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(71) Applicant: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 450 Brookline Avenue, Boston, MA 02215 (US).

(72) Inventors: **GRAY, Nathanael**; 26 Greenview Avenue, Boston, MD 02130 (US). **TAN, Li**; 400 Brookline Ave., Apt. 5B, Boston, MA 02115 (US).

(74) Agent: **WEATHERHEAD, Robin, A.**; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

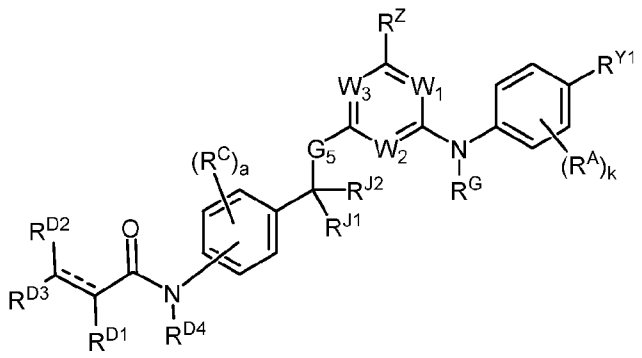
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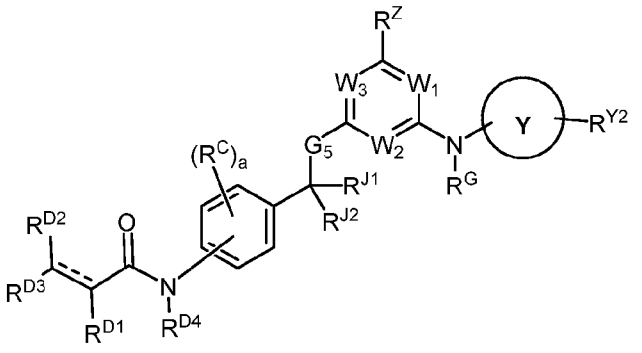
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(54) Title: HYDROPHOBICALLY TAGGED JANUS KINASE INHIBITORS AND USES THEREOF



(I)



(II)

(57) Abstract: The present invention provides Janus kinase inhibitors, such as compounds of Formula (I) and Formula (II) wherein R^{Y1} and R^{Y2} comprise a tagged hydrophobic moiety R^{H}. The compounds may covalently or non-covalently bind a kinase (e.g., Janus kinase 3 (JAK3)). The hydrophobic moiety R^{H} may signal to the intracellular protein homeostasis machinery to induce degradation of the targeted kinase. Also provided are pharmaceutical compositions, kits, methods, and uses that involve the compounds for reducing the activity of a kinase and/or treating and/or preventing a condition associated with aberrant activity of a kinase (*e.g.*, a proliferative disease, inflammatory disorder, autoimmune disorder, painful condition, and/or viral infection).

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HYDROPHOBICALLY TAGGED JANUS KINASE INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, 61/983,190, filed April 23, 2014, which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

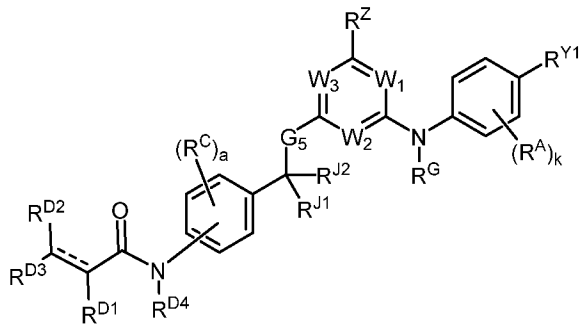
[0002] Kinase inhibitors are rapidly becoming one of the most validated and pursued class of drug targets. Janus kinases (JAKs) comprise a family of 4 kinases that play multiple roles downstream of cytokine signalling in both immune and non-immune cells. Autoimmunity is driven by an aberrant adaptive immune response to self-antigens and JAK-STAT signalling is known to play a key role in this process. Thus JAK inhibitors have considerable potential for the development of drugs to treat autoimmunity. JAK3 is an especially attractive target as, unlike other JAKs, its expression is restricted to the immune system. Several pharmaceutical companies have considerable efforts underway to develop JAK3 inhibitors. While the FDA recently approved the JAK3 inhibitor Tofacitnib (XELJANZ®), which is actually a pan-JAK inhibitor, it was rejected by CHMP in Europe due to safety concerns. This highlights the fact that while pan-JAK inhibitors are effective in RA, they carry a range of adverse side effects, many of which may relate to the functions of JAKs outside the adaptive immune system. Therefore, development of selective small molecule inhibitors of JAK3 would potentially represent a promising class of novel therapeutics.

