIDK	154	Lys1	-6.9
PKN1	UniRef100_Q16512	VLLSEFRPSGELFAIKALK	155	Lys1	-32.1
PKR	UniRef100_P19525	DLKPSNIFLVDTK	156	Lys2	-28.4
PLK1	UniRef100_P53350	CFEISDADTKEVFAGKIVP K	157	Lys1	-9.1
PRP4	UniRef100_Q13523	CNILHADIKPDNILVNESK	158	Lys2	-20.1
PRPK	UniRef100_Q96S44	FLSGLELVKQGAEAR	159	ATP Loop	-13.7
PYK2	UniRef100_Q14289	YIEDEDYYKASVTR	160	Activation Loop	10.9
RAF1	UniRef100_P04049	DMKSNNIFLHEGLTVK	161	Lys2	36.6
RIPK3	UniRef100_Q9Y572	DLKPSNVLLDPELHVK	162	Lys2	32.6
ROCK1, ROCK2	UniRef100_O75116, UniRef100_Q13464	DVKPDNMLLDK	163	Lys2	22.0
RSK1 domain1	UniRef100_Q15418	DLKPENILLDEEGHIKLTDF GLSKEAIDHEK	164	Lys2	-20.9
RSK1 domain1, RSK2 domain1, RSK3 domain1	UniRef100_Q15418, UniRef100_P51812, UniRef100_Q15349	DLKPENILLDEEGHIK	165	Lys2	-17.7
RSK1 domain2	UniRef100_Q15418	DLKPSNILYVDESGNPECL R	166	Lys2	-16.3
RSK2 domain1	UniRef100_P51812	DLKPENILLDEEGHIKLTDF GLSKESIDHEK	167	Lys2	-3.3

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
RSK2 domain2	UniRef100_P51812	DLKPSNILYVDESGNPESIR	168	Lys2	-24.1
RSK3 domain1	UniRef100_Q15349	DLKPENILLDEEGHIKITDF GLSK	169	Lys2	-32.6
RSK4 domain1	UniRef100_Q9UK32	DLKPENILLDEIGHIK	170	Lys2	27.6
RSKL1	UniRef100_Q96S38	VLGVIDKVLLVMDTR	171	ATP	31.5
SGK3	UniRef100_Q96BR1	FYAVKVLQK	172	Lys1	-10.2
SLK	UniRef100_Q9H2G2	DLKAGNILFTLDGDIK	173	Lys2	-14.3
SMG1	UniRef100_Q96Q15	DTVTIHSVGGTITILPTKTK PK	174	ATP	-4.0
SNRK	UniRef100_Q9NRH2	DLKPENVVFFEK	175	Lys2	18.0
SRC	UniRef100_P12931	VAIKTLKPGTMSPEAFLQE AQVMKK	176	Lys1	76.1
SRPK1	UniRef100_Q96SB4	IIHTDIKPENILLSVNEQYIR	177	Lys2	-34.1
STK33	UniRef100_Q9BYT3	DLKLENIMVK	178	Lys2	12.9
STLK5	UniRef100_Q7RTN6	YSVKVLPWLSPEVLQQNL QGYDAK	179	Activation Loop	5.0
SYK	UniRef100_P43405	ISDFGLSKALR	180	Activation Loop	17.4
TAK1	UniRef100_O43318	DLKPPNLLLVAGGTVLK	181	Lys2	32.0
TAO1, TAO3	UniRef100_Q9H2K8, UniRef100_Q7L7X3	DIKAGNILLTEPGQVK	182	Lys2	76.5
TAO2	UniRef100_Q9UL54	DVKAGNILLSEPGLVK	183	Lys2	86.0
TBK1	UniRef100_Q9UHD2	TGDLFAIKVFNNISFLRPV DVQMR	184	Lys1	18.2
TEC	UniRef100_P42680	YVLDDQYTSSSGAKFPVK	185	Activation Loop	-12.8
TLK1	UniRef100_Q9UKI8	YLNEIKPPIIHYDLKPGNILL VDGTACGEIK	186	Lys2	4.9
TLK2	UniRef100_Q86UE8	YLNEIKPPIIHYDLKPGNILL VNGTACGEIK	187	Lys2	7.1
TYK2 domain2	UniRef100_P29597	IGDFGLAKAVPEGHEYYR	188	Activation Loop	-18.1
ULK1	UniRef100_O75385	DLKPQNILLSNPAGR	189	Lys2	-6.0

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Compound A-4 (1.0 μM)
ULK3	UniRef100_D3DW67, UniRef100_Q6PHR2	NISHLDLKPQNILLSSLEKP HLK	190	Lys2	-4.4
VRK2	UniRef100_Q86Y07	MLDVLEYIHENEYVHGDIK AANLLLGYK	191	Lys2	27.9
Wee1	UniRef100_P30291	YIHSMSLVHMDIKPSNIFIS R	192	Lys2	23.2
Wnk1, Wnk2	UniRef100_Q9Y3S1, UniRef100_D3DUP1, UniRef100_Q9H4A3	GSFKTVYK	193	ATP Loop	24.2
Wnk1, Wnk2, Wnk3	UniRef100_Q9Y3S1, UniRef100_D3DUP1, UniRef100_Q9BYP7, UniRef100_Q9H4A3	DLKCDNIFITGPTGSVK	194	Lys2	0.2
YANK3	UniRef100_Q86UX6	DVKPDNILLDER	195	Lys2	27.7
ZAK	UniRef100_Q9NYL2	WISQDKEVAVKK	196	Lys1	75.7
ZAP70	UniRef100_P43403	ISDFGLSKALGADDSYYTA R	197	Activation Loop	49.2
ZC1/HGK, ZC2/TNIK, ZC3/MINK	UniRef100_O95819, UniRef100_Q9UKE5, UniRef100_Q8N4C8	DIKGQNVLLTENAEVK	198	Lys2	19.2
ZC2/TNIK	UniRef100_Q9UKE5	TGQLAAIKVMDVTGDEEE EIKQEINMLKK	199	Lys1	23.9

Table 5.

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
ABL, ARG	UniRef100_P00519, UniRef100_P42684	LMTGDTYTAHAGAKFPIK	200	Activation Loop	98.4
ACK	UniRef100_Q07912	TVSVAVKCLKPDVLSQPEA MDDFIR	201	Lys1	8.5
AGK	UniRef100_Q53H12	ATVFLNPAACKGK	202	ATP	5.9
AKT1	UniRef100_P31749	GTFGKVILVK	203	ATP Loop	-23.9
AKT2, AKT3	UniRef100_Q9Y243, UniRef100_P31751	GTFGKVILVR	204	ATP Loop	-19.7
AMPKa1, AMPKa2	UniRef100_P54646, UniRef100_Q96E92	DLKPENVLLDAHMNAK	205	Lys2	-17.5
ANPa	UniRef100_P16066	GMLFLHNGAICSHGNLKS SNCVVDGR	206	Lys2	-5.3
ARAF	UniRef100_P10398	DLKSNNIFLHEGLTVK	207	Lys2	2.0
ATR	UniRef100_Q13535	FYIMMCKPK	208	ATP	-20.3

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
AurA	UniRef100_O14965	FILALKVLFK	209	Lys1	14.6
AurA	UniRef100_O14965	DIKPENLLLGSAGELK	210	Lys2	6.1
AurA, AurB, AurC	UniRef100_O14965, UniRef100_Q9UQB9, UniRef100_Q96GD4	GKFGNVYLAR	211	ATP Loop	-2.4
AurB	UniRef100_Q96GD4	SHFIVALKVLFK	212	Lys1	3.3
BARK1	UniRef100_P25098	DLKPANILLDEHGHVR	213	Lys2	-13.6
BRAF	UniRef100_P15056	DLKSNNIFLHEDLTVK	214	Lys2	18.9
BTK	UniRef100_Q06187	YVLDDEYTSSVGSKFPVR	215	Activation Loop	-10.2
CaMK1a	UniRef100_Q14012	LVAIKCIAK	216	Lys1	-5.4
CaMK1d	UniRef100_Q8IU85	LFAVKCIPK	217	Lys1	-1.8
CaMK2d	UniRef100_Q13557	IPTGQEYAAKIINTKK	218	Lys1	-7.3
CaMK2g	UniRef100_Q13555	TSTQEYAAKIINTK	219	Lys1	2.0
CaMK4	UniRef100_Q16566	DLKPENLLYATPAPDAPLK	220	Lys2	-2.0
CaMKK2	UniRef100_Q96RR4	DIKPSNLLVGEDGHIK	221	Lys2	16.2
CASK	UniRef100_O14936	ETGQQFAVKIVDVAK	222	Lys1	7.1
CDC2	UniRef100_Q5H9N4	DLKPQNLLIDDKGTIK	223	Lys2	9.0
CDK11, CDK8	UniRef100_P49336, UniRef100_Q9BWU1	DLKPANILVMGEGPER	224	Lys2	49.2
CDK2	UniRef100_P24941	DLKPQNLLINTEGAIK	225	Lys2	34.5
CDK4	UniRef100_P11802	DLKPENILVTSGGTVK	226	Lys2	11.4
CDK5	UniRef100_Q00535	DLKPQNLLINR	227	Lys2	11.3
CDK6	UniRef100_Q00534	DLKPQNILVTSSGQIK	228	Lys2	13.6
CDK7	UniRef100_P50613	DLKPNNLLLDENGVLK	229	Lys2	-7.3
CDK9	UniRef100_P50750	DMKAANVLITR	230	Lys2	-13.1
CHK1	UniRef100_B4DT73	DIKPENLLLDER	231	Lys2	12.2
CHK2	UniRef100_O96017	DLKPENVLLSSQEEDCLIK	232	Lys2	-1.6
CK1a	UniRef100_P48729	DIKPDNFLMGIGR	233	Lys2	-19.6
CK1d, CK1e	UniRef100_P49674, UniRef100_P48730	DVKPDNFLMGLGKK	234	Lys2	-9.3
CK1g1, CK1g2, CK1g3	UniRef100_Q9Y6M4, UniRef100_P78368, UniRef100_Q9HCP0	KIGCGNFGELR	235	ATP Loop	1.3
CK1g2	UniRef100_P78368	DVKPENFLVGRPGTK	236	Lys2	-23.3
CLK2	UniRef100_P49760	LTHTDLKPENILFVNSDYELTYNLEK	237	Lys2	-30.3
CLK3	UniRef100_P49761	YEIVGNLGEGTFGKVVECLDHAR	238	ATP Loop	-4.0

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
CSK	UniRef100_P41240	VSDFGLTKEASSTQDTGKLPVK	239	Activation Loop	20.0
DGKA	UniRef100_P23743	IDPVPNTHPLLVFVNPKSGGK	240	ATP	-16.3
DGKH	UniRef100_Q86XP1	ATFSFCVSPLLVFVNSKSGDNQGVK	241	ATP	32.6
DGKQ	UniRef100_P52824	GRLLTALVLPDLLHAKLPPDSCPLLVFVNPKSGGLK	242	ATP	-23.2
DNAPK	UniRef100_P78527	KGGSWIQEINVAEK	243	ATP	-35.9
DNAPK	UniRef100_P78527	EHPFLVKGGEDLR	244	ATP	-63.7
eEF2K	UniRef100_O00418	YIKYNSNSGFVR	245	ATP	-22.0
Erk1	UniRef100_P27361	DLKPSNLLINTTCDLK	246	Lys2	-16.3
Erk2	UniRef100_P28482	DLKPSNLLLNTTCDLK	247	Lys2	-2.7
Erk3	UniRef100_Q16659	DLKPANLFINTEDLVLK	248	Lys2	31.8
Erk5	UniRef100_Q13164	DLKPSNLLVNENCELK	249	Lys2	-42.7
FER	UniRef100_P16591	TSVAVKTCKEDLPQELK	250	Lys1	74.0
FES	UniRef100_P07332	LRADNTLVAVKSCR	251	Lys1	36.1
FGR	UniRef100_P09769	LIKDDEYNPCQGSKFPIK	252	Activation Loop	70.3
FRAP	UniRef100_P42345	IQSIAPSLQVITSKQRPR	253	ATP	-3.3
FRK	UniRef100_P42685	HEIKLPVK	254	Activation Loop	98.0
FYN, SRC, YES	UniRef100_P12931, UniRef100_P07947, UniRef100_P06241	QGAKFPIKWTAPEAALYGR	255	Activation Loop	88.2
GCK	UniRef100_Q12851	DIKGANLLLTLQGDVK	256	Lys2	96.3
GCN2	UniRef100_Q9P2K8	DLKPVNIFLDSDDHVK	257	Lys2	5.4
GPRK6	UniRef100_P43250	DLKPENILLDDHGHIR	258	Lys2	-1.9
GSK3A	UniRef100_P49840	DIKPQNLLVDPDTAVLK	259	Lys2	25.5
GSK3B	UniRef100_P49841	DIKPQNLLLDPDTAVLK	260	Lys2	-3.5
HPK1	UniRef100_Q92918	DIKGANILINDAGEVR	261	Lys2	88.2
IKKa	UniRef100_O15111	DLKPENIVLQDVGGK	262	Lys2	-3.1
IKKb	UniRef100_O14920	DLKPENIVLQQGEQR	263	Lys2	-12.2
IKKe	UniRef100_Q14164	SGELVAVKVFNTTSYLRPR	264	Lys1	-3.9
ILK	UniRef100_Q13418	WQGNDIVVKVLK	265	Lys1	-0.4
ILK	UniRef100_Q13418	ISMADVKFSFQCPGR	266	Protein Kinase Domain	6.8
IRAK1	UniRef100_P51617	AIQFLHQDSPSLIHGDIKSSNVLLDER	267	Lys2	7.6
IRAK3	UniRef100_Q9Y616	VEIQNLTYAVKLFK	268	Lys1	-7.1

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
IRAK4	UniRef100_Q9NWZ3	DIKSANILLDEAFTAK	269	Lys2	6.3
IRE1	UniRef100_O75460	DLKPHNILISMPNAHGK	270	Lys2	-0.6
ITPK1	UniRef100_Q13572	ESIFFNSHNVSKPESSSVLTELDKIEGVFERPSDEVIR	271	ATP	-16.2
JAK1 domain1	UniRef100_P23458	QLASALSYLEDKDLVHGNVCTKNLLLAR	272	Protein Kinase Domain	9.0
JAK1 domain2	UniRef100_P23458	IGDFGLTKAIETDKEYYTVK	273	Activation Loop	29.3
JAK1 domain2	UniRef100_P23458	YDPEGDNTGEQVAVKSLKPESGGNHIADLKK	274	Lys1	24.0
JAK3 domain2	UniRef100_P52333	IADFGLAKLLPLDKDYYVVR	275	Activation Loop	-4.3
JNK1, JNK2, JNK3	UniRef100_P45983, UniRef100_P53779, UniRef100_P45984	DLKPSNIVVK	276	Lys2	31.5
KHS1	UniRef100_Q9Y4K4	NVHTGELAAVKIIK	277	Lys1	33.9
KHS2	UniRef100_Q8IVH8	NVNTGELAAIKVIK	278	Lys1	3.8
KSR1	UniRef100_Q8IVT5	SKNVFYDNGKVVITDFGLFGISGVVR	279	Activation Loop	-0.2
KSR1, KSR2	UniRef100_Q6VAB6, UniRef100_Q8IVT5	SKNVFYDNGK	280	Activation Loop	1.4
LATS1	UniRef100_O95835	ALYATKTLR	281	Lys1	15.8
LATS2	UniRef100_Q9NRM7	DIKPDNILIDLDGHIK	282	Lys2	0.8
LCK	UniRef100_P06239	EGAKFPIKWTAPEAINYGTFTIK	283	Activation Loop	83.8
LKB1	UniRef100_Q15831	DIKPGNLLLTTGGTLK	284	Lys2	3.6
LOK	UniRef100_O94804	DLKAGNVLMTLEGDIR	285	Lys2	28.8
LRRK2	UniRef100_Q5S007	DLKPHNVLLFTLYPNAAIIAK	286	Lys2	-11.8
LYN	UniRef100_P07948	VAVKTLKPGTMSVQAFLEEANLMK	287	Lys1	85.7
MAP2K1	UniRef100_Q02750	IMHRDVKPSNILVNSR	288	Lys2	6.6
MAP2K1, MAP2K2	UniRef100_P36507, UniRef100_Q02750	KLIHLEIKPAIR	289	Lys1	9.4
MAP2K1, MAP2K2	UniRef100_P36507, UniRef100_Q02750	DVKPSNILVNSR	290	Lys2	2.2
MAP2K2	UniRef100_P36507	HQIMHRDVKPSNILVNSR	291	Lys2	3.9
MAP2K3	UniRef100_P46734	DVKPSNVLINK	292	Lys2	-1.0
MAP2K4	UniRef100_P45985	DIKPSNILLDR	293	Lys2	0.4
MAP2K5	UniRef100_Q13163	DVKPSNMLVNTR	294	Lys2	-46.0

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
MAP2K6	UniRef100_P52564	DVKPSNVLINALGQVK	295	Lys2	2.0
MAP2K7	UniRef100_O14733	DVKPSNILLDER	296	Lys2	19.3
MAP3K1	UniRef100_Q13233	DVKGANLLIDSTGQR	297	Lys2	27.5
MAP3K2	UniRef100_Q9Y2U5	ELAVKQVQFDPDSPETSK EVNALECEIQLLK	298	Lys1	-1.1
MAP3K2, MAP3K3	UniRef100_Q9Y2U5, UniRef100_Q99759	DIKGANILR	299	Lys2	8.4
MAP3K3	UniRef100_Q99759	ELASKQVQFDPDSPETSKE VSALECEIQLLK	300	Lys1	10.0
MAP3K4	UniRef100_Q9Y6R4	DIKGANIFLTSSGLIK	301	Lys2	17.3
MAP3K5	UniRef100_Q99683	DIKGDNVLINTYSGVLK	302	Lys2	-10.2
MAP3K6	UniRef100_O95382	DIKGDNVLINTFSGLLK	303	Lys2	2.1
MARK2, MARK3	UniRef100_P27448, UniRef100_Q7KZI7	DLKAENLLLDADMNIK	304	Lys2	-15.6
MARK3	UniRef100_P27448	EVAIKIIDKTQLNPTSLQK	305	Lys1	2.6
MARK3, MARK4	UniRef100_Q96L34, UniRef100_P27448	EVAIKIIDK	306	Lys1	-7.5
MARK4	UniRef100_Q96L34	DLKAENLLLDAEANIK	307	Lys2	-28.5
MAST1, MAST2	UniRef100_Q6P0Q8, UniRef100_Q9Y2H9	DLKPDNLLITSMGHIK	308	Lys2	-24.8
MAST3	UniRef100_O60307	DLKPDNLLITSLGHIK	309	Lys2	-4.7
MASTL	UniRef100_Q96GX5	GAFGKVYLGQK	310	ATP Loop	1.1
MASTL	UniRef100_Q96GX5	LYAVKVVK	311	Lys1	-7.6
MELK	UniRef100_Q14680	DLKPENLLFDEYHK	312	Lys2	-3.0
MER, TYRO3	UniRef100_Q06418, UniRef100_Q12866	KIYSGDYYR	313	Activation Loop	21.2
MET	UniRef100_P08581	DMYDKEYYSVHNK	314	Activation Loop	5.7
MLK3	UniRef100_Q16584	DLKSNNILLLQPIESDDME HK	315	Lys2	-0.2
MLK4	UniRef100_Q5TCX8	DLKSSNILLLEK	316	Lys2	1.5
MLKL	UniRef100_Q8NB16	APVAIKVFK	317	Lys1	-5.5
MPSK1	UniRef100_O75716	DLKPTNILLGDEGQPVLM DLGSMNQACIHVEGSR	318	Lys2	-2.3
MSK1 domain1	UniRef100_O75582	DIKLENILLDSNGHVVLTD FGLSK	319	Lys2	-21.5
MSK2 domain1	UniRef100_O75676	DLKLENVLLDSEGHIVLTD FGLSK	320	Lys2	-8.1
MST1	UniRef100_Q13043	ETGQIVAIKQVPVESDLQE IIK	321	Lys1	7.5

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
MST2	UniRef100_Q13188	ESGQVVAIKQVPVESDLQEIIK	322	Lys1	8.6
MST3	UniRef100_Q9Y6E0	DIKAANVLLSEHGEVK	323	Lys2	-8.9
MST4	UniRef100_Q9P289	TQQVVAIKIIDLEEAEDEIEDIQQEITVLSQCDSSYVTK	324	Lys1	-37.3
MST4, YSK1	UniRef100_O00506, UniRef100_Q9P289	DIKAANVLLSEQGDVK	325	Lys2	-2.4
MYO3A, MYO3B	UniRef100_Q8NEV4, UniRef100_Q8WXR4	DVKGNNILLTTEGGVK	326	Lys2	22.9
NDR1	UniRef100_Q15208	DIKPDNLLLDSK	327	Lys2	2.3
NDR2	UniRef100_Q9Y2H1	DIKPDNLLLDAK	328	Lys2	9.8
NEK1	UniRef100_Q96PY6	DIKSQNIFLTK	329	Lys2	-7.1
NEK2	UniRef100_P51955	DLKPANVFLDGK	330	Lys2	12.5
NEK3	UniRef100_P51956	SKNIFLTQNGK	331	Activation Loop	-8.6
NEK4	UniRef100_P51957	DLKTQNVFLTR	332	Lys2	2.8
NEK6, NEK7	UniRef100_Q8TDX7, UniRef100_Q9HC98	DIKPANVFITATGVVK	333	Lys2	-1.8
NEK7	UniRef100_Q8TDX7	AACLLDGVPVALKK	334	Lys1	2.7
NEK8	UniRef100_Q86SG6	DLKTQNILLDK	335	Lys2	-7.8
NEK9	UniRef100_Q8TD19	DIKTLNIFLTK	336	Lys2	-10.7
NLK	UniRef100_Q9UBE8	DIKPGNLLVNSNCVLK	337	Lys2	22.3
OSR1	UniRef100_C9JIG9, UniRef100_O95747	DVKAGNILLGEDGSVQIADFGVSAFLATGGDITR	338	Lys2	32.2
p38a	UniRef100_Q16539	DLKPSNLAVNEDCELK	339	Lys2	76.1
p38a	UniRef100_Q16539	QELNKTIWEVPER	340	Protein Kinase Domain	88.4
p38d, p38g	UniRef100_O15264, UniRef100_P53778	DLKPGNLAVNEDCELK	341	Lys2	51.5
p70S6K	UniRef100_P23443	DLKPENIMLNHQGHVK	342	Lys2	-74.1
p70S6Kb	UniRef100_Q9UBS0	DLKPENIMLSSQGHIK	343	Lys2	3.5
PAN3	UniRef100_Q58A45	VMDPTKILITGK	344	ATP	7.3
PCTAIRE1	UniRef100_Q00536	SKLTDNLVALKEIR	345	Lys1	53.3
PCTAIRE2, PCTAIRE3	UniRef100_Q00537, UniRef100_Q07002	SKLTENLVALKEIR	346	Lys1	72.9
PDHK1	UniRef100_Q15118	SPGQPIQVVYVPSHLYHMVFELFKNAMR	347	ATP	-23.7
PEK	UniRef100_Q9NZJ5	DLKPSNIFFTMDDVVK	348	Lys2	-21.9
PFTAIRE1	UniRef100_O94921	LVALKVIR	349	Lys1	64.0

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
PHKg1	UniRef100_Q16816	DLKPENILLDDNMNIK	350	Protein Kinase Domain	-0.9
PHKg2	UniRef100_P15735	ATGHEFAVKIMEVTAER	351	Lys1	7.1
PI4K2B	UniRef100_Q8TCG2	SEEPYGQLNPKWTK	352	ATP	33.4
PI4KA, PI4KAP2	UniRef100_A4QPH2, UniRef100_P42356	SGTPMQSAAKAPYLAK	353	ATP	2.1
PI4KB	UniRef100_Q9UBF8	VPHTQAVVLNSKDK	354	ATP	23.7
PIK3C2B	UniRef100_O00750	VIFKCGDDLRQDMLTLQ MIR	355	ATP	-15.7
PIK3C3	UniRef100_Q8NEB9	TEDGGKYPVIFKHGDDLR	356	ATP	-29.7
PIK3CB	UniRef100_P42338	VFGEDSVGVIFKNGDDLR QDMLTLQMLR	357	ATP	-3.9
PIK3CD	UniRef100_O00329	VNWLAHNVSKDNRQ	358	ATP	-22.8
PIK3CG	UniRef100_P48736	KKPLWLEFK	359	ATP	-20.1
PIP4K2A	UniRef100_P48426	AKELPTLKDNDFINEGQK	360	ATP	-19.5
PIP4K2C	UniRef100_Q8TBX8	TLVIKEVSSEDIADMHSNL SNYHQYIVK	361	ATP	-7.3
PIP5K3	UniRef100_Q9Y2I7	GGKSGAAFYATEDDRFILK	362	ATP	21.7
PITSLRE	UniRef100_P21127	DLKTSNLLLSHAGILK	363	Lys2	10.2
PKCa, PKCb	UniRef100_P05771, UniRef100_P17252	DLKLDNVMLDSEGHIK	364	Lys2	-86.4
PKCe	UniRef100_Q02156	DLKLDNILLDAEGHCK	365	Lys2	27.7
PKCi	UniRef100_P41743	IYAMKVVK	366	Lys1	-54.3
PKD2	UniRef100_Q9BZL6	DVAVKVIDK	367	Lys1	-5.4
PKN1	UniRef100_Q16512	VLLSEFRPSGELFAIKALK	368	Lys1	1.8
PKR	UniRef100_P19525	DLKPSNIFLVDTK	369	Lys2	-1.7
PLK1	UniRef100_P53350	CFEISDADTKEVFAGKIVP K	370	Lys1	18.8
PLK4	UniRef100_O00444	AESIHTGLEVAIKMIDKK	371	Lys1	-17.3
PRP4	UniRef100_Q13523	CNILHADIKPDNILVNESK	372	Lys2	-5.5
PRPK	UniRef100_Q96S44	FLSGLELVKQGAEAR	373	ATP Loop	-16.0
PYK2	UniRef100_Q14289	YIEDEDYYKASVTR	374	Activation Loop	30.5
RIPK1	UniRef100_Q13546	DLKPENILVDNDFHIK	375	Lys2	23.1
RIPK3	UniRef100_Q9Y572	DLKPSNVLLDPELHVK	376	Lys2	70.2
ROCK1, ROCK2	UniRef100_O75116, UniRef100_Q13464	DVKPDNMLLDK	377	Lys2	-0.2

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
RSK1 domain1	UniRef100_Q15418	DLKPENILLDEEGHIKLTDF GLSKEAIDHEK	378	Lys2	-29.6
RSK1 domain1, RSK2 domain1, RSK3 domain1	UniRef100_P51812, UniRef100_Q15418, UniRef100_Q15349	DLKPENILLDEEGHIK	379	Lys2	-25.1
RSK1 domain2	UniRef100_Q15418	DLKPSNILYVDESGNPECL R	380	Lys2	1.0
RSK2 domain1	UniRef100_P51812	DLKPENILLDEEGHIKLTDF GLSKESIDHEK	381	Lys2	-36.7
RSK2 domain2	UniRef100_P51812	DLKPSNILYVDESGNPESIR	382	Lys2	2.8
RSK3 domain1	UniRef100_Q15349	DLKPENILLDEEGHIKITDF GLSK	383	Lys2	-37.8
RSKL1	UniRef100_Q96S38	VLGVIDKVLLVMDTR	384	ATP	21.8
SGK3	UniRef100_Q96BR1	FYAVKVLQK	385	Lys1	16.6
SLK	UniRef100_Q9H2G2	DLKAGNILFTLDGDIK	386	Lys2	13.8
SMG1	UniRef100_Q96Q15	DTVTIHSVGGTITILPTKTK PK	387	ATP	-3.6
SNRK	UniRef100_Q9NRH2	DLKPENVVFFEK	388	Lys2	24.5
SRC	UniRef100_P12931	VAIKTLKPGTMSPEAFLQE AQVMKK	389	Lys1	82.7
SRPK1	UniRef100_Q96SB4	IIHTDIKPENILLSVNEQYIR	390	Lys2	-9.1
SRPK1, SRPK2	UniRef100_P78362, UniRef100_Q96SB4	FVAMKVVK	391	Lys1	-38.7
STK33	UniRef100_Q9BYT3	DLKLENIMVK	392	Lys2	-8.0
STLK5	UniRef100_Q7RTN6	YSVKVLPWLSPEVLQQNL QGYDAK	393	Activation Loop	12.0
SYK	UniRef100_P43405	ISDFGLSKALR	394	Activation Loop	6.6
TAK1	UniRef100_O43318	DLKPPNLLLVAGGTVLK	395	Lys2	0.4
TAO1, TAO3	UniRef100_Q7L7X3, UniRef100_Q9H2K8	DIKAGNILLTEPGQVK	396	Lys2	87.1
TAO2	UniRef100_Q9UL54	DVKAGNILLSEPGLVK	397	Lys2	92.0
TBK1	UniRef100_Q9UHD2	TGDLFAIKVFNNISFLRPV DVQMR	398	Lys1	-18.0
TEC	UniRef100_P42680	YVLDDQYTSSSGAKFPVK	399	Activation Loop	20.6
TLK1	UniRef100_Q9UKI8	YLNEIKPPIIHYDLKPGNILL VDGTACGEIK	400	Lys2	11.5

Kinase	Reference	Sequence	SEQ ID NO:	Labeling Site	Cmpd. A-14 (1.0 μM)
TLK2	UniRef100_Q86UE8	YLNEIKPPIIHYDLKPGNILLVNGTACGEIK	401	Lys2	10.2
ULK1	UniRef100_O75385	DLKPQNILLSNPAGR	402	Lys2	8.8
ULK3	UniRef100_D3DW67	NISHLDLKPQNILLSSLEKPHLK	403	Lys2	27.1
VRK2	UniRef100_Q86Y07	MLDVLEYIHENEYVHGDIKAANLLLGYK	404	Lys2	-1.2
Wnk1, Wnk2	UniRef100_Q9Y3S1, UniRef100_D3DUP1	GSFKTVYK	405	ATP Loop	11.2
Wnk1, Wnk2, Wnk3	UniRef100_Q9Y3S1, UniRef100_D3DUP1, UniRef100_Q9BYP7	DLKCDNIFITGPTGSVK	406	Lys2	-1.1
YANK3	UniRef100_Q86UX6	DVKPDNILLDER	407	Lys2	-43.1
ZAK	UniRef100_Q9NYL2	WISQDKEVAVKK	408	Lys1	75.8
ZAP70	UniRef100_P43403	ISDFGLSKALGADDSYYTAR	409	Activation Loop	10.7
ZC1/HGK, ZC2/TNIK, ZC3/MINK	UniRef100_O95819, UniRef100_Q9UKE5, UniRef100_Q8N4C8	DIKGQNVLLTENAEVK	410	Lys2	57.5
ZC2/TNIK	UniRef100_Q9UKE5	TGQLAAIKVMDVTGDEEEEIKQEINMLKK	411	Lys1	46.0

Example 3. p-BTK and p-Hck inhibition

Protocol for PhosFlow Studies

[00249] PhosFlow was performed to detect levels of phosphorylation for BTK-pY223 (BD Biosciences) and Hck-pY410 (Abcam) in BCWM.1 cells, in BCWM cells that stably overexpress HCK (BCWM.1_HCK-wt) and in BCWM.1 cells that stably overexpress the T338M mutant of HCK (BCWM.1_HCK-mu).. Cells were fixed with BD Phosflow Fix Buffer I (BD Biosciences) at 37ºC for 10 min, then washed twice with BD Phosflow Perm/Wash Buffer I (BD Biosciences). Cells were suspended in BD Phosflow Perm/Wash Buffer I at 10 million/ml and antibodies aliquoted to flow tubes with 100μl cells. Cells were incubated at room temperature for 30 min in the dark. Cells were washed twice with BD Phosflow Perm/Wash Buffer I before performing flow analysis using a BD™ FACSCanto II flow cytometer.

Protocol for apoptosis analysis

[00250] Apoptosis analysis of WM patient primary lymphoplasmacytic cells (LPCs) was preformed following A-5 and A-14 treatment of Bone marrow mononuclear cells (BMMC) from WM patients for 24 hours. Apoptosis analysis was performed using Annexin V/ Propidium iodide staining with the Apoptosis Detection Kit I (BD Pharmingen) in CD19-APC-cy7 antibody (BD Pharmingen) gated LPCs population.

Results

[00251] PhosFlow studies indicate both A-5 and A-14 inhibit Hck and BTK phosphorylation in BCWM.1 cells and BCWM.1 cells with genetic engineered expression of Hck wild type (-wt) and T338M gatekeeper mutant (-mu) with both 0.5μM and 0.1μM doses (shown by *Table 6* and *Table 7*, respectively). In addition, the expression of Hck-wt or Hck-mu increased the resistance to the inhibition of both Hck and BTK phosphorylations by A-5 and A-14, with more resistance presented in Hck-mu expressing BCWM.1 cells. Both A-5 and A-14 induced significant apoptosis in WM patient primary LPCs compared with DMSO control, as shown in *Table 8*.

Table 6.

Relative MFI %	p-BTK						p-Hck					
	BCWM.1		BCWM.1_Hck-wt		BCWM.1_Hck-mu		BCWM.1		BCWM.1_Hck-wt		BCWM.1_Hck-mu	
(0.5μM drugs)	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min
DMSO	100	100	100	100	100	100	100	100	100	100	100	100
A-5	56.3	42.3	73.6	69.9	100.7	90.4	68.2	49	80.4	77.7	102.2	81.1
A-14	51.5	27.4	65.6	29.7	112.1	83.9	59.3	35.6	68.6	41.5	89.7	52.3

Table 7.

Relative MFI %	p-BTK						p-Hck					
	BCWM.1		BCWM.1_Hck-wt		BCWM.1_Hck-mu		BCWM.1		BCWM.1_Hck-wt		BCWM.1_Hck-mu	
(0.1μM drugs)	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min	15 min	90 min
DMSO	100	100	100	100	100	100	100	100	100	100	100	100
A-5	68.1	52.7	82.1	78.3	70.9	70.4	76.3	50.5	76	80.6	95.3	69.6
A-14	81.8	50.1	76.3	72	75.3	61.2	73.6	57.8	75.8	78.9	83.1	63.7

Table 8.

	Treatments	Dose (1.0 μM)		Dose (0.5 μM)		Dose (0.2 μM)	
		Apoptosis (%)	Apoptosis Relative to DMSO	Apoptosis (%)	Apoptosis Relative to DMSO	Apoptosis (%)	Apoptosis Relative to DMSO
Patient 1	Untreated	40.9	114.30%				
	DMSO	39.2	100%				
	A-5	57.7	147.20%				
Patient 2	N	14.2	97.30%				
	DMSO	14.6	100%				
	A-5	28.9	197.90%				
Patient 3	N	14.529	95.49%				
	DMSO	15.216	100.00%				
	A-5	29.48	193.70%				
Patient 4	N	29.83	103.00%				
	DMSO	29.75	100.00%				
	A-5	48.56	163.20%				
Patient 5	N	18.69	110.70%				
	DMSO	16.89	100%				
	A-5	30.5	180.60%	23.25	137.70%		
	A-14	46.86	277.40%	39.24	232.30%		
Patient 6	N	8.66	117.50%				
	DMSO	7.37	100%				
	A-5	17.82	241.80%				
	A-14	20.88	283.30%				
Patient 7	DMSO	6.46	100.00%				
	A-5	18.2	281.70%	17.23	266.70%		
	A-14	31.51	487.80%	22.62	350.20%		
Patient 8	DMSO	5.38	100.00%				
	A-5	17.31	321.75%	11.04	205.20%		
	A-14	31.58	586.99%	12.9	239.78%		
Patient 9	DMSO	7.6	100.00%				
	A-14	43.7	575.00%			24.8	326.32%
Patient 10	N	17.6	113.50%				
	DMSO	15.5	100%				
	A-5	28.7	185.20%			21.5	138.70%
	A-14	52	335.50%			27.9	180.00%
Patient 11	N	26.2	112.70%				
	DMSO	25.5	100%				
	A-5	47	184.30%			30.2	118.40%
	A-14	71.8	281.60%			53.1	208.20%

EQUIVALENTS AND SCOPE

[00252] 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.

[00253] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should 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.

[00254] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

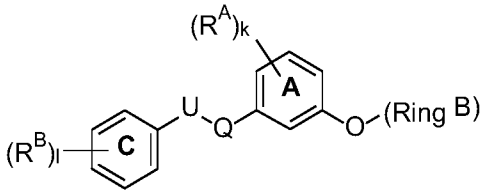
[00255] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art

will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



,

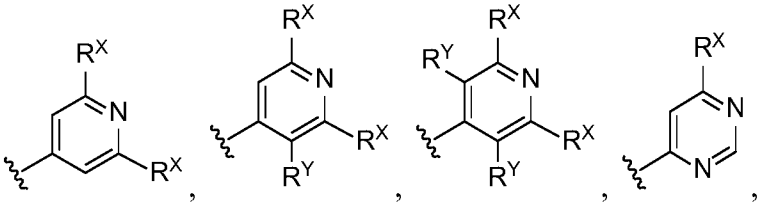
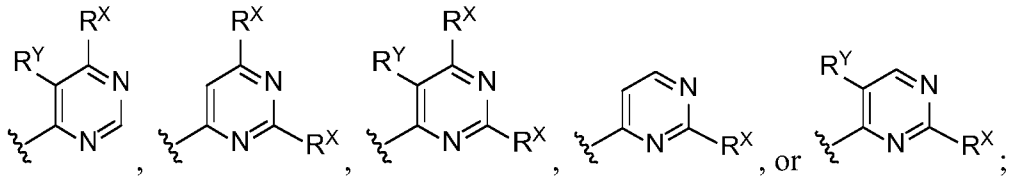
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof;

wherein:

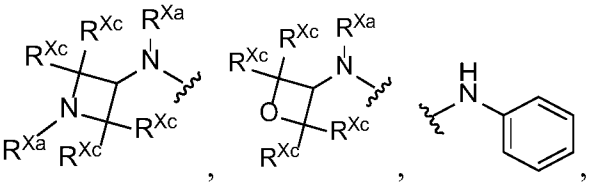
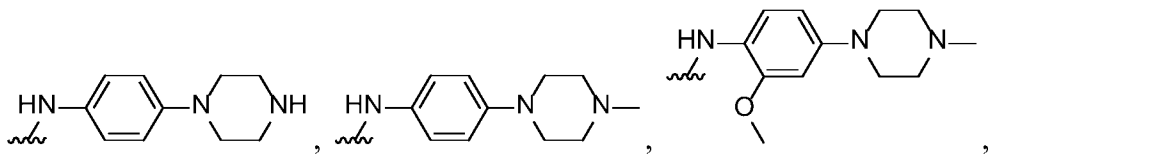
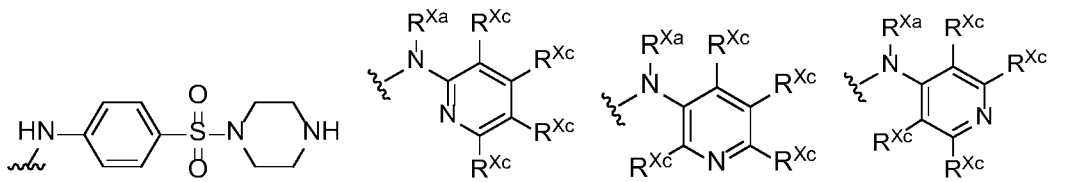
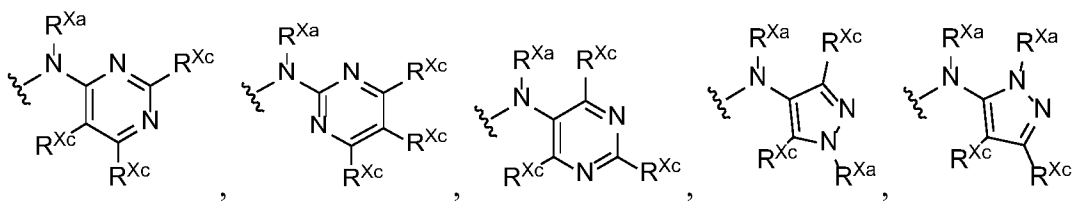
each instance of R^A is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, $–OR^{A1}$, $–N(R^{A1})_2$, –CN, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}S(=O)_2R^{A1}$, $–S(=O)_2R^{A1}$, or $–S(=O)_2N(R^{A1})_2$;