[0003] Inducing protein degradation using hydrophobic tags is a strategy that has recently received attention from the scientific community. For example, Crews and co–workers discovered that covalent attachment of a hydrophobic tag to a dehalogenase fusion protein is effective in modulating the level of the transgenic fusion protein. See, *e.g.,* Neklesa *et al., Nature Chemical Biology* (2011) 7:538–543. Hydrophobic tags used to induce protein degradation may eventually be found useful in a variety of applications, such as, for example, tagged therapeutic agents and tagged research tools for inducing protein degradatation *in vivo* and *in vitro*. However, the development of such hydrophobically tagged agents and tools is underrealized and continues to remain of great interest.

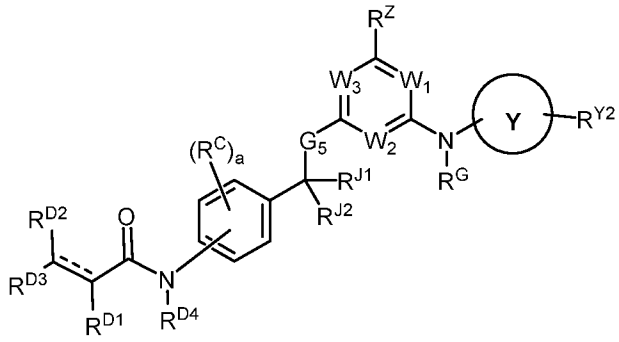
SUMMARY OF THE INVENTION

[0004] Thus, the present invention is based on the development of kinase inhibitors, such as the compounds described herein (*i.e.*, compounds of Formula (**I**) and (**II**)). The compounds described herein possess a kinase recognition element that binds the kinase either covalently or non-covalently. The compounds described herein are further "tagged" with a hydrophobic moiety R^H. While the precise function of these hydrophobic moeties are unknown, it has been observed that such functionality can lead to improved bioactivity through mechanisms not directly associated with enzymatic inhibition.

[0005] The present invention is based on the development of compounds of Formula (**I**) and (**II**):



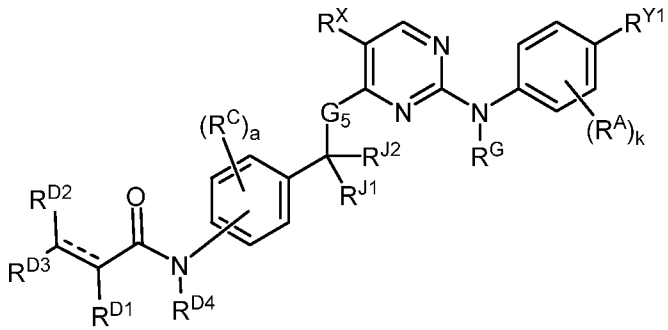
(**I**)



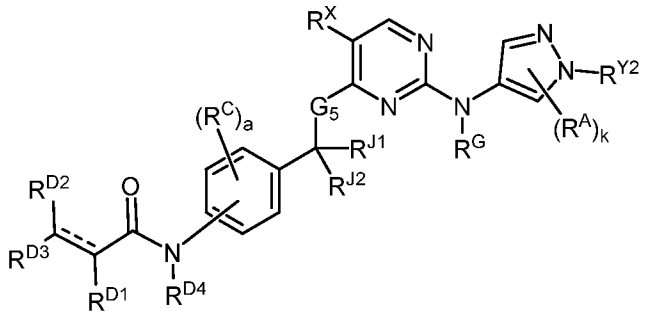
(**II**)

and pharmaceutically acceptable salts thereof, wherein ----, R^{D1}, R^{D2}, R^{D3}, R^{D4}, G_5, R^A, R^C, R^G, R^{J1}, R^{J2}, R^Z, W_1, W_2, W_3, R^{Y1}, R^{Y2}, a, k, y, and x are as described herein.