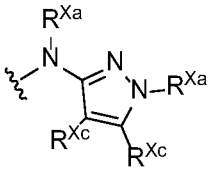
each instance of R^B is independently selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $–OR^{A1}$, $–N(R^{A1})_2$,–CN, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}S(=O)_2R^{A1}$, $–S(=O)_2R^{A1}$, or $–S(=O)_2N(R^{A1})_2$, provided that at least one instance of R^B is optionally substituted heterocyclyl, optionally substituted $–(CH_2)$(heterocyclyl), optionally substituted $–(CH_2)_2$(heterocyclyl), or optionally substituted $–(CH_2)_3$(heterocyclyl);

each instance of R^{A1} is independently selected from the group consisting of hydrogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, and a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form an optionally substituted heterocyclic ring;

Ring B is of the formula:  ,  , or ;

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

each instance of R^X is independently selected from the group consisting of R^D, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, and $-N(R^{A1})(R^{Xa})$, provided that at least one instance of R^X is $-NH_2$, $-NH(acyl)$, $-N(R^{A1})N(R^{A1})_2$,  ,  ,  ,  .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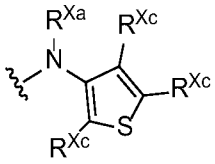
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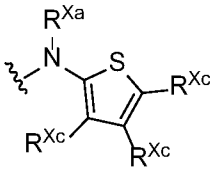
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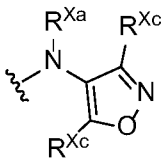
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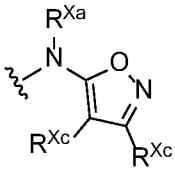
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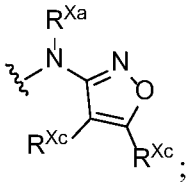

;

each instance of R^{Xa} is 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, optionally substituted heteroaryl, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-S(=O)R^{A1}$, $-S(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, $-S(=O)_2OR^{A1}$, $-S(=O)_2N(R^{A1})_2$, $-N(R^{A1})_2$, and nitrogen protecting groups;

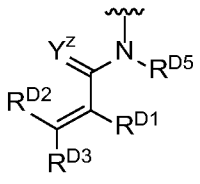
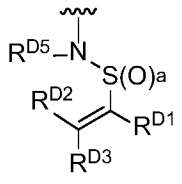
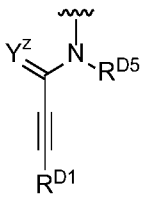
each instance of R^{Xc} is selected from the group consisting of hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-N_3$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-NR^{A1}S(=O)_2R^{A1}$, $-NR^{A1}S(=O)R^{A1}$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, $-OC(=O)N(R^{A1})_2$, $-S(=O)R^{A1}$, $-S(=O)N(R^{A1})_2$, $-S(=O)_2R^{A1}$, and $-S(=O)_2N(R^{A1})_2$;

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

l is 1, 2, 3, 4, or 5;

Q and U are taken together to be $-NR^A(C=O)-$ or $-(C=O)NR^A-$;

R^D is an electrophilic moiety of any one of Formulae (**i-1**)-(**i-18**):


(**i-1**),

(**i-2**),

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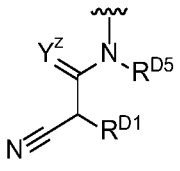
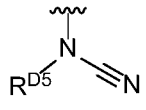

(**i-4**),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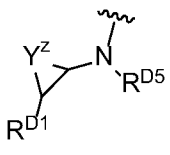
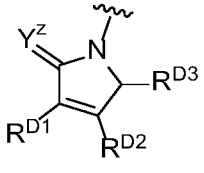
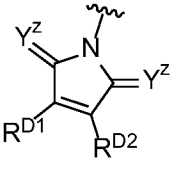

(**i-6**),

(**i-7**),

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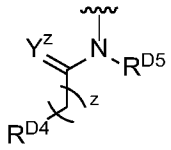
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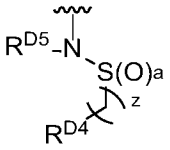
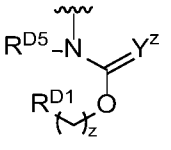

(**i-10**),

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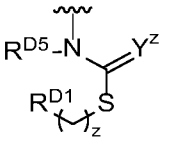
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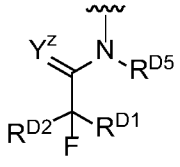
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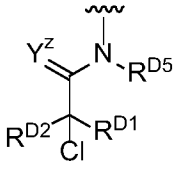
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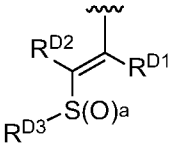
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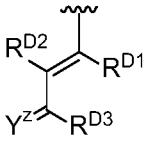
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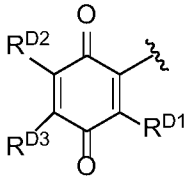
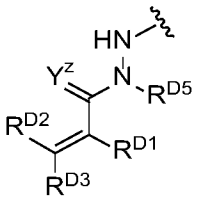

(**i-17**), and

(**i-18**);

R^{D1} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D1a}$, $–N(R^{D1a})_2$, $–SR^{D1a}$, $–CH_2OR^{D1a}$, $–CH_2N(R^{D1a})_2$, $–CH_2SR^{D1a}$, $–C(=O)R^{D1a}$, $–C(=O)OR^{D1a}$, $–C(=O)SR^{D1a}$, $–C(=O)N(R^{D1a})_2$, $–C(=S)R^{D1a}$, $–C(=S)OR^{D1a}$, $–C(=S)SR^{D1a}$, $–C(=S)N(R^{D1a})_2$, $–C(=NR^{D1a})R^{D1a}$, $–C(=NR^{D1a})OR^{D1a}$, $–C(=NR^{D1a})SR^{D1a}$, and $–C(=NR^{D1a})N(R^{D1a})_2$, wherein each occurrence of R^{D1a} 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^{D1a} groups are joined to form an optionally substituted heterocyclic ring;

R^{D2} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D2a}$, $–N(R^{D2a})_2$, $–SR^{D2a}$, $–CH_2OR^{D2a}$, $–CH_2N(R^{D2a})_2$, $–CH_2SR^{D2a}$, $–C(=O)R^{D2a}$, $–C(=O)OR^{D2a}$, $–C(=O)SR^{D2a}$, $–C(=O)N(R^{D2a})_2$, $–C(=S)R^{D2a}$, $–C(=S)OR^{D2a}$, $–C(=S)SR^{D2a}$, $–C(=S)N(R^{D2a})_2$, $–C(=NR^{D2a})R^{D2a}$, $–C(=NR^{D2a})OR^{D2a}$, $–C(=NR^{D2a})SR^{D2a}$, and $–C(=NR^{D2a})N(R^{D2a})_2$, wherein each occurrence of R^{D2a} 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^{D2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{D3} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D3a}$, $–N(R^{D3a})_2$, $–SR^{D3a}$, $–CH_2OR^{D3a}$, $–CH_2N(R^{D3a})_2$, $–CH_2SR^{D3a}$, $–C(=O)R^{D3a}$, $–C(=O)OR^{D3a}$, $–C(=O)SR^{D3a}$, $–C(=O)N(R^{D3a})_2$, $–C(=S)R^{D3a}$, $–C(=S)OR^{D3a}$, $–C(=S)SR^{D3a}$, $–C(=S)N(R^{D3a})_2$, $–C(=NR^{D3a})R^{D3a}$, $–C(=NR^{D3a})OR^{D3a}$, $–C(=NR^{D3a})SR^{D3a}$, and $–C(=NR^{D3a})N(R^{D3a})_2$, wherein each occurrence of R^{D3a} 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^{D3a} groups are joined to form an optionally substituted heterocyclic ring;

optionally R^{D1} and R^{D3}, or R^{D2} and R^{D3}, or R^{D1} and R^{D2} are joined to form an optionally substituted carbocyclic or optionally substituted heterocyclic ring;

R^{D4} is a leaving group;

R^{D5} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

Y^Z is –O–, –S–, or $–NR^{D6}–$, wherein R^{D6} is hydrogen, substituted or unsubstituted C_{1-6} alkyl, or a nitrogen protecting group;

a is 1 or 2; and

z is 0, 1, 2, 3, 4, 5, or 6;wherein each optional substituent is independently 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, $–C(OR^{cc})_2$, $–CO_2R^{aa}$, $–OC(=O)R^{aa}$, $–OCO_2R^{aa}$, $–C(=O)N(R^{bb})_2$, $–OC(=O)N(R^{bb})_2$, $–NR^{bb}C(=O)R^{aa}$, $–NR^{bb}CO_2R^{aa}$, $–NR^{bb}C(=O)N(R^{bb})_2$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{bb})OR^{aa}$, $–OC(=NR^{bb})R^{aa}$, $–OC(=NR^{bb})OR^{aa}$, $–C(=NR^{bb})N(R^{bb})_2$, $–OC(=NR^{bb})N(R^{bb})_2$, $–NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $–C(=O)NR^{bb}SO_2R^{aa}$, $–NR^{bb}SO_2R^{aa}$, $–SO_2N(R^{bb})_2$, $–SO_2R^{aa}$, $–SO_2OR^{aa}$, $–OSO_2R^{aa}$, $–S(=O)R^{aa}$, $–OS(=O)R^{aa}$, $–Si(R^{aa})_3$, $–OSi(R^{aa})_3$ $–C(=S)N(R^{bb})_2$, $–C(=O)SR^{aa}$, $–C(=S)SR^{aa}$, $–SC(=S)SR^{aa}$, $–SC(=O)SR^{aa}$, $–OC(=O)SR^{aa}$, $–SC(=O)OR^{aa}$, $–SC(=O)R^{aa}$, $–P(=O)_2R^{aa}$, $–OP(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–OP(=O)(R^{aa})_2$, $–OP(=O)(OR^{cc})_2$, $–P(=O)_2N(R^{bb})_2$, $–OP(=O)_2N(R^{bb})_2$, $–P(=O)(NR^{bb})_2$, $–OP(=O)(NR^{bb})_2$, $–NR^{bb}P(=O)(OR^{cc})_2$, $–NR^{bb}P(=O)(NR^{bb})_2$, $–P(R^{cc})_2$, $–P(R^{cc})_3$, $–OP(R^{cc})_2$, $–OP(R^{cc})_3$, $–B(R^{aa})_2$, $–B(OR^{cc})_2$, $–BR^{aa}(OR^{cc})$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl,

C_{2-10} alkynyl, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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 $=NOR^{cc}$;

wherein:

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, heteroC_{1-10} alkyl, heteroC_{2-10}alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, 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, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, heteroC_{1-10}alkyl, heteroC_{2-10}alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

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, heteroC_{1-10} alkyl, heteroC_{2-10} alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, 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, $–OR^{ee}$, $–ON(R^{ff})_2$, $–N(R^{ff})_2$, $–N(R^{ff})_3{}^+X^-$, $–N(OR^{ee})R^{ff}$, –

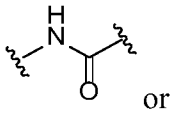
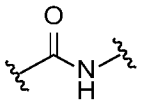
SH, –SR^{ee}, –SSR^{ee}, –$C(=O)R^{ee}$, –CO_2H, –CO_2R^{ee}, –$OC(=O)R^{ee}$, –OCO_2R^{ee}, –$C(=O)N(R^{ff})_2$, –$OC(=O)N(R^{ff})_2$, –$NR^{ff}C(=O)R^{ee}$, –$NR^{ff}CO_2R^{ee}$, –$NR^{ff}C(=O)N(R^{ff})_2$, –$C(=NR^{ff})OR^{ee}$, –$OC(=NR^{ff})R^{ee}$, –$OC(=NR^{ff})OR^{ee}$, –$C(=NR^{ff})N(R^{ff})_2$, –$OC(=NR^{ff})N(R^{ff})_2$, –$NR^{ff}C(=NR^{ff})N(R^{ff})_2$,–$NR^{ff}SO_2R^{ee}$, –$SO_2N(R^{ff})_2$, –$SO_2R^{ee}$, –$SO_2OR^{ee}$, –$OSO_2R^{ee}$, –$S(=O)R^{ee}$, –$Si(R^{ee})_3$, –$OSi(R^{ee})_3$, –$C(=S)N(R^{ff})_2$, –$C(=O)SR^{ee}$, –$C(=S)SR^{ee}$, –$SC(=S)SR^{ee}$, –$P(=O)_2R^{ee}$, –$P(=O)(R^{ee})_2$, –$OP(=O)(R^{ee})_2$, –$OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{2-6}alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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, heteroC_{1-6} alkyl, heteroC_{2-6}alkenyl, heteroC_{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, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

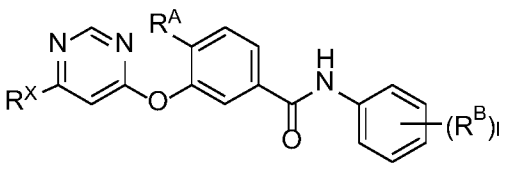
each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{2-6}alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–10 membered heterocyclyl or 5–10 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{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, –$CO_2(C_{1-6}$ 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, $-P(=O)_2(C_{1-6}\ alkyl)$, $-P(=O)(C_{1-6}\ alkyl)_2$, $-OP(=O)(C_{1-6}\ alkyl)_2$, $-OP(=O)(OC_{1-6}\ alkyl)_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, heteroC_{1-6}alkyl, heteroC_{2-6}alkenyl, heteroC_{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.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein Q and U are taken together to be  or  .

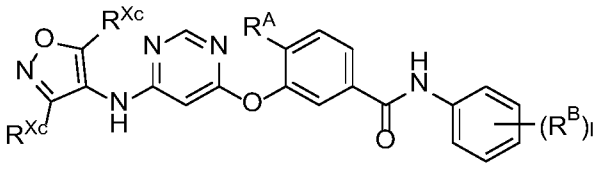
3. The compound of any one of claims 1 or 2, wherein the compound is of Formula (**A1**):



(**A1**),

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

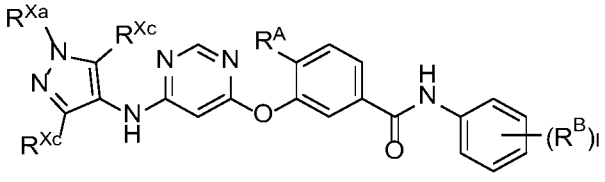
4. The compound of any one of claims 1-3, wherein the compound is of Formula (**A1-a**):



(**A1-a**)

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

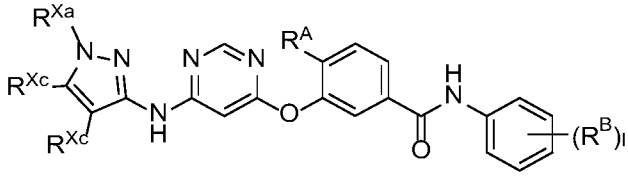
5. The compound of any one of claims 1-3, wherein the compound is of Formula (**A1-b**):



(**A1-b**)

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

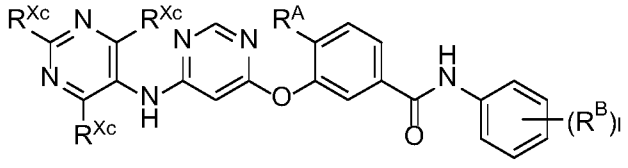
6. The compound of any one of claims 1-3, wherein the compound is of Formula (**A1-c**):



(**A1-c**)

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

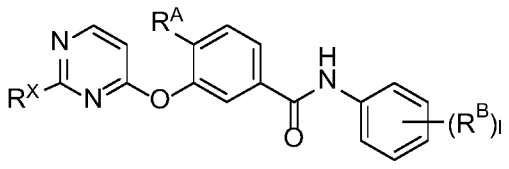
7. The compound of any one of claims 1-3, wherein the compound is of Formula (**A1-d**):



(**A1-d**)

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

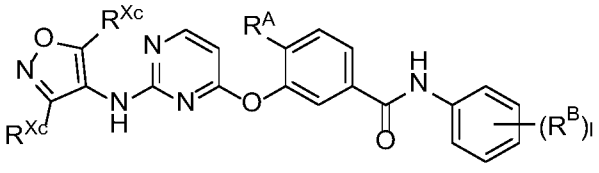
8. The compound of any one of claims 1 or 2, wherein the compound is of Formula (**A2**):



(**A2**),

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

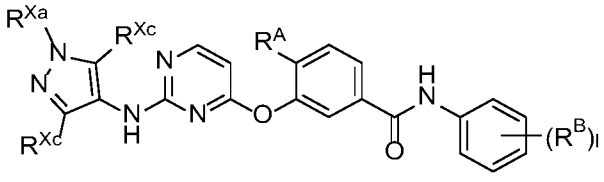
9. The compound of any one of claims 1, 2 or 8, wherein the compound is of Formula (**A2-a**):



(**A2-a**),

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

10. The compound of any one of claims 1, 2, or 8, wherein the compound is of Formula (**A2-b**):

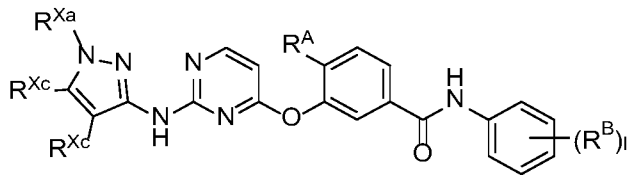


(**A2-b**),

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

wherein.

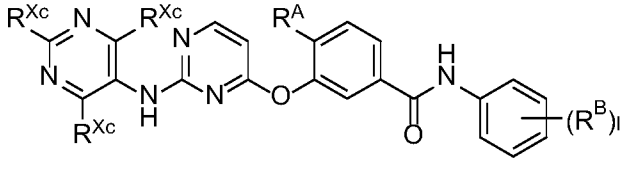
11. The compound of any one of claims 1, 2, or 8, wherein the compound is of Formula (**A2-c**):



(**A2-c**),

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

12. The compound of any one of claims 1, 2, or 8, wherein the compound is of Formula (**A2-d**):

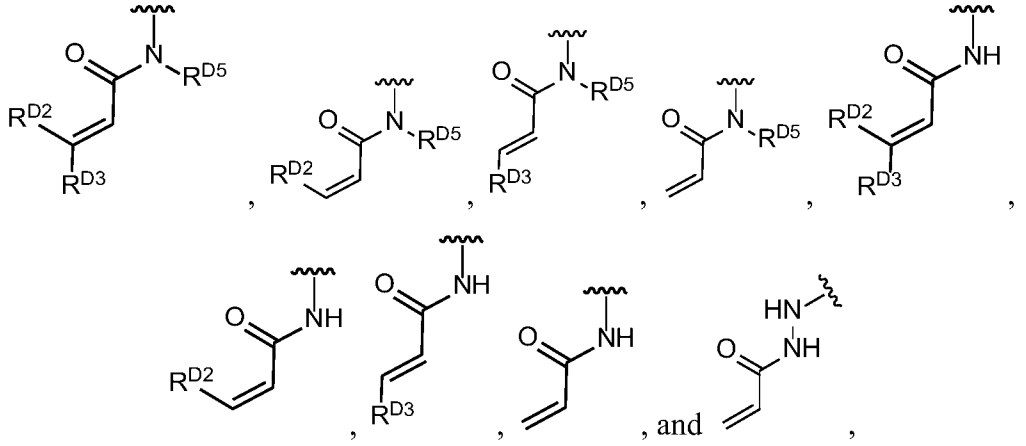


(**A2-d**),

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

13. The compound of any one of claims 1 or 2, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^D is a Michael acceptor.

14. The compound of claim 13 , or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^D is selected from the group consisting of:



wherein,

R^{D2} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D2a}$, $–N(R^{D2a})_2$, $–SR^{D2a}$, $–CH_2OR^{D2a}$, $–CH_2N(R^{D2a})_2$, $–CH_2SR^{D2a}$, $–C(=O)R^{D2a}$, $–C(=O)OR^{D2a}$, $–C(=O)SR^{D2a}$, $–C(=O)N(R^{D2a})_2$, $–C(=S)R^{D2a}$, $–C(=S)OR^{D2a}$, $–C(=S)SR^{D2a}$, $–C(=S)N(R^{D2a})_2$, $–C(=NR^{D2a})R^{D2a}$, $–C(=NR^{D2a})OR^{D2a}$, $–C(=NR^{D2a})SR^{D2a}$, and $–C(=NR^{D2a})N(R^{D2a})_2$, wherein each occurrence of R^{D2a} 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^{D2a} groups are joined to form an optionally substituted heterocyclic ring;

R^{D3} is selected from the group consisting of hydrogen, halogen, optionally substituted acyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, –CN, $–NO_2$, $–OR^{D3a}$, $–N(R^{D3a})_2$, $–SR^{D3a}$, $–CH_2OR^{D3a}$, $–CH_2N(R^{D3a})_2$, $–CH_2SR^{D3a}$, $–C(=O)R^{D3a}$, $–C(=O)OR^{D3a}$, $–C(=O)SR^{D3a}$, $–C(=O)N(R^{D3a})_2$, $–C(=S)R^{D3a}$, $–C(=S)OR^{D3a}$, $–C(=S)SR^{D3a}$, $–C(=S)N(R^{D3a})_2$, $–C(=NR^{D3a})R^{D3a}$,

$-C(=NR^{D3a})OR^{D3a}$, $-C(=NR^{D3a})SR^{D3a}$, and $-C(=NR^{D3a})N(R^{D3a})_2$, wherein each occurrence of R^{D3a} 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^{D3a} groups are joined to form an optionally substituted heterocyclic ring.

15. The compound of any one of claims 1-14, 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.

16. The compound of claim 15, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^A is methyl.

17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein l is 1.

18. The compound of claim 17, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^B is *meta* to the point of attachment of the amide linker, U.

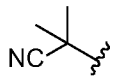
19. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein l is 2.

20. The compound of claim 19, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein two R^B groups are *meta* to the point of attachment of the amide linker, U.

21. The compound of claim 19, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is *meta* to the point of attachment of the amide linker, U; and the second R^B group is *para* to the point of attachment of the amide linker, U.

22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is substituted or unsubstituted C_{1-6}alkyl.

23. The compound of claim 22, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein, one R^B group is C_{1-6}alkyl substituted with one -CN group.

24. The compound of claim 23, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein, one R^B group is 

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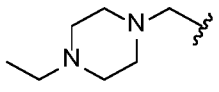
25. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is substituted or unsubstituted –CH_2–(piperazinyl).

26. The compound of claim 25, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is 

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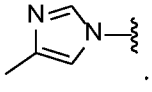
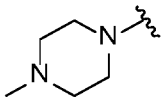
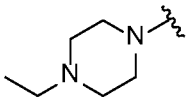
27. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein, one R^B group is haloalkyl.

28. The compound of claim 27, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is –CF_3.

29. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is substituted or unsubstituted imidazolyl.

30. The compound of claim 29, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is  .

31. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is substituted or unsubstituted piperazinyl.

32. The compound of claim 31, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is  or  .

33. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein one R^B group is substituted or unsubstituted morpholine.

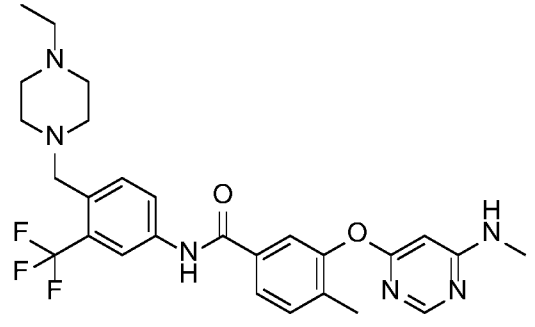
34. The compound of any one of claims 1-16 or 19-21, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein two R^B groups are substituted or unsubstituted morpholine.

35. The compound of any one of claims 1-34, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein all instances of R^{Xc} are hydrogen.

36. The compound of any one of claims 1-3, 5, 6, 8, 10, 11, 13-35, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^{Xa} is substituted or unsubstituted $C_{1\text{-}6}$alkyl.

37. The compound of claim 36, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R^{Xa} is methyl or ethyl.

38. A compound of the formula:



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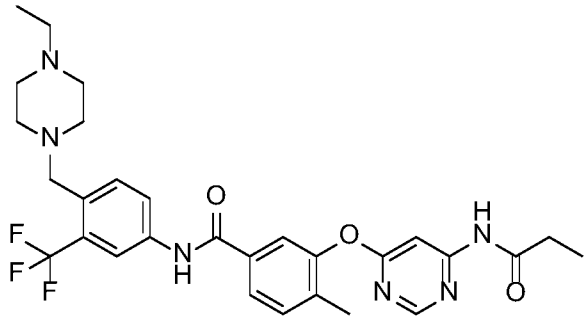

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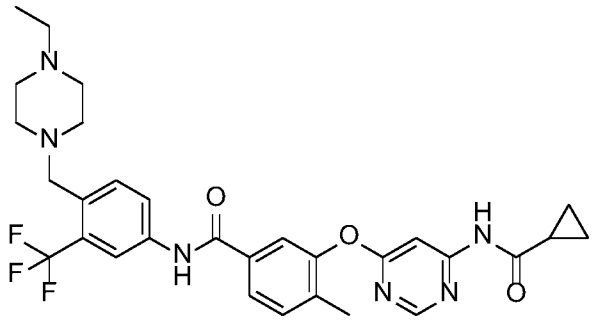

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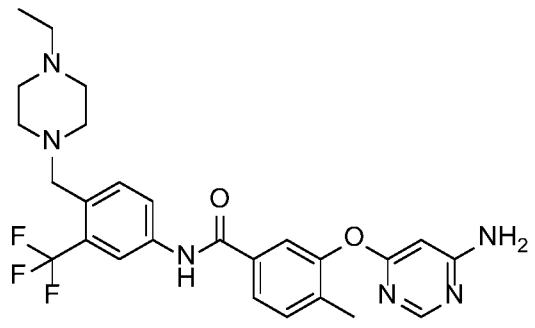

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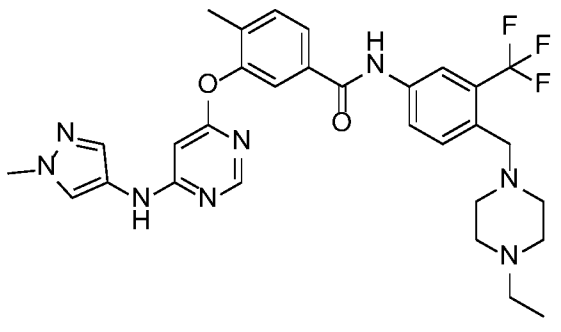

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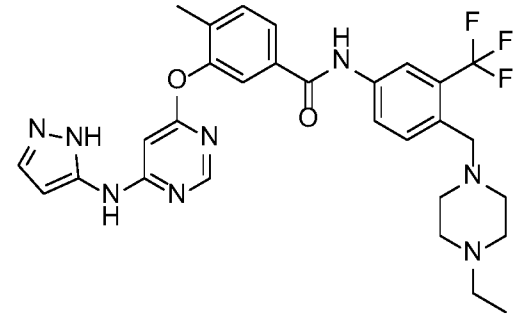

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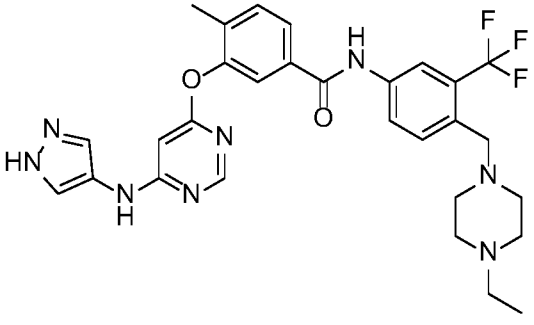

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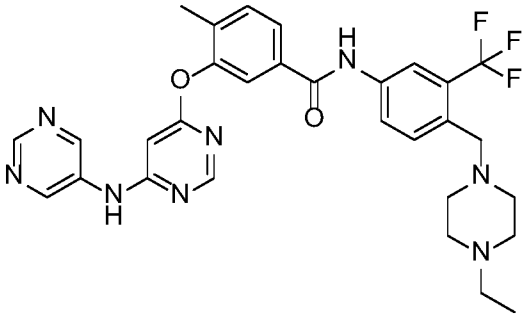

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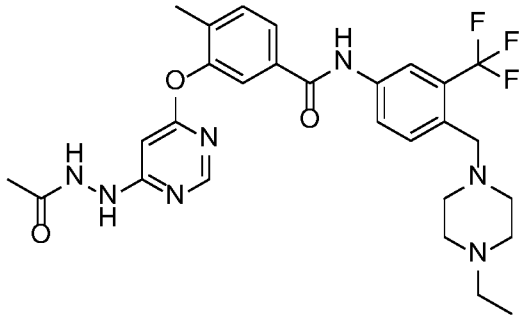

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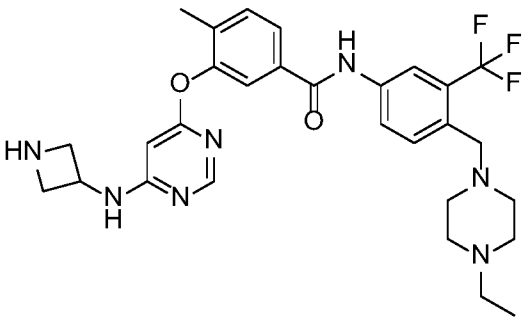

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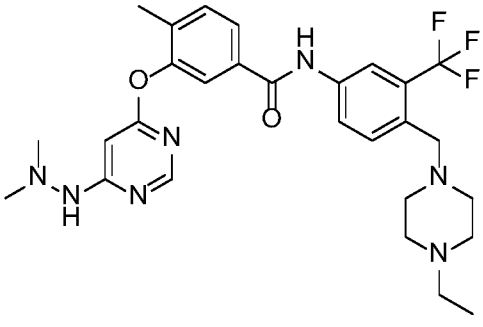

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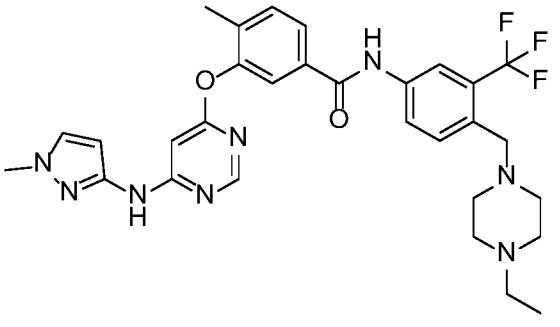

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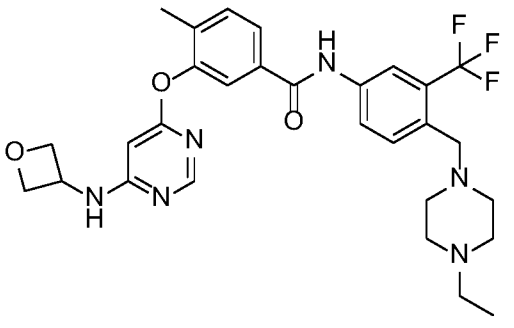

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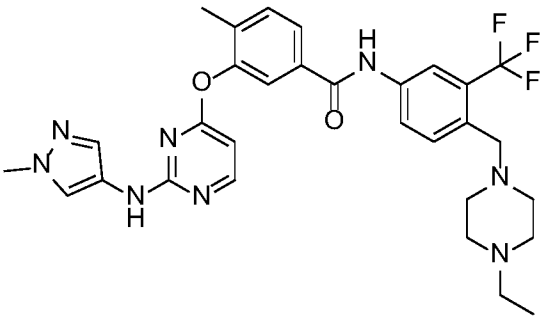

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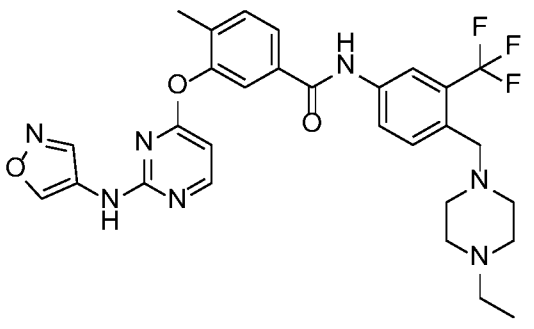

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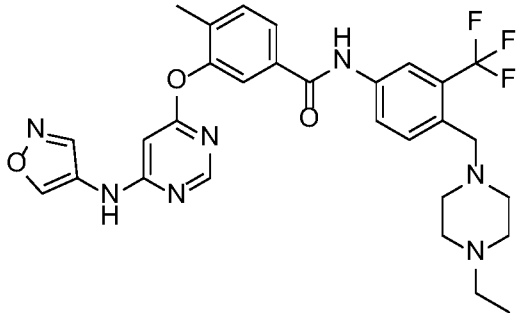

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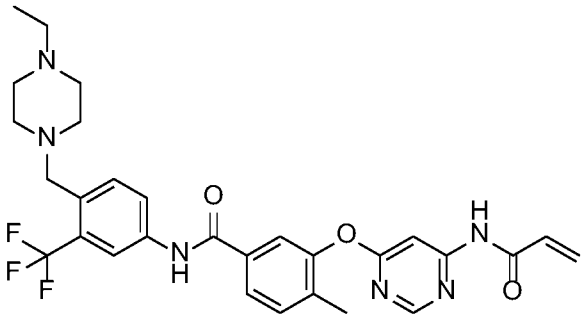

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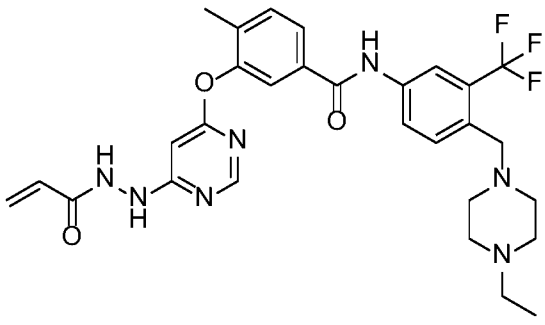

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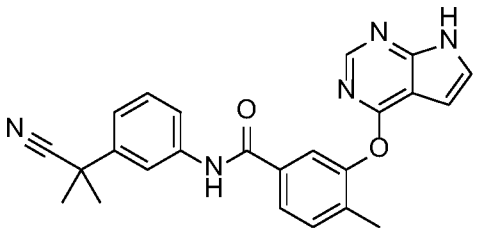


(**I-11**),

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

39. A pharmaceutical composition comprising a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, and a pharmaceutically acceptable excipient.

40. The pharmaceutical composition of claim 39 further comprising an additional pharmaceutical agent.

41. The pharmaceutical composition of any one of claims 39 or 40 comprising an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof, and optionally a pharmaceutically acceptable carrier, for treating a B-cell neoplasm.

42[[44]]. The pharmaceutical composition of any one of claims 39-41 further comprising one or more additional chemotherapeutic agents.

43. The pharmaceutical composition of claim [[44]]42, wherein the B-cell neoplasm is Waldenström's macroglobulinemia.

44. A method of treating a B cell neoplasm in a subject comprising administering an effective amount of a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof or a pharmaceutical composition of any one of claims 39-43 to the subject.

45. The method of claim 44, wherein the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, inhibits transforming growth factor b-activated kinase-1 (TAK1), hematopoietic cell kinase (HCK), or both TAK1 and HCK.

46. The method of any one of claims 44 or 45, wherein the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, inhibits hematopoietic progenitor kinase 1(HPK1).

47. The method of any one of claims 44-46, wherein the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, is administered in combination with an inhibitor of Bruton's tyrosine kinase (BTK), interleukin-1 receptor-associated kinase 1 (IRAK1), interleukin-1 receptor-associated kinase 4 (IRAK4), transforming growth factor b-activated kinase-1 (TAK1), or a Src family kinase.

48. The method of claim 47, wherein the BTK inhibitor is a benzonaphthyridinone.

49. The method of any one of claims 44-48, wherein the B cell neoplasm is Hodgkin's lymphoma.

50. The method of any one of claims 44-48, wherein the B cell neoplasm is non-Hodgkin's lymphoma.

51. The method of claims 50, wherein the lymphoma is Waldenström's macroglobulinemia, diffuse large B cell lymphoma, Follicular lymphoma, Mucosa-Associated Lymphatic Tissue lymphoma (MALT), Small cell lymphocytic lymphoma, Chronic lymphocytic leukemia, Mantle cell lymphoma (MCL), Burkitt lymphoma, Mediastinal large B cell lymphoma, Nodal marginal zone B cell lymphoma (NMZL), Splenic marginal zone lymphoma (SMZL), Intravascular large B-cell lymphoma, Primary effusion lymphoma, or Lymphomatoid granulomatosis.

52. The method of claim 44, wherein the B cell neoplasm is Waldenström's macroglobulinemia.

53. The method of any one of claims 49-52, wherein the subject has a mutation at position 38182641 in chromosome 3p22.2.

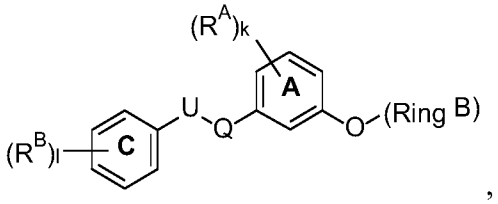
54. The method of any one of claims 44-53, wherein the subject is receiving therapy for the B cell neoplasm.

55. The method of any one of claims 44-54, wherein the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, is co-administered with one or more chemotherapeutic agents.

56. A kit comprising a container, a compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition of any one of claims 39-43, and instructions for use in a subject.

57. The kit of claim 57 further comprising one or more additional known chemotherapeutic agents.

58. The compound of any one of claims 1-38, wherein the compound is of the formula:



,

or a pharmaceutically acceptable salt thereof.

59. Use of the compound of any one of claims 1-38, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, or isotopically labeled derivative thereof or a pharmaceutical composition of any one of claims 39-43, for the manufacture of a medicament for the treatment a B cell neoplasm in a subject.

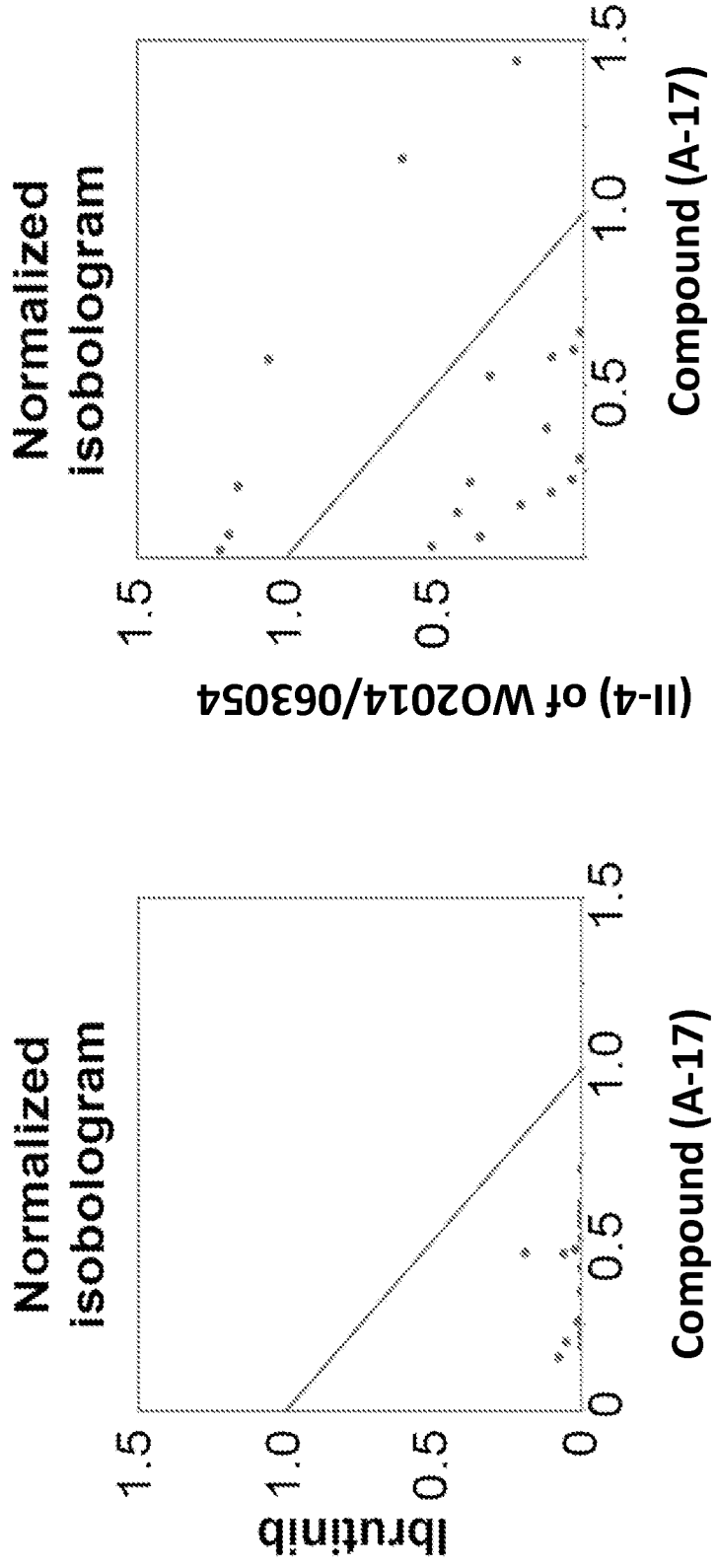

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Figure 1

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<210> 35
<211> 25
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<213> Homo sapiens

<400> 35

Ala Thr Phe Ser Phe Cys Val Ser Pro Leu Leu Val Phe Val Asn Ser
1 5 10 15

Lys Ser Gly Asp Asn Gln Gly Val Lys
20 25

<210> 36
<211> 36
<212> PRT
<213> Homo sapiens

<400> 36

Gly Arg Leu Leu Thr Ala Leu Val Leu Pro Asp Leu Leu His Ala Lys
1 5 10 15

Leu Pro Pro Asp Ser Cys Pro Leu Leu Val Phe Val Asn Pro Lys Ser
20 25 30

Gly Gly Leu Lys
35

<210> 37
<211> 14
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<213> Homo sapiens

<400> 37

Lys Gly Gly Ser Trp Ile Gln Glu Ile Asn Val Ala Glu Lys
1 5 10

<210> 38
<211> 13
<212> PRT
<213> Homo sapiens

<400> 38

Glu His Pro Phe Leu Val Lys Gly Gly Glu Asp Leu Arg
1 5 10

<210> 39
<211> 12
<212> PRT
<213> Homo sapiens

<400> 39

Tyr Ile Lys Tyr Asn Ser Asn Ser Gly Phe Val Arg
1 5 10

<210> 40
<211> 22
<212> PRT
<213> Homo sapiens

<400> 40

Tyr Leu Gln Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly
1 5 10 15

Gly Lys Ile Pro Val Arg
20

<210> 41
<211> 22
<212> PRT
<213> Homo sapiens

<400> 41

Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu Gly
1 5 10 15

Gly Lys Ile Pro Ile Arg
20

<210> 42
<211> 16
<212> PRT
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<400> 42

Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn Thr Thr Cys Asp Leu Lys
1 5 10 15

<210> 43
<211> 16
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<213> Homo sapiens

<400> 43

Asp Leu Lys Pro Ser Asn Leu Leu Leu Asn Thr Thr Cys Asp Leu Lys
1 5 10 15

<210> 44

<211> 16
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<213> Homo sapiens

<400> 44

Asp Leu Lys Pro Ser Asn Leu Leu Val Asn Glu Asn Cys Glu Leu Lys
1 5 10 15

<210> 45
<211> 17
<212> PRT
<213> Homo sapiens

<400> 45

Thr Ser Val Ala Val Lys Thr Cys Lys Glu Asp Leu Pro Gln Glu Leu
1 5 10 15

Lys

<210> 46
<211> 14
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<400> 46

Leu Arg Ala Asp Asn Thr Leu Val Ala Val Lys Ser Cys Arg
1 5 10

<210> 47
<211> 18
<212> PRT
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<400> 47

Leu Ile Lys Asp Asp Glu Tyr Asn Pro Cys Gln Gly Ser Lys Phe Pro
1 5 10 15

Ile Lys

<210> 48
<211> 18
<212> PRT
<213> Homo sapiens

<400> 48

Ile Gln Ser Ile Ala Pro Ser Leu Gln Val Ile Thr Ser Lys Gln Arg
1 5 10 15

Pro Arg

<210> 49
<211> 8

<212> PRT
<213> Homo sapiens

<400> 49

His Glu Ile Lys Leu Pro Val Lys
1 5

<210> 50
<211> 19
<212> PRT
<213> Homo sapiens

<400> 50

Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ala Leu
1 5 10 15

Tyr Gly Arg

<210> 51
<211> 16
<212> PRT
<213> Homo sapiens

<400> 51

Asp Ile Lys Gly Ala Asn Leu Leu Leu Thr Leu Gln Gly Asp Val Lys
1 5 10 15

<210> 52
<211> 16
<212> PRT
<213> Homo sapiens

<400> 52

Asp Leu Lys Pro Val Asn Ile Phe Leu Asp Ser Asp Asp His Val Lys
1 5 10 15

<210> 53
<211> 17
<212> PRT
<213> Homo sapiens

<400> 53

Asp Ile Lys Pro Gln Asn Leu Leu Val Asp Pro Asp Thr Ala Val Leu
1 5 10 15

Lys

<210> 54
<211> 17
<212> PRT
<213> Homo sapiens

<400> 54

Asp Ile Lys Pro Gln Asn Leu Leu Leu Asp Pro Asp Thr Ala Val Leu
1 5 10 15

Lys

<210> 55
<211> 16
<212> PRT
<213> Homo sapiens

<400> 55

Asp Ile Lys Gly Ala Asn Ile Leu Ile Asn Asp Ala Gly Glu Val Arg
1 5 10 15

<210> 56
<211> 15
<212> PRT
<213> Homo sapiens

<400> 56

Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Asp Val Gly Gly Lys
1 5 10 15

<210> 57
<211> 15
<212> PRT
<213> Homo sapiens

<400> 57

Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Gln Gly Glu Gln Arg
1 5 10 15

<210> 58
<211> 19
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<213> Homo sapiens

<400> 58

Ser Gly Glu Leu Val Ala Val Lys Val Phe Asn Thr Thr Ser Tyr Leu
1 5 10 15

Arg Pro Arg

<210> 59
<211> 12
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<213> Homo sapiens

<400> 59

Trp Gln Gly Asn Asp Ile Val Val Lys Val Leu Lys
1 5 10

<210> 60

<211> 27
<212> PRT
<213> Homo sapiens

<400> 60

Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu Ile His Gly Asp
1 5 10 15

Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg
20 25

<210> 61
<211> 16
<212> PRT
<213> Homo sapiens

<400> 61

Asp Ile Lys Ser Ala Asn Ile Leu Leu Asp Glu Ala Phe Thr Ala Lys
1 5 10 15

<210> 62
<211> 17
<212> PRT
<213> Homo sapiens

<400> 62

Asp Leu Lys Pro His Asn Ile Leu Ile Ser Met Pro Asn Ala His Gly
1 5 10 15

Lys

<210> 63
<211> 38
<212> PRT
<213> Homo sapiens

<400> 63

Glu Ser Ile Phe Phe Asn Ser His Asn Val Ser Lys Pro Glu Ser Ser
1 5 10 15

Ser Val Leu Thr Glu Leu Asp Lys Ile Glu Gly Val Phe Glu Arg Pro
20 25 30

Ser Asp Glu Val Ile Arg
35

<210> 64
<211> 28
<212> PRT
<213> Homo sapiens

<400> 64

Gln Leu Ala Ser Ala Leu Ser Tyr Leu Glu Asp Lys Asp Leu Val His
1 5 10 15

Gly Asn Val Cys Thr Lys Asn Leu Leu Leu Ala Arg
20 25

<210> 65
<211> 20
<212> PRT
<213> Homo sapiens

<400> 65

Ile Gly Asp Phe Gly Leu Thr Lys Ala Ile Glu Thr Asp Lys Glu Tyr
1 5 10 15

Tyr Thr Val Lys
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<210> 66
<211> 20
<212> PRT
<213> Homo sapiens

<400> 66

Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp Tyr
1 5 10 15

Tyr Val Val Arg
20

<210> 67
<211> 10
<212> PRT
<213> Homo sapiens

<400> 67

Asp Leu Lys Pro Ser Asn Ile Val Val Lys
1 5 10

<210> 68
<211> 14
<212> PRT
<213> Homo sapiens

<400> 68

Asn Val His Thr Gly Glu Leu Ala Ala Val Lys Ile Ile Lys
1 5 10

<210> 69
<211> 26
<212> PRT
<213> Homo sapiens

<400> 69

Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys Val Val Ile Thr Asp Phe
1 5 10 15

Gly Leu Phe Gly Ile Ser Gly Val Val Arg
20 25

<210> 70
<211> 10
<212> PRT
<213> Homo sapiens

<400> 70

Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys
1 5 10

<210> 71
<211> 9
<212> PRT
<213> Homo sapiens

<400> 71

Ala Leu Tyr Ala Thr Lys Thr Leu Arg
1 5

<210> 72
<211> 16
<212> PRT
<213> Homo sapiens

<400> 72

Asp Ile Lys Pro Asp Asn Ile Leu Ile Asp Leu Asp Gly His Ile Lys
1 5 10 15

<210> 73
<211> 23
<212> PRT
<213> Homo sapiens

<400> 73

Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ile Asn
1 5 10 15

Tyr Gly Thr Phe Thr Ile Lys
20

<210> 74
<211> 16
<212> PRT
<213> Homo sapiens

<400> 74

Asp Ile Lys Pro Gly Asn Leu Leu Leu Thr Thr Gly Gly Thr Leu Lys
1 5 10 15

<210> 75
<211> 16
<212> PRT
<213> Homo sapiens

<400> 75

Asp Leu Lys Ala Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg
1 5 10 15

<210> 76
<211> 21
<212> PRT
<213> Homo sapiens

<400> 76

Asp Leu Lys Pro His Asn Val Leu Leu Phe Thr Leu Tyr Pro Asn Ala
1 5 10 15

Ala Ile Ile Ala Lys
20

<210> 77
<211> 24
<212> PRT
<213> Homo sapiens

<400> 77

Val Ala Val Lys Thr Leu Lys Pro Gly Thr Met Ser Val Gln Ala Phe
1 5 10 15

Leu Glu Glu Ala Asn Leu Met Lys
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<210> 78
<211> 16
<212> PRT
<213> Homo sapiens

<400> 78

Ile Met His Arg Asp Val Lys Pro Ser Asn Ile Leu Val Asn Ser Arg
1 5 10 15

<210> 79
<211> 12
<212> PRT
<213> Homo sapiens

<400> 79

Asp Val Lys Pro Ser Asn Ile Leu Val Asn Ser Arg
1 5 10

<210> 80
<211> 11
<212> PRT
<213> Homo sapiens

<400> 80

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys
1 5 10

<210> 81
<211> 11
<212> PRT
<213> Homo sapiens

<400> 81

Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg
1 5 10

<210> 82
<211> 12
<212> PRT
<213> Homo sapiens

<400> 82

Asp Val Lys Pro Ser Asn Met Leu Val Asn Thr Arg
1 5 10

<210> 83
<211> 16
<212> PRT
<213> Homo sapiens

<400> 83

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly Gln Val Lys
1 5 10 15

<210> 84
<211> 12
<212> PRT
<213> Homo sapiens

<400> 84

Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg
1 5 10

<210> 85
<211> 15
<212> PRT
<213> Homo sapiens

<400> 85

Asp Val Lys Gly Ala Asn Leu Leu Ile Asp Ser Thr Gly Gln Arg
1 5 10 15

<210> 86
<211> 31
<212> PRT
<213> Homo sapiens

<400> 86

Glu Leu Ala Val Lys Gln Val Gln Phe Asp Pro Asp Ser Pro Glu Thr
1 5 10 15

Ser Lys Glu Val Asn Ala Leu Glu Cys Glu Ile Gln Leu Leu Lys
20 25 30

<210> 87
<211> 9
<212> PRT
<213> Homo sapiens

<400> 87

Asp Ile Lys Gly Ala Asn Ile Leu Arg
1 5

<210> 88
<211> 31
<212> PRT
<213> Homo sapiens

<400> 88

Glu Leu Ala Ser Lys Gln Val Gln Phe Asp Pro Asp Ser Pro Glu Thr
1 5 10 15

Ser Lys Glu Val Ser Ala Leu Glu Cys Glu Ile Gln Leu Leu Lys
20 25 30

<210> 89
<211> 16
<212> PRT
<213> Homo sapiens

<400> 89

Asp Ile Lys Gly Ala Asn Ile Phe Leu Thr Ser Ser Gly Leu Ile Lys
1 5 10 15

<210> 90
<211> 17
<212> PRT
<213> Homo sapiens

<400> 90

Asp Ile Lys Gly Asp Asn Val Leu Ile Asn Thr Tyr Ser Gly Val Leu
1 5 10 15

Lys

<210> 91
<211> 17
<212> PRT
<213> Homo sapiens

<400> 91

Asp Ile Lys Gly Asp Asn Val Leu Ile Asn Thr Phe Ser Gly Leu Leu
1 5 10 15

Lys

<210> 92
<211> 16
<212> PRT
<213> Homo sapiens

<400> 92

Asp Leu Lys Ala Glu Asn Leu Leu Leu Asp Ala Asp Met Asn Ile Lys
1 5 10 15

<210> 93
<211> 19
<212> PRT
<213> Homo sapiens

<400> 93

Glu Val Ala Ile Lys Ile Ile Asp Lys Thr Gln Leu Asn Pro Thr Ser
1 5 10 15

Leu Gln Lys

<210> 94
<211> 9
<212> PRT
<213> Homo sapiens

<400> 94

Glu Val Ala Ile Lys Ile Ile Asp Lys
1 5

<210> 95
<211> 16
<212> PRT
<213> Homo sapiens

<400> 95

Asp Leu Lys Ala Glu Asn Leu Leu Leu Asp Ala Glu Ala Asn Ile Lys
1 5 10 15

<210> 96
<211> 16
<212> PRT
<213> Homo sapiens

<400> 96

Asp Leu Lys Pro Asp Asn Leu Leu Ile Thr Ser Met Gly His Ile Lys
1 5 10 15

<210> 97
<211> 16
<212> PRT
<213> Homo sapiens

<400> 97

Asp Leu Lys Pro Asp Asn Leu Leu Ile Thr Ser Leu Gly His Ile Lys
1 5 10 15

<210> 98
<211> 11
<212> PRT
<213> Homo sapiens

<400> 98

Gly Ala Phe Gly Lys Val Tyr Leu Gly Gln Lys
1 5 10

<210> 99
<211> 8
<212> PRT
<213> Homo sapiens

<400> 99

Leu Tyr Ala Val Lys Val Val Lys
1 5

<210> 100
<211> 14
<212> PRT
<213> Homo sapiens

<400> 100

Asp Leu Lys Pro Glu Asn Leu Leu Phe Asp Glu Tyr His Lys
1 5 10

<210> 101
<211> 20
<212> PRT
<213> Homo sapiens

<400> 101

Asn Cys Met Leu Arg Asp Asp Met Thr Val Cys Val Ala Asp Phe Gly
1 5 10 15

Leu Ser Lys Lys
20

<210> 102
<211> 9
<212> PRT
<213> Homo sapiens

<400> 102

Lys Ile Tyr Ser Gly Asp Tyr Tyr Arg
1 5

<210> 103
<211> 13
<212> PRT
<213> Homo sapiens

<400> 103

Asp Met Tyr Asp Lys Glu Tyr Tyr Ser Val His Asn Lys
1 5 10

<210> 104
<211> 21
<212> PRT
<213> Homo sapiens

<400> 104

Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro Ile Glu Ser Asp
1 5 10 15

Asp Met Glu His Lys
20

<210> 105
<211> 12
<212> PRT
<213> Homo sapiens

<400> 105

Asp Leu Lys Ser Ser Asn Ile Leu Leu Leu Glu Lys
1 5 10

<210> 106
<211> 9
<212> PRT
<213> Homo sapiens

<400> 106

Ala Pro Val Ala Ile Lys Val Phe Lys
1 5

<210> 107
<211> 34
<212> PRT
<213> Homo sapiens

<400> 107

Asp Leu Lys Pro Thr Asn Ile Leu Leu Gly Asp Glu Gly Gln Pro Val
1 5 10 15

Leu Met Asp Leu Gly Ser Met Asn Gln Ala Cys Ile His Val Glu Gly
20 25 30

Ser Arg

<210> 108
<211> 24
<212> PRT
<213> Homo sapiens

<400> 108

Asp Ile Lys Leu Glu Asn Ile Leu Leu Asp Ser Asn Gly His Val Val
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys
20

<210> 109
<211> 24
<212> PRT
<213> Homo sapiens

<400> 109

Asp Leu Lys Leu Glu Asn Val Leu Leu Asp Ser Glu Gly His Ile Val
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys
20

<210> 110
<211> 22
<212> PRT
<213> Homo sapiens

<400> 110

Glu Thr Gly Gln Ile Val Ala Ile Lys Gln Val Pro Val Glu Ser Asp
1 5 10 15

Leu Gln Glu Ile Ile Lys
20

<210> 111
<211> 22
<212> PRT
<213> Homo sapiens

<400> 111

Glu Ser Gly Gln Val Val Ala Ile Lys Gln Val Pro Val Glu Ser Asp
1 5 10 15

Leu Gln Glu Ile Ile Lys
20

<210> 112
<211> 16
<212> PRT
<213> Homo sapiens

<400> 112

Asp Ile Lys Ala Ala Asn Val Leu Leu Ser Glu His Gly Glu Val Lys
1 5 10 15

<210> 113
<211> 39

<212> PRT
<213> Homo sapiens

<400> 113

Thr Gln Gln Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu
1 5 10 15

Asp Glu Ile Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys
20 25 30

Asp Ser Ser Tyr Val Thr Lys
35

<210> 114
<211> 16
<212> PRT
<213> Homo sapiens

<400> 114

Asp Ile Lys Ala Ala Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys
1 5 10 15

<210> 115
<211> 16
<212> PRT
<213> Homo sapiens

<400> 115

Asp Val Lys Gly Asn Asn Ile Leu Leu Thr Thr Glu Gly Gly Val Lys
1 5 10 15

<210> 116
<211> 12
<212> PRT
<213> Homo sapiens

<400> 116

Asp Ile Lys Pro Asp Asn Leu Leu Leu Asp Ser Lys
1 5 10

<210> 117
<211> 12
<212> PRT
<213> Homo sapiens

<400> 117

Asp Ile Lys Pro Asp Asn Leu Leu Leu Asp Ala Lys
1 5 10

<210> 118
<211> 11
<212> PRT
<213> Homo sapiens

<400> 118

Asp Ile Lys Ser Gln Asn Ile Phe Leu Thr Lys
1 5 10

<210> 119
<211> 12
<212> PRT
<213> Homo sapiens

<400> 119

Asp Leu Lys Pro Ala Asn Val Phe Leu Asp Gly Lys
1 5 10

<210> 120
<211> 11
<212> PRT
<213> Homo sapiens

<400> 120

Ser Lys Asn Ile Phe Leu Thr Gln Asn Gly Lys
1 5 10

<210> 121
<211> 11
<212> PRT
<213> Homo sapiens

<400> 121

Asp Leu Lys Thr Gln Asn Val Phe Leu Thr Arg
1 5 10

<210> 122
<211> 16
<212> PRT
<213> Homo sapiens

<400> 122

Asp Ile Lys Pro Ala Asn Val Phe Ile Thr Ala Thr Gly Val Val Lys
1 5 10 15

<210> 123
<211> 14
<212> PRT
<213> Homo sapiens

<400> 123

Ala Ala Cys Leu Leu Asp Gly Val Pro Val Ala Leu Lys Lys
1 5 10

<210> 124
<211> 11
<212> PRT
<213> Homo sapiens

<400> 124

Asp Leu Lys Thr Gln Asn Ile Leu Leu Asp Lys
1 5 10

<210> 125
<211> 11
<212> PRT
<213> Homo sapiens

<400> 125

Asp Ile Lys Thr Leu Asn Ile Phe Leu Thr Lys
1 5 10

<210> 126
<211> 34
<212> PRT
<213> Homo sapiens

<400> 126

Asp Val Lys Ala Gly Asn Ile Leu Leu Gly Glu Asp Gly Ser Val Gln
1 5 10 15

Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly Asp Ile
20 25 30

Thr Arg

<210> 127
<211> 16
<212> PRT
<213> Homo sapiens

<400> 127

Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys
1 5 10 15

<210> 128
<211> 13
<212> PRT
<213> Homo sapiens

<400> 128

Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg
1 5 10

<210> 129
<211> 13
<212> PRT
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<400> 129

Gln Glu Leu Asn Lys Thr Val Trp Glu Val Pro Gln Arg
1 5 10

<210> 130
<211> 16
<212> PRT

<213> Homo sapiens

<400> 130

Asp Leu Lys Pro Gly Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys
1 5 10 15

<210> 131
<211> 16
<212> PRT
<213> Homo sapiens

<400> 131

Asp Leu Lys Pro Glu Asn Ile Met Leu Asn His Gln Gly His Val Lys
1 5 10 15

<210> 132
<211> 16
<212> PRT
<213> Homo sapiens

<400> 132

Asp Leu Lys Pro Glu Asn Ile Met Leu Ser Ser Gln Gly His Ile Lys
1 5 10 15

<210> 133
<211> 12
<212> PRT
<213> Homo sapiens

<400> 133

Val Met Asp Pro Thr Lys Ile Leu Ile Thr Gly Lys
1 5 10

<210> 134
<211> 14
<212> PRT
<213> Homo sapiens

<400> 134

Ser Lys Leu Thr Asp Asn Leu Val Ala Leu Lys Glu Ile Arg
1 5 10

<210> 135
<211> 14
<212> PRT
<213> Homo sapiens

<400> 135

Ser Lys Leu Thr Glu Asn Leu Val Ala Leu Lys Glu Ile Arg
1 5 10

<210> 136
<211> 9
<212> PRT
<213> Homo sapiens

<400> 136

Glu Tyr Ala Ile Lys Ile Leu Glu Lys
1 5

<210> 137
<211> 16
<212> PRT
<213> Homo sapiens

<400> 137

Asp Leu Lys Pro Ser Asn Ile Phe Phe Thr Met Asp Asp Val Val Lys
1 5 10 15

<210> 138
<211> 8
<212> PRT
<213> Homo sapiens

<400> 138

Leu Val Ala Leu Lys Val Ile Arg
1 5

<210> 139
<211> 16
<212> PRT
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<400> 139

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Asp Asn Met Asn Ile Lys
1 5 10 15

<210> 140
<211> 17
<212> PRT
<213> Homo sapiens

<400> 140

Ala Thr Gly His Glu Phe Ala Val Lys Ile Met Glu Val Thr Ala Glu
1 5 10 15

Arg

<210> 141
<211> 16
<212> PRT
<213> Homo sapiens

<400> 141

Ser Gly Thr Pro Met Gln Ser Ala Ala Lys Ala Pro Tyr Leu Ala Lys
1 5 10 15

<210> 142
<211> 14
<212> PRT

<213> Homo sapiens

<400> 142

Val Pro His Thr Gln Ala Val Val Leu Asn Ser Lys Asp Lys
1 5 10

<210> 143
<211> 20
<212> PRT
<213> Homo sapiens

<400> 143

Val Ile Phe Lys Cys Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu
1 5 10 15

Gln Met Ile Arg
20

<210> 144
<211> 18
<212> PRT
<213> Homo sapiens

<400> 144

Thr Glu Asp Gly Gly Lys Tyr Pro Val Ile Phe Lys His Gly Asp Asp
1 5 10 15

Leu Arg

<210> 145
<211> 28
<212> PRT
<213> Homo sapiens

<400> 145

Val Phe Gly Glu Asp Ser Val Gly Val Ile Phe Lys Asn Gly Asp Asp
1 5 10 15

Leu Arg Gln Asp Met Leu Thr Leu Gln Met Leu Arg
20 25

<210> 146
<211> 14
<212> PRT
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<400> 146

Val Asn Trp Leu Ala His Asn Val Ser Lys Asp Asn Arg Gln
1 5 10

<210> 147
<211> 9
<212> PRT
<213> Homo sapiens

<400> 147

Lys Lys Pro Leu Trp Leu Glu Phe Lys
1 5

<210> 148
<211> 18
<212> PRT
<213> Homo sapiens

<400> 148

Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn Glu Gly
1 5 10 15

Gln Lys

<210> 149
<211> 18
<212> PRT
<213> Homo sapiens

<400> 149

Ala Lys Asp Leu Pro Thr Phe Lys Asp Asn Asp Phe Leu Asn Glu Gly
1 5 10 15

Gln Lys

<210> 150
<211> 28
<212> PRT
<213> Homo sapiens

<400> 150

Thr Leu Val Ile Lys Glu Val Ser Ser Glu Asp Ile Ala Asp Met His
1 5 10 15

Ser Asn Leu Ser Asn Tyr His Gln Tyr Ile Val Lys
20 25

<210> 151
<211> 19
<212> PRT
<213> Homo sapiens

<400> 151

Gly Gly Lys Ser Gly Ala Ala Phe Tyr Ala Thr Glu Asp Asp Arg Phe
1 5 10 15

Ile Leu Lys

<210> 152

<211> 16
<212> PRT
<213> Homo sapiens

<400> 152

Asp Leu Lys Thr Ser Asn Leu Leu Leu Ser His Ala Gly Ile Leu Lys
1 5 10 15

<210> 153
<211> 16
<212> PRT
<213> Homo sapiens

<400> 153

Asp Leu Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile Lys
1 5 10 15

<210> 154
<211> 9
<212> PRT
<213> Homo sapiens

<400> 154

Asp Val Ala Val Lys Val Ile Asp Lys
1 5

<210> 155
<211> 19
<212> PRT
<213> Homo sapiens

<400> 155

Val Leu Leu Ser Glu Phe Arg Pro Ser Gly Glu Leu Phe Ala Ile Lys
1 5 10 15

Ala Leu Lys

<210> 156
<211> 13
<212> PRT
<213> Homo sapiens

<400> 156

Asp Leu Lys Pro Ser Asn Ile Phe Leu Val Asp Thr Lys
1 5 10

<210> 157
<211> 20
<212> PRT
<213> Homo sapiens

<400> 157

Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala Gly Lys
1 5 10 15

Ile Val Pro Lys
            20

<210> 158
<211> 19
<212> PRT
<213> Homo sapiens

<400> 158

Cys Asn Ile Leu His Ala Asp Ile Lys Pro Asp Asn Ile Leu Val Asn
1   5   10   15

Glu Ser Lys

<210> 159
<211> 15
<212> PRT
<213> Homo sapiens

<400> 159

Phe Leu Ser Gly Leu Glu Leu Val Lys Gln Gly Ala Glu Ala Arg
1   5   10   15

<210> 160
<211> 14
<212> PRT
<213> Homo sapiens

<400> 160

Tyr Ile Glu Asp Glu Asp Tyr Tyr Lys Ala Ser Val Thr Arg
1   5   10

<210> 161
<211> 16
<212> PRT
<213> Homo sapiens

<400> 161

Asp Met Lys Ser Asn Asn Ile Phe Leu His Glu Gly Leu Thr Val Lys
1   5   10   15

<210> 162
<211> 16
<212> PRT
<213> Homo sapiens

<400> 162

Asp Leu Lys Pro Ser Asn Val Leu Leu Asp Pro Glu Leu His Val Lys
1   5   10   15

<210> 163
<211> 11
<212> PRT
<213> Homo sapiens

<400> 163

Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys
1 5 10

<210> 164
<211> 31
<212> PRT
<213> Homo sapiens

<400> 164

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys Glu Ala Ile Asp His Glu Lys
20 25 30

<210> 165
<211> 16
<212> PRT
<213> Homo sapiens

<400> 165

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

<210> 166
<211> 20
<212> PRT
<213> Homo sapiens

<400> 166

Asp Leu Lys Pro Ser Asn Ile Leu Tyr Val Asp Glu Ser Gly Asn Pro
1 5 10 15

Glu Cys Leu Arg
20

<210> 167
<211> 31
<212> PRT
<213> Homo sapiens

<400> 167

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys Glu Ser Ile Asp His Glu Lys
20 25 30

<210> 168
<211> 20
<212> PRT
<213> Homo sapiens

<400> 168

Asp Leu Lys Pro Ser Asn Ile Leu Tyr Val Asp Glu Ser Gly Asn Pro
1 5 10 15

Glu Ser Ile Arg
20

<210> 169
<211> 24
<212> PRT
<213> Homo sapiens

<400> 169

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Ile Thr Asp Phe Gly Leu Ser Lys
20

<210> 170
<211> 16
<212> PRT
<213> Homo sapiens

<400> 170

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Ile Gly His Ile Lys
1 5 10 15

<210> 171
<211> 15
<212> PRT
<213> Homo sapiens

<400> 171

Val Leu Gly Val Ile Asp Lys Val Leu Leu Val Met Asp Thr Arg
1 5 10 15

<210> 172
<211> 9
<212> PRT
<213> Homo sapiens

<400> 172

Phe Tyr Ala Val Lys Val Leu Gln Lys
1 5

<210> 173
<211> 16
<212> PRT
<213> Homo sapiens

<400> 173

Asp Leu Lys Ala Gly Asn Ile Leu Phe Thr Leu Asp Gly Asp Ile Lys
1 5 10 15

<210> 174
<211> 22
<212> PRT
<213> Homo sapiens

<400> 174

Asp Thr Val Thr Ile His Ser Val Gly Gly Thr Ile Thr Ile Leu Pro
1 5 10 15

Thr Lys Thr Lys Pro Lys
20

<210> 175
<211> 12
<212> PRT
<213> Homo sapiens

<400> 175

Asp Leu Lys Pro Glu Asn Val Val Phe Phe Glu Lys
1 5 10

<210> 176
<211> 25
<212> PRT
<213> Homo sapiens

<400> 176

Val Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser Pro Glu Ala Phe
1 5 10 15

Leu Gln Glu Ala Gln Val Met Lys Lys
20 25

<210> 177
<211> 21
<212> PRT
<213> Homo sapiens

<400> 177

Ile Ile His Thr Asp Ile Lys Pro Glu Asn Ile Leu Leu Ser Val Asn
1 5 10 15

Glu Gln Tyr Ile Arg
20

<210> 178
<211> 10
<212> PRT
<213> Homo sapiens

<400> 178

Asp Leu Lys Leu Glu Asn Ile Met Val Lys
1 5 10

<210> 179
<211> 24
<212> PRT
<213> Homo sapiens

<400> 179

Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln Gln
1 5 10 15

Asn Leu Gln Gly Tyr Asp Ala Lys
20

<210> 180
<211> 11
<212> PRT
<213> Homo sapiens

<400> 180

Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg
1 5 10

<210> 181
<211> 17
<212> PRT
<213> Homo sapiens

<400> 181

Asp Leu Lys Pro Pro Asn Leu Leu Leu Val Ala Gly Gly Thr Val Leu
1 5 10 15

Lys

<210> 182
<211> 16
<212> PRT
<213> Homo sapiens

<400> 182

Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr Glu Pro Gly Gln Val Lys
1 5 10 15

<210> 183
<211> 16
<212> PRT
<213> Homo sapiens

<400> 183

Asp Val Lys Ala Gly Asn Ile Leu Leu Ser Glu Pro Gly Leu Val Lys
1 5 10 15

<210> 184
<211> 24
<212> PRT
<213> Homo sapiens

<400> 184

Thr Gly Asp Leu Phe Ala Ile Lys Val Phe Asn Asn Ile Ser Phe Leu
1 5 10 15

Arg Pro Val Asp Val Gln Met Arg
20

<210> 185
<211> 18
<212> PRT
<213> Homo sapiens

<400> 185

Tyr Val Leu Asp Asp Gln Tyr Thr Ser Ser Ser Gly Ala Lys Phe Pro
1 5 10 15

Val Lys

<210> 186
<211> 31
<212> PRT
<213> Homo sapiens

<400> 186

Tyr Leu Asn Glu Ile Lys Pro Pro Ile Ile His Tyr Asp Leu Lys Pro
1 5 10 15

Gly Asn Ile Leu Leu Val Asp Gly Thr Ala Cys Gly Glu Ile Lys
20 25 30

<210> 187
<211> 31
<212> PRT
<213> Homo sapiens

<400> 187

Tyr Leu Asn Glu Ile Lys Pro Pro Ile Ile His Tyr Asp Leu Lys Pro
1 5 10 15

Gly Asn Ile Leu Leu Val Asn Gly Thr Ala Cys Gly Glu Ile Lys
20 25 30

<210> 188
<211> 18
<212> PRT
<213> Homo sapiens

<400> 188

Ile Gly Asp Phe Gly Leu Ala Lys Ala Val Pro Glu Gly His Glu Tyr
1 5 10 15

Tyr Arg

<210> 189
<211> 15
<212> PRT
<213> Homo sapiens

<400> 189

Asp Leu Lys Pro Gln Asn Ile Leu Leu Ser Asn Pro Ala Gly Arg
1 5 10 15

<210> 190
<211> 23
<212> PRT
<213> Homo sapiens

<400> 190

Asn Ile Ser His Leu Asp Leu Lys Pro Gln Asn Ile Leu Leu Ser Ser
1 5 10 15

Leu Glu Lys Pro His Leu Lys
20

<210> 191
<211> 28
<212> PRT
<213> Homo sapiens

<400> 191

Met Leu Asp Val Leu Glu Tyr Ile His Glu Asn Glu Tyr Val His Gly
1 5 10 15

Asp Ile Lys Ala Ala Asn Leu Leu Leu Gly Tyr Lys
20 25

<210> 192
<211> 21
<212> PRT
<213> Homo sapiens

<400> 192

Tyr Ile His Ser Met Ser Leu Val His Met Asp Ile Lys Pro Ser Asn
1 5 10 15

Ile Phe Ile Ser Arg
20

<210> 193
<211> 8
<212> PRT
<213> Homo sapiens

<400> 193

Gly Ser Phe Lys Thr Val Tyr Lys
1 5

<210> 194
<211> 17
<212> PRT
<213> Homo sapiens

<400> 194

Asp Leu Lys Cys Asp Asn Ile Phe Ile Thr Gly Pro Thr Gly Ser Val
1 5 10 15

Lys

<210> 195
<211> 12
<212> PRT
<213> Homo sapiens

<400> 195

Asp Val Lys Pro Asp Asn Ile Leu Leu Asp Glu Arg
1 5 10

<210> 196
<211> 12
<212> PRT
<213> Homo sapiens

<400> 196

Trp Ile Ser Gln Asp Lys Glu Val Ala Val Lys Lys
1 5 10

<210> 197
<211> 20
<212> PRT
<213> Homo sapiens

<400> 197

Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Gly Ala Asp Asp Ser Tyr
1 5 10 15

Tyr Thr Ala Arg
20

<210> 198
<211> 16
<212> PRT
<213> Homo sapiens

<400> 198

Asp Ile Lys Gly Gln Asn Val Leu Leu Thr Glu Asn Ala Glu Val Lys
1 5 10 15

<210> 199
<211> 29
<212> PRT
<213> Homo sapiens

<400> 199

Thr Gly Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Gly Asp Glu
1 5 10 15

Glu Glu Glu Ile Lys Gln Glu Ile Asn Met Leu Lys Lys
20 25

<210> 200
<211> 18
<212> PRT
<213> Homo sapiens

<400> 200

Leu Met Thr Gly Asp Thr Tyr Thr Ala His Ala Gly Ala Lys Phe Pro
1 5 10 15

Ile Lys

<210> 201
<211> 25
<212> PRT
<213> Homo sapiens

<400> 201

Thr Val Ser Val Ala Val Lys Cys Leu Lys Pro Asp Val Leu Ser Gln
1 5 10 15

Pro Glu Ala Met Asp Asp Phe Ile Arg
20 25

<210> 202
<211> 13
<212> PRT
<213> Homo sapiens

<400> 202

Ala Thr Val Phe Leu Asn Pro Ala Ala Cys Lys Gly Lys
1 5 10

<210> 203
<211> 10
<212> PRT
<213> Homo sapiens

<400> 203

Gly Thr Phe Gly Lys Val Ile Leu Val Lys
1 5 10

<210> 204
<211> 10
<212> PRT
<213> Homo sapiens

<400> 204

Gly Thr Phe Gly Lys Val Ile Leu Val Arg
1 5 10

<210> 205
<211> 16
<212> PRT
<213> Homo sapiens

<400> 205

Asp Leu Lys Pro Glu Asn Val Leu Leu Asp Ala His Met Asn Ala Lys
1 5 10 15

<210> 206
<211> 26
<212> PRT
<213> Homo sapiens

<400> 206

Gly Met Leu Phe Leu His Asn Gly Ala Ile Cys Ser His Gly Asn Leu
1 5 10 15

Lys Ser Ser Asn Cys Val Val Asp Gly Arg
20 25

<210> 207
<211> 16
<212> PRT
<213> Homo sapiens

<400> 207

Asp Leu Lys Ser Asn Asn Ile Phe Leu His Glu Gly Leu Thr Val Lys
1 5 10 15

<210> 208
<211> 9
<212> PRT
<213> Homo sapiens

<400> 208

Phe Tyr Ile Met Met Cys Lys Pro Lys
1 5

<210> 209
<211> 10
<212> PRT
<213> Homo sapiens

<400> 209

Phe Ile Leu Ala Leu Lys Val Leu Phe Lys
1 5 10

<210> 210
<211> 16
<212> PRT

<213> Homo sapiens

<400> 210

Asp Ile Lys Pro Glu Asn Leu Leu Leu Gly Ser Ala Gly Glu Leu Lys
1 5 10 15

<210> 211
<211> 10
<212> PRT
<213> Homo sapiens

<400> 211

Gly Lys Phe Gly Asn Val Tyr Leu Ala Arg
1 5 10

<210> 212
<211> 12
<212> PRT
<213> Homo sapiens

<400> 212

Ser His Phe Ile Val Ala Leu Lys Val Leu Phe Lys
1 5 10

<210> 213
<211> 16
<212> PRT
<213> Homo sapiens

<400> 213

Asp Leu Lys Pro Ala Asn Ile Leu Leu Asp Glu His Gly His Val Arg
1 5 10 15

<210> 214
<211> 16
<212> PRT
<213> Homo sapiens

<400> 214

Asp Leu Lys Ser Asn Asn Ile Phe Leu His Glu Asp Leu Thr Val Lys
1 5 10 15

<210> 215
<211> 18
<212> PRT
<213> Homo sapiens

<400> 215

Tyr Val Leu Asp Asp Glu Tyr Thr Ser Ser Val Gly Ser Lys Phe Pro
1 5 10 15

Val Arg

<210> 216

<211> 9
<212> PRT
<213> Homo sapiens

<400> 216

Leu Val Ala Ile Lys Cys Ile Ala Lys
1 5

<210> 217
<211> 9
<212> PRT
<213> Homo sapiens

<400> 217

Leu Phe Ala Val Lys Cys Ile Pro Lys
1 5

<210> 218
<211> 16
<212> PRT
<213> Homo sapiens

<400> 218

Ile Pro Thr Gly Gln Glu Tyr Ala Ala Lys Ile Ile Asn Thr Lys Lys
1 5 10 15

<210> 219
<211> 14
<212> PRT
<213> Homo sapiens

<400> 219

Thr Ser Thr Gln Glu Tyr Ala Ala Lys Ile Ile Asn Thr Lys
1 5 10

<210> 220
<211> 19
<212> PRT
<213> Homo sapiens

<400> 220

Asp Leu Lys Pro Glu Asn Leu Leu Tyr Ala Thr Pro Ala Pro Asp Ala
1 5 10 15

Pro Leu Lys

<210> 221
<211> 16
<212> PRT
<213> Homo sapiens

<400> 221

Asp Ile Lys Pro Ser Asn Leu Leu Val Gly Glu Asp Gly His Ile Lys
1 5 10 15

<210> 222
<211> 15
<212> PRT
<213> Homo sapiens

<400> 222

Glu Thr Gly Gln Gln Phe Ala Val Lys Ile Val Asp Val Ala Lys
1 5 10 15

<210> 223
<211> 16
<212> PRT
<213> Homo sapiens

<400> 223

Asp Leu Lys Pro Gln Asn Leu Leu Ile Asp Asp Lys Gly Thr Ile Lys
1 5 10 15

<210> 224
<211> 16
<212> PRT
<213> Homo sapiens

<400> 224

Asp Leu Lys Pro Ala Asn Ile Leu Val Met Gly Glu Gly Pro Glu Arg
1 5 10 15

<210> 225
<211> 16
<212> PRT
<213> Homo sapiens

<400> 225

Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Thr Glu Gly Ala Ile Lys
1 5 10 15

<210> 226
<211> 16
<212> PRT
<213> Homo sapiens

<400> 226

Asp Leu Lys Pro Glu Asn Ile Leu Val Thr Ser Gly Gly Thr Val Lys
1 5 10 15

<210> 227
<211> 11
<212> PRT
<213> Homo sapiens

<400> 227

Asp Leu Lys Pro Gln Asn Leu Leu Ile Asn Arg
1 5 10

<210> 228

<211> 16
<212> PRT
<213> Homo sapiens

<400> 228

Asp Leu Lys Pro Gln Asn Ile Leu Val Thr Ser Ser Gly Gln Ile Lys
1 5 10 15

<210> 229
<211> 16
<212> PRT
<213> Homo sapiens

<400> 229

Asp Leu Lys Pro Asn Asn Leu Leu Leu Asp Glu Asn Gly Val Leu Lys
1 5 10 15

<210> 230
<211> 11
<212> PRT
<213> Homo sapiens

<400> 230

Asp Met Lys Ala Ala Asn Val Leu Ile Thr Arg
1 5 10

<210> 231
<211> 12
<212> PRT
<213> Homo sapiens

<400> 231

Asp Ile Lys Pro Glu Asn Leu Leu Leu Asp Glu Arg
1 5 10

<210> 232
<211> 19
<212> PRT
<213> Homo sapiens

<400> 232

Asp Leu Lys Pro Glu Asn Val Leu Leu Ser Ser Gln Glu Glu Asp Cys
1 5 10 15

Leu Ile Lys

<210> 233
<211> 13
<212> PRT
<213> Homo sapiens

<400> 233

Asp Ile Lys Pro Asp Asn Phe Leu Met Gly Ile Gly Arg
1 5 10

<210> 234
<211> 14
<212> PRT
<213> Homo sapiens

<400> 234

Asp Val Lys Pro Asp Asn Phe Leu Met Gly Leu Gly Lys Lys
1 5 10

<210> 235
<211> 11
<212> PRT
<213> Homo sapiens

<400> 235

Lys Ile Gly Cys Gly Asn Phe Gly Glu Leu Arg
1 5 10

<210> 236
<211> 15
<212> PRT
<213> Homo sapiens

<400> 236

Asp Val Lys Pro Glu Asn Phe Leu Val Gly Arg Pro Gly Thr Lys
1 5 10 15

<210> 237
<211> 26
<212> PRT
<213> Homo sapiens

<400> 237

Leu Thr His Thr Asp Leu Lys Pro Glu Asn Ile Leu Phe Val Asn Ser
1 5 10 15

Asp Tyr Glu Leu Thr Tyr Asn Leu Glu Lys
20 25

<210> 238
<211> 23
<212> PRT
<213> Homo sapiens

<400> 238

Tyr Glu Ile Val Gly Asn Leu Gly Glu Gly Thr Phe Gly Lys Val Val
1 5 10 15

Glu Cys Leu Asp His Ala Arg
20

<210> 239
<211> 22
<212> PRT
<213> Homo sapiens

<400> 239

Val Ser Asp Phe Gly Leu Thr Lys Glu Ala Ser Ser Thr Gln Asp Thr
1 5 10 15

Gly Lys Leu Pro Val Lys
20

<210> 240
<211> 21
<212> PRT
<213> Homo sapiens

<400> 240

Ile Asp Pro Val Pro Asn Thr His Pro Leu Leu Val Phe Val Asn Pro
1 5 10 15

Lys Ser Gly Gly Lys
20

<210> 241
<211> 25
<212> PRT
<213> Homo sapiens

<400> 241

Ala Thr Phe Ser Phe Cys Val Ser Pro Leu Leu Val Phe Val Asn Ser
1 5 10 15

Lys Ser Gly Asp Asn Gln Gly Val Lys
20 25

<210> 242
<211> 36
<212> PRT
<213> Homo sapiens

<400> 242

Gly Arg Leu Leu Thr Ala Leu Val Leu Pro Asp Leu Leu His Ala Lys
1 5 10 15

Leu Pro Pro Asp Ser Cys Pro Leu Leu Val Phe Val Asn Pro Lys Ser
20 25 30

Gly Gly Leu Lys
35

<210> 243
<211> 14
<212> PRT
<213> Homo sapiens

<400> 243

Lys Gly Gly Ser Trp Ile Gln Glu Ile Asn Val Ala Glu Lys

1 5 10

<210> 244
<211> 13
<212> PRT
<213> Homo sapiens

<400> 244

Glu His Pro Phe Leu Val Lys Gly Gly Glu Asp Leu Arg
1 5 10

<210> 245
<211> 12
<212> PRT
<213> Homo sapiens

<400> 245

Tyr Ile Lys Tyr Asn Ser Asn Ser Gly Phe Val Arg
1 5 10

<210> 246
<211> 16
<212> PRT
<213> Homo sapiens

<400> 246

Asp Leu Lys Pro Ser Asn Leu Leu Ile Asn Thr Thr Cys Asp Leu Lys
1 5 10 15

<210> 247
<211> 16
<212> PRT
<213> Homo sapiens

<400> 247

Asp Leu Lys Pro Ser Asn Leu Leu Leu Asn Thr Thr Cys Asp Leu Lys
1 5 10 15

<210> 248
<211> 17
<212> PRT
<213> Homo sapiens

<400> 248

Asp Leu Lys Pro Ala Asn Leu Phe Ile Asn Thr Glu Asp Leu Val Leu
1 5 10 15

Lys

<210> 249
<211> 16
<212> PRT
<213> Homo sapiens

<400> 249

Asp Leu Lys Pro Ser Asn Leu Leu Val Asn Glu Asn Cys Glu Leu Lys
1 5 10 15

<210> 250
<211> 17
<212> PRT
<213> Homo sapiens

<400> 250

Thr Ser Val Ala Val Lys Thr Cys Lys Glu Asp Leu Pro Gln Glu Leu
1 5 10 15

Lys

<210> 251
<211> 14
<212> PRT
<213> Homo sapiens

<400> 251

Leu Arg Ala Asp Asn Thr Leu Val Ala Val Lys Ser Cys Arg
1 5 10

<210> 252
<211> 18
<212> PRT
<213> Homo sapiens

<400> 252

Leu Ile Lys Asp Asp Glu Tyr Asn Pro Cys Gln Gly Ser Lys Phe Pro
1 5 10 15

Ile Lys

<210> 253
<211> 18
<212> PRT
<213> Homo sapiens

<400> 253

Ile Gln Ser Ile Ala Pro Ser Leu Gln Val Ile Thr Ser Lys Gln Arg
1 5 10 15

Pro Arg

<210> 254
<211> 8
<212> PRT
<213> Homo sapiens

<400> 254

His Glu Ile Lys Leu Pro Val Lys
1 5

<210> 255
<211> 19
<212> PRT
<213> Homo sapiens

<400> 255

Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ala Leu
1 5 10 15

Tyr Gly Arg

<210> 256
<211> 16
<212> PRT
<213> Homo sapiens

<400> 256

Asp Ile Lys Gly Ala Asn Leu Leu Leu Thr Leu Gln Gly Asp Val Lys
1 5 10 15

<210> 257
<211> 16
<212> PRT
<213> Homo sapiens

<400> 257

Asp Leu Lys Pro Val Asn Ile Phe Leu Asp Ser Asp Asp His Val Lys
1 5 10 15

<210> 258
<211> 16
<212> PRT
<213> Homo sapiens

<400> 258

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Asp His Gly His Ile Arg
1 5 10 15

<210> 259
<211> 17
<212> PRT
<213> Homo sapiens

<400> 259

Asp Ile Lys Pro Gln Asn Leu Leu Val Asp Pro Asp Thr Ala Val Leu
1 5 10 15

Lys

<210> 260

<211> 17
<212> PRT
<213> Homo sapiens

<400> 260

Asp Ile Lys Pro Gln Asn Leu Leu Leu Asp Pro Asp Thr Ala Val Leu
1 5 10 15

Lys

<210> 261
<211> 16
<212> PRT
<213> Homo sapiens

<400> 261

Asp Ile Lys Gly Ala Asn Ile Leu Ile Asn Asp Ala Gly Glu Val Arg
1 5 10 15

<210> 262
<211> 15
<212> PRT
<213> Homo sapiens

<400> 262

Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Asp Val Gly Gly Lys
1 5 10 15

<210> 263
<211> 15
<212> PRT
<213> Homo sapiens

<400> 263

Asp Leu Lys Pro Glu Asn Ile Val Leu Gln Gln Gly Glu Gln Arg
1 5 10 15

<210> 264
<211> 19
<212> PRT
<213> Homo sapiens

<400> 264

Ser Gly Glu Leu Val Ala Val Lys Val Phe Asn Thr Thr Ser Tyr Leu
1 5 10 15

Arg Pro Arg

<210> 265
<211> 12
<212> PRT
<213> Homo sapiens

<400> 265

Trp Gln Gly Asn Asp Ile Val Val Lys Val Leu Lys
1 5 10

<210> 266
<211> 15
<212> PRT
<213> Homo sapiens

<400> 266

Ile Ser Met Ala Asp Val Lys Phe Ser Phe Gln Cys Pro Gly Arg
1 5 10 15

<210> 267
<211> 27
<212> PRT
<213> Homo sapiens

<400> 267

Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu Ile His Gly Asp
1 5 10 15

Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg
20 25

<210> 268
<211> 14
<212> PRT
<213> Homo sapiens

<400> 268

Val Glu Ile Gln Asn Leu Thr Tyr Ala Val Lys Leu Phe Lys
1 5 10

<210> 269
<211> 16
<212> PRT
<213> Homo sapiens

<400> 269

Asp Ile Lys Ser Ala Asn Ile Leu Leu Asp Glu Ala Phe Thr Ala Lys
1 5 10 15

<210> 270
<211> 17
<212> PRT
<213> Homo sapiens

<400> 270

Asp Leu Lys Pro His Asn Ile Leu Ile Ser Met Pro Asn Ala His Gly
1 5 10 15

Lys

<210> 271
<211> 38
<212> PRT
<213> Homo sapiens

<400> 271

Glu Ser Ile Phe Phe Asn Ser His Asn Val Ser Lys Pro Glu Ser Ser
1 5 10 15

Ser Val Leu Thr Glu Leu Asp Lys Ile Glu Gly Val Phe Glu Arg Pro
20 25 30

Ser Asp Glu Val Ile Arg
35

<210> 272
<211> 28
<212> PRT
<213> Homo sapiens

<400> 272

Gln Leu Ala Ser Ala Leu Ser Tyr Leu Glu Asp Lys Asp Leu Val His
1 5 10 15

Gly Asn Val Cys Thr Lys Asn Leu Leu Leu Ala Arg
20 25

<210> 273
<211> 20
<212> PRT
<213> Homo sapiens

<400> 273

Ile Gly Asp Phe Gly Leu Thr Lys Ala Ile Glu Thr Asp Lys Glu Tyr
1 5 10 15

Tyr Thr Val Lys
20

<210> 274
<211> 31
<212> PRT
<213> Homo sapiens

<400> 274

Tyr Asp Pro Glu Gly Asp Asn Thr Gly Glu Gln Val Ala Val Lys Ser
1 5 10 15

Leu Lys Pro Glu Ser Gly Gly Asn His Ile Ala Asp Leu Lys Lys
20 25 30

<210> 275
<211> 20
<212> PRT
<213> Homo sapiens

<400> 275

Ile Ala Asp Phe Gly Leu Ala Lys Leu Leu Pro Leu Asp Lys Asp Tyr
1 5 10 15

Tyr Val Val Arg
20

<210> 276
<211> 10
<212> PRT
<213> Homo sapiens

<400> 276

Asp Leu Lys Pro Ser Asn Ile Val Val Lys
1 5 10

<210> 277
<211> 14
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<400> 277

Asn Val His Thr Gly Glu Leu Ala Ala Val Lys Ile Ile Lys
1 5 10

<210> 278
<211> 14
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<213> Homo sapiens

<400> 278

Asn Val Asn Thr Gly Glu Leu Ala Ala Ile Lys Val Ile Lys
1 5 10

<210> 279
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<400> 279

Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys Val Val Ile Thr Asp Phe
1 5 10 15

Gly Leu Phe Gly Ile Ser Gly Val Val Arg
20 25

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<400> 280

Ser Lys Asn Val Phe Tyr Asp Asn Gly Lys
1 5 10

<210> 281
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<213> Homo sapiens

<400> 281

Ala Leu Tyr Ala Thr Lys Thr Leu Arg
1 5

<210> 282
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<400> 282

Asp Ile Lys Pro Asp Asn Ile Leu Ile Asp Leu Asp Gly His Ile Lys
1 5 10 15

<210> 283
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<400> 283

Glu Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ala Ile Asn
1 5 10 15

Tyr Gly Thr Phe Thr Ile Lys
20

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<400> 284

Asp Ile Lys Pro Gly Asn Leu Leu Leu Thr Thr Gly Gly Thr Leu Lys
1 5 10 15

<210> 285
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<400> 285

Asp Leu Lys Ala Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg
1 5 10 15

<210> 286
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<400> 286

Asp Leu Lys Pro His Asn Val Leu Leu Phe Thr Leu Tyr Pro Asn Ala
1 5 10 15

Ala Ile Ile Ala Lys
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<400> 287

Val Ala Val Lys Thr Leu Lys Pro Gly Thr Met Ser Val Gln Ala Phe
1 5 10 15

Leu Glu Glu Ala Asn Leu Met Lys
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<400> 288

Ile Met His Arg Asp Val Lys Pro Ser Asn Ile Leu Val Asn Ser Arg
1 5 10 15

<210> 289
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<400> 289

Lys Leu Ile His Leu Glu Ile Lys Pro Ala Ile Arg
1 5 10

<210> 290
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<400> 290

Asp Val Lys Pro Ser Asn Ile Leu Val Asn Ser Arg
1 5 10

<210> 291
<211> 18
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<400> 291

His Gln Ile Met His Arg Asp Val Lys Pro Ser Asn Ile Leu Val Asn
1 5 10 15

Ser Arg

<210> 292
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<400> 292

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Lys
1 5 10

<210> 293
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<400> 293

Asp Ile Lys Pro Ser Asn Ile Leu Leu Asp Arg
1 5 10

<210> 294
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<212> PRT
<213> Homo sapiens

<400> 294

Asp Val Lys Pro Ser Asn Met Leu Val Asn Thr Arg
1 5 10

<210> 295
<211> 16
<212> PRT
<213> Homo sapiens

<400> 295

Asp Val Lys Pro Ser Asn Val Leu Ile Asn Ala Leu Gly Gln Val Lys
1 5 10 15

<210> 296
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<400> 296

Asp Val Lys Pro Ser Asn Ile Leu Leu Asp Glu Arg
1 5 10

<210> 297
<211> 15
<212> PRT
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<400> 297

Asp Val Lys Gly Ala Asn Leu Leu Ile Asp Ser Thr Gly Gln Arg
1 5 10 15

<210> 298
<211> 31
<212> PRT
<213> Homo sapiens

<400> 298

Glu Leu Ala Val Lys Gln Val Gln Phe Asp Pro Asp Ser Pro Glu Thr
1 5 10 15

Ser Lys Glu Val Asn Ala Leu Glu Cys Glu Ile Gln Leu Leu Lys
20 25 30

<210> 299
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<213> Homo sapiens

<400> 299

Asp Ile Lys Gly Ala Asn Ile Leu Arg
1 5

<210> 300
<211> 31
<212> PRT
<213> Homo sapiens

<400> 300

Glu Leu Ala Ser Lys Gln Val Gln Phe Asp Pro Asp Ser Pro Glu Thr
1 5 10 15

Ser Lys Glu Val Ser Ala Leu Glu Cys Glu Ile Gln Leu Leu Lys
20 25 30

<210> 301
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<212> PRT
<213> Homo sapiens

<400> 301

Asp Ile Lys Gly Ala Asn Ile Phe Leu Thr Ser Ser Gly Leu Ile Lys
1 5 10 15

<210> 302
<211> 17
<212> PRT
<213> Homo sapiens

<400> 302

Asp Ile Lys Gly Asp Asn Val Leu Ile Asn Thr Tyr Ser Gly Val Leu
1 5 10 15

Lys

<210> 303
<211> 17
<212> PRT
<213> Homo sapiens

<400> 303

Asp Ile Lys Gly Asp Asn Val Leu Ile Asn Thr Phe Ser Gly Leu Leu
1 5 10 15

Lys

<210> 304
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<212> PRT
<213> Homo sapiens

<400> 304

Asp Leu Lys Ala Glu Asn Leu Leu Leu Asp Ala Asp Met Asn Ile Lys
1 5 10 15

<210> 305
<211> 19
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<213> Homo sapiens

<400> 305

Glu Val Ala Ile Lys Ile Ile Asp Lys Thr Gln Leu Asn Pro Thr Ser
1 5 10 15

Leu Gln Lys

<210> 306
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<212> PRT
<213> Homo sapiens

<400> 306

Glu Val Ala Ile Lys Ile Ile Asp Lys
1 5

<210> 307
<211> 16
<212> PRT
<213> Homo sapiens

<400> 307

Asp Leu Lys Ala Glu Asn Leu Leu Leu Asp Ala Glu Ala Asn Ile Lys
1 5 10 15

<210> 308
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<212> PRT
<213> Homo sapiens

<400> 308

Asp Leu Lys Pro Asp Asn Leu Leu Ile Thr Ser Met Gly His Ile Lys
1 5 10 15

<210> 309
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<213> Homo sapiens

<400> 309

Asp Leu Lys Pro Asp Asn Leu Leu Ile Thr Ser Leu Gly His Ile Lys
1 5 10 15

<210> 310
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<212> PRT
<213> Homo sapiens

<400> 310

Gly Ala Phe Gly Lys Val Tyr Leu Gly Gln Lys
1 5 10

<210> 311
<211> 8
<212> PRT
<213> Homo sapiens

<400> 311

Leu Tyr Ala Val Lys Val Val Lys
1 5

<210> 312
<211> 14
<212> PRT
<213> Homo sapiens

<400> 312

Asp Leu Lys Pro Glu Asn Leu Leu Phe Asp Glu Tyr His Lys
1 5 10

<210> 313
<211> 9
<212> PRT
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<400> 313

Lys Ile Tyr Ser Gly Asp Tyr Tyr Arg
1 5

<210> 314
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<212> PRT
<213> Homo sapiens

<400> 314

Asp Met Tyr Asp Lys Glu Tyr Tyr Ser Val His Asn Lys
1 5 10

<210> 315
<211> 21
<212> PRT
<213> Homo sapiens

<400> 315

Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro Ile Glu Ser Asp
1 5 10 15

Asp Met Glu His Lys
20

<210> 316
<211> 12
<212> PRT
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<400> 316

Asp Leu Lys Ser Ser Asn Ile Leu Leu Leu Glu Lys
1 5 10

<210> 317
<211> 9
<212> PRT
<213> Homo sapiens

<400> 317

Ala Pro Val Ala Ile Lys Val Phe Lys
1 5

<210> 318
<211> 34
<212> PRT
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<400> 318

Asp Leu Lys Pro Thr Asn Ile Leu Leu Gly Asp Glu Gly Gln Pro Val
1 5 10 15

Leu Met Asp Leu Gly Ser Met Asn Gln Ala Cys Ile His Val Glu Gly
20 25 30

Ser Arg

<210> 319
<211> 24
<212> PRT
<213> Homo sapiens

<400> 319

Asp Ile Lys Leu Glu Asn Ile Leu Leu Asp Ser Asn Gly His Val Val

1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys
20

<210> 320
<211> 24
<212> PRT
<213> Homo sapiens

<400> 320

Asp Leu Lys Leu Glu Asn Val Leu Leu Asp Ser Glu Gly His Ile Val
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys
20

<210> 321
<211> 22
<212> PRT
<213> Homo sapiens

<400> 321

Glu Thr Gly Gln Ile Val Ala Ile Lys Gln Val Pro Val Glu Ser Asp
1 5 10 15

Leu Gln Glu Ile Ile Lys
20

<210> 322
<211> 22
<212> PRT
<213> Homo sapiens

<400> 322

Glu Ser Gly Gln Val Val Ala Ile Lys Gln Val Pro Val Glu Ser Asp
1 5 10 15

Leu Gln Glu Ile Ile Lys
20

<210> 323
<211> 16
<212> PRT
<213> Homo sapiens

<400> 323

Asp Ile Lys Ala Ala Asn Val Leu Leu Ser Glu His Gly Glu Val Lys
1 5 10 15

<210> 324
<211> 39
<212> PRT
<213> Homo sapiens

<400> 324

Thr Gln Gln Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu
1 5 10 15

Asp Glu Ile Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys
20 25 30

Asp Ser Ser Tyr Val Thr Lys
35

<210> 325
<211> 16
<212> PRT
<213> Homo sapiens

<400> 325

Asp Ile Lys Ala Ala Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys
1 5 10 15

<210> 326
<211> 16
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<213> Homo sapiens

<400> 326

Asp Val Lys Gly Asn Asn Ile Leu Leu Thr Thr Glu Gly Gly Val Lys
1 5 10 15

<210> 327
<211> 12
<212> PRT
<213> Homo sapiens

<400> 327

Asp Ile Lys Pro Asp Asn Leu Leu Leu Asp Ser Lys
1 5 10

<210> 328
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<400> 328

Asp Ile Lys Pro Asp Asn Leu Leu Leu Asp Ala Lys
1 5 10

<210> 329
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<400> 329

Asp Ile Lys Ser Gln Asn Ile Phe Leu Thr Lys
1 5 10

<210> 330
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<212> PRT
<213> Homo sapiens

<400> 330

Asp Leu Lys Pro Ala Asn Val Phe Leu Asp Gly Lys
1 5 10

<210> 331
<211> 11
<212> PRT
<213> Homo sapiens

<400> 331

Ser Lys Asn Ile Phe Leu Thr Gln Asn Gly Lys
1 5 10

<210> 332
<211> 11
<212> PRT
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<400> 332

Asp Leu Lys Thr Gln Asn Val Phe Leu Thr Arg
1 5 10

<210> 333
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<212> PRT
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<400> 333

Asp Ile Lys Pro Ala Asn Val Phe Ile Thr Ala Thr Gly Val Val Lys
1 5 10 15

<210> 334
<211> 14
<212> PRT
<213> Homo sapiens

<400> 334

Ala Ala Cys Leu Leu Asp Gly Val Pro Val Ala Leu Lys Lys
1 5 10

<210> 335
<211> 11
<212> PRT
<213> Homo sapiens

<400> 335

Asp Leu Lys Thr Gln Asn Ile Leu Leu Asp Lys
1 5 10

<210> 336

<211> 11
<212> PRT
<213> Homo sapiens

<400> 336

Asp Ile Lys Thr Leu Asn Ile Phe Leu Thr Lys
1 5 10

<210> 337
<211> 16
<212> PRT
<213> Homo sapiens

<400> 337

Asp Ile Lys Pro Gly Asn Leu Leu Val Asn Ser Asn Cys Val Leu Lys
1 5 10 15

<210> 338
<211> 34
<212> PRT
<213> Homo sapiens

<400> 338

Asp Val Lys Ala Gly Asn Ile Leu Leu Gly Glu Asp Gly Ser Val Gln
1 5 10 15

Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly Asp Ile
20 25 30

Thr Arg

<210> 339
<211> 16
<212> PRT
<213> Homo sapiens

<400> 339

Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys
1 5 10 15

<210> 340
<211> 13
<212> PRT
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<400> 340

Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg
1 5 10

<210> 341
<211> 16
<212> PRT
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<400> 341

Asp Leu Lys Pro Gly Asn Leu Ala Val Asn Glu Asp Cys Glu Leu Lys
1 5 10 15

<210> 342
<211> 16
<212> PRT
<213> Homo sapiens

<400> 342

Asp Leu Lys Pro Glu Asn Ile Met Leu Asn His Gln Gly His Val Lys
1 5 10 15

<210> 343
<211> 16
<212> PRT
<213> Homo sapiens

<400> 343

Asp Leu Lys Pro Glu Asn Ile Met Leu Ser Ser Gln Gly His Ile Lys
1 5 10 15

<210> 344
<211> 12
<212> PRT
<213> Homo sapiens

<400> 344

Val Met Asp Pro Thr Lys Ile Leu Ile Thr Gly Lys
1 5 10

<210> 345
<211> 14
<212> PRT
<213> Homo sapiens

<400> 345

Ser Lys Leu Thr Asp Asn Leu Val Ala Leu Lys Glu Ile Arg
1 5 10

<210> 346
<211> 14
<212> PRT
<213> Homo sapiens

<400> 346

Ser Lys Leu Thr Glu Asn Leu Val Ala Leu Lys Glu Ile Arg
1 5 10

<210> 347
<211> 28
<212> PRT
<213> Homo sapiens

<400> 347

Ser Pro Gly Gln Pro Ile Gln Val Val Tyr Val Pro Ser His Leu Tyr

1 5 10 15

His Met Val Phe Glu Leu Phe Lys Asn Ala Met Arg
20 25

<210> 348
<211> 16
<212> PRT
<213> Homo sapiens

<400> 348

Asp Leu Lys Pro Ser Asn Ile Phe Phe Thr Met Asp Asp Val Val Lys
1 5 10 15

<210> 349
<211> 8
<212> PRT
<213> Homo sapiens

<400> 349

Leu Val Ala Leu Lys Val Ile Arg
1 5

<210> 350
<211> 16
<212> PRT
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<400> 350

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Asp Asn Met Asn Ile Lys
1 5 10 15

<210> 351
<211> 17
<212> PRT
<213> Homo sapiens

<400> 351

Ala Thr Gly His Glu Phe Ala Val Lys Ile Met Glu Val Thr Ala Glu
1 5 10 15

Arg

<210> 352
<211> 14
<212> PRT
<213> Homo sapiens

<400> 352

Ser Glu Glu Pro Tyr Gly Gln Leu Asn Pro Lys Trp Thr Lys
1 5 10

<210> 353
<211> 16

<212> PRT
<213> Homo sapiens

<400> 353

Ser Gly Thr Pro Met Gln Ser Ala Ala Lys Ala Pro Tyr Leu Ala Lys
1 5 10 15

<210> 354
<211> 14
<212> PRT
<213> Homo sapiens

<400> 354

Val Pro His Thr Gln Ala Val Val Leu Asn Ser Lys Asp Lys
1 5 10

<210> 355
<211> 20
<212> PRT
<213> Homo sapiens

<400> 355

Val Ile Phe Lys Cys Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu
1 5 10 15

Gln Met Ile Arg
20

<210> 356
<211> 18
<212> PRT
<213> Homo sapiens

<400> 356

Thr Glu Asp Gly Gly Lys Tyr Pro Val Ile Phe Lys His Gly Asp Asp
1 5 10 15

Leu Arg

<210> 357
<211> 28
<212> PRT
<213> Homo sapiens

<400> 357

Val Phe Gly Glu Asp Ser Val Gly Val Ile Phe Lys Asn Gly Asp Asp
1 5 10 15

Leu Arg Gln Asp Met Leu Thr Leu Gln Met Leu Arg
20 25

<210> 358
<211> 14
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<213> Homo sapiens

<400> 358

Val Asn Trp Leu Ala His Asn Val Ser Lys Asp Asn Arg Gln
1 5 10

<210> 359
<211> 9
<212> PRT
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<400> 359

Lys Lys Pro Leu Trp Leu Glu Phe Lys
1 5

<210> 360
<211> 18
<212> PRT
<213> Homo sapiens

<400> 360

Ala Lys Glu Leu Pro Thr Leu Lys Asp Asn Asp Phe Ile Asn Glu Gly
1 5 10 15

Gln Lys

<210> 361
<211> 28
<212> PRT
<213> Homo sapiens

<400> 361

Thr Leu Val Ile Lys Glu Val Ser Ser Glu Asp Ile Ala Asp Met His
1 5 10 15

Ser Asn Leu Ser Asn Tyr His Gln Tyr Ile Val Lys
20 25

<210> 362
<211> 19
<212> PRT
<213> Homo sapiens

<400> 362

Gly Gly Lys Ser Gly Ala Ala Phe Tyr Ala Thr Glu Asp Asp Arg Phe
1 5 10 15

Ile Leu Lys

<210> 363
<211> 16
<212> PRT
<213> Homo sapiens

<400> 363

Asp Leu Lys Thr Ser Asn Leu Leu Leu Ser His Ala Gly Ile Leu Lys
1 5 10 15

<210> 364
<211> 16
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<400> 364

Asp Leu Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile Lys
1 5 10 15

<210> 365
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<400> 365

Asp Leu Lys Leu Asp Asn Ile Leu Leu Asp Ala Glu Gly His Cys Lys
1 5 10 15

<210> 366
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<212> PRT
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<400> 366

Ile Tyr Ala Met Lys Val Val Lys
1 5

<210> 367
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<212> PRT
<213> Homo sapiens

<400> 367

Asp Val Ala Val Lys Val Ile Asp Lys
1 5

<210> 368
<211> 19
<212> PRT
<213> Homo sapiens

<400> 368

Val Leu Leu Ser Glu Phe Arg Pro Ser Gly Glu Leu Phe Ala Ile Lys
1 5 10 15

Ala Leu Lys

<210> 369
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<212> PRT
<213> Homo sapiens

<400> 369

Asp Leu Lys Pro Ser Asn Ile Phe Leu Val Asp Thr Lys
1 5 10

<210> 370
<211> 20
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<400> 370

Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala Gly Lys
1 5 10 15

Ile Val Pro Lys
20

<210> 371
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<212> PRT
<213> Homo sapiens

<400> 371

Ala Glu Ser Ile His Thr Gly Leu Glu Val Ala Ile Lys Met Ile Asp
1 5 10 15

Lys Lys

<210> 372
<211> 19
<212> PRT
<213> Homo sapiens

<400> 372

Cys Asn Ile Leu His Ala Asp Ile Lys Pro Asp Asn Ile Leu Val Asn
1 5 10 15

Glu Ser Lys

<210> 373
<211> 15
<212> PRT
<213> Homo sapiens

<400> 373

Phe Leu Ser Gly Leu Glu Leu Val Lys Gln Gly Ala Glu Ala Arg
1 5 10 15

<210> 374
<211> 14
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<213> Homo sapiens

<400> 374

Tyr Ile Glu Asp Glu Asp Tyr Tyr Lys Ala Ser Val Thr Arg
1 5 10

<210> 375
<211> 16
<212> PRT
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<400> 375

Asp Leu Lys Pro Glu Asn Ile Leu Val Asp Asn Asp Phe His Ile Lys
1 5 10 15

<210> 376
<211> 16
<212> PRT
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<400> 376

Asp Leu Lys Pro Ser Asn Val Leu Leu Asp Pro Glu Leu His Val Lys
1 5 10 15

<210> 377
<211> 11
<212> PRT
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<400> 377

Asp Val Lys Pro Asp Asn Met Leu Leu Asp Lys
1 5 10

<210> 378
<211> 31
<212> PRT
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<400> 378

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys Glu Ala Ile Asp His Glu Lys
20 25 30

<210> 379
<211> 16
<212> PRT
<213> Homo sapiens

<400> 379

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

<210> 380

<211> 20
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<400> 380

Asp Leu Lys Pro Ser Asn Ile Leu Tyr Val Asp Glu Ser Gly Asn Pro
1 5 10 15

Glu Cys Leu Arg
20

<210> 381
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<212> PRT
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<400> 381

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Leu Thr Asp Phe Gly Leu Ser Lys Glu Ser Ile Asp His Glu Lys
20 25 30

<210> 382
<211> 20
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<213> Homo sapiens

<400> 382

Asp Leu Lys Pro Ser Asn Ile Leu Tyr Val Asp Glu Ser Gly Asn Pro
1 5 10 15

Glu Ser Ile Arg
20

<210> 383
<211> 24
<212> PRT
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<400> 383

Asp Leu Lys Pro Glu Asn Ile Leu Leu Asp Glu Glu Gly His Ile Lys
1 5 10 15

Ile Thr Asp Phe Gly Leu Ser Lys
20

<210> 384
<211> 15
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<400> 384

Val Leu Gly Val Ile Asp Lys Val Leu Leu Val Met Asp Thr Arg
1 5 10 15

<210> 385
<211> 9
<212> PRT
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<400> 385

Phe Tyr Ala Val Lys Val Leu Gln Lys
1 5

<210> 386
<211> 16
<212> PRT
<213> Homo sapiens

<400> 386

Asp Leu Lys Ala Gly Asn Ile Leu Phe Thr Leu Asp Gly Asp Ile Lys
1 5 10 15

<210> 387
<211> 22
<212> PRT
<213> Homo sapiens

<400> 387

Asp Thr Val Thr Ile His Ser Val Gly Gly Thr Ile Thr Ile Leu Pro
1 5 10 15

Thr Lys Thr Lys Pro Lys
20

<210> 388
<211> 12
<212> PRT
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<400> 388

Asp Leu Lys Pro Glu Asn Val Val Phe Phe Glu Lys
1 5 10

<210> 389
<211> 25
<212> PRT
<213> Homo sapiens

<400> 389

Val Ala Ile Lys Thr Leu Lys Pro Gly Thr Met Ser Pro Glu Ala Phe
1 5 10 15

Leu Gln Glu Ala Gln Val Met Lys Lys
20 25

<210> 390
<211> 21
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<213> Homo sapiens

<400> 390

Ile Ile His Thr Asp Ile Lys Pro Glu Asn Ile Leu Leu Ser Val Asn
1 5 10 15

Glu Gln Tyr Ile Arg
20

<210> 391
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<400> 391

Phe Val Ala Met Lys Val Val Lys
1 5

<210> 392
<211> 10
<212> PRT
<213> Homo sapiens

<400> 392

Asp Leu Lys Leu Glu Asn Ile Met Val Lys
1 5 10

<210> 393
<211> 24
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<400> 393

Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln Gln
1 5 10 15

Asn Leu Gln Gly Tyr Asp Ala Lys
20

<210> 394
<211> 11
<212> PRT
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<400> 394

Ile Ser Asp Phe Gly Leu Ser Lys Ala Leu Arg
1 5 10

<210> 395
<211> 17
<212> PRT
<213> Homo sapiens

<400> 395

Asp Leu Lys Pro Pro Asn Leu Leu Leu Val Ala Gly Gly Thr Val Leu

1 5 10 15

Lys

<210> 396
<211> 16
<212> PRT
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<400> 396

Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr Glu Pro Gly Gln Val Lys
1 5 10 15

<210> 397
<211> 16
<212> PRT
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<400> 397

Asp Val Lys Ala Gly Asn Ile Leu Leu Ser Glu Pro Gly Leu Val Lys
1 5 10 15

<210> 398
<211> 24
<212> PRT
<213> Homo sapiens

<400> 398

Thr Gly Asp Leu Phe Ala Ile Lys Val Phe Asn Asn Ile Ser Phe Leu
1 5 10 15

Arg Pro Val Asp Val Gln Met Arg
20

<210> 399
<211> 18
<212> PRT
<213> Homo sapiens

<400> 399

Tyr Val Leu Asp Asp Gln Tyr Thr Ser Ser Ser Gly Ala Lys Phe Pro
1 5 10 15

Val Lys

<210> 400
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Gly Asn Ile Leu Leu Val Asp Gly Thr Ala Cys Gly Glu Ile Lys
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Gly Asn Ile Leu Leu Val Asn Gly Thr Ala Cys Gly Glu Ile Lys
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Leu Glu Lys Pro His Leu Lys
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Asp Ile Lys Ala Ala Asn Leu Leu Leu Gly Tyr Lys
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Gly Ser Phe Lys Thr Val Tyr Lys
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Lys

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Trp Ile Ser Gln Asp Lys Glu Val Ala Val Lys Lys
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Tyr Thr Ala Arg
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<400> 411

Thr Gly Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Gly Asp Glu
1 5 10 15

Glu Glu Glu Ile Lys Gln Glu Ile Asn Met Leu Lys Lys
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