[0006] In certain embodiments, the compounds of Formula (**I**) and (**II**) are of Formula:



(**I-A**)



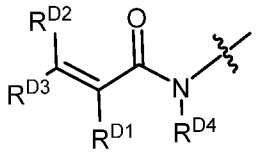
(**II-A**)

or pharmaceutically acceptable salts thereof.

[0007] In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit JAK, *e.g.,* JAK1, JAK2, JAK3, or TYK2. In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit JAK3. In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit JAK3 selectively. In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit JAK3 up to 100-fold selectively over JAK1 and/or JAK2, which do not possess an equivalently placed cysteine residue.

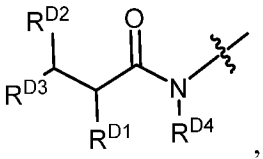
[0008] In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit EGFR. In certain aspects, the kinase inhibitors of Formula (**I**) or (**II**) inhibit a gatekeeper mutant (T790M) of EGFR.

[0009] In certain embodiments, the compounds described herein comprises group of formula



, *i.e.,* wherein ==== provided in a compound of Formula (**I**) or (**II**) is a double bond, wherein such group in certain embodiments covalently reacts with and/or binds to the kinase.

[0010] Alternatively, in certain embodiments, the compounds describe herein comprises a group of formula:



, *i.e.,* wherein ==== provided in a compound of Formula (**I**) or (**II**) is a single bond.

[0011] In another aspect, provided are pharmaceutical compositions comprising a compound of Formula (**I**) or (**II**) and a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition may be useful for reducing the activity of a kinase 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, inflammatory disorder, autoimmune disorder, painful condition, or viral infection).

[0012] In another aspect, provided are methods for reducing the activity of a kinase in a subject in need thereof. In certain embodiments, the method includes administering to the subject a compound described herein, or a pharmaceutical composition thereof, in an amount sufficient to reduce the activity of the kinase.

[0013] In another aspect, provided are methods 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, inflammatory disorder, autoimmune disorder, painful condition, or viral infection). In certain embodiments, the method includes administering to the subject a compound described herein, or a pharmaceutical composition thereof, in an amount sufficient to treat and/or prevent the condition.

[0014] In another aspect, provided are kits comprising a container with a compound described herein, 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 reducing 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).

[0015] The details of one or more embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, the Examples, and the Claims.

DEFINITIONS

Chemical definitions

[0016] 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.

[0017] 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. "Racemic" refers to a compound in which the percent by weight of one enantiomer is equal to the percent by weight of the other enantiomer.

[0018] The terms "enantiomerically enriched," "enantiomerically pure" and "non–racemic," as used interchangeably herein, refer to a compound in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer compared to a control mixture of the racemic composition (*e.g.,* greater than 1:1 by weight). For example, an enantiomerically enriched enantiomer, means a compound having greater than 50% by weight of one enantiomer relative to the other enantiomer, *e.g.*, at least 75% by weight, or at least 80% by weight. In some embodiments, the enrichment can be much greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non–racemic" compound, which refers to a compound with at least 85% by weight of one enantiomer relative to other enantiomer, *e.g.*, at least 90% by weight, or at least 95% by weight.

[0019] Enantiomers 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 enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *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).

[0020] 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.

[0021] 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.

[0022] 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), n–propyl (C_3), isopropyl (C_3), n–butyl (C_4), tert–butyl (C_4), sec–butyl (C_4), iso–butyl (C_4), n–pentyl (C_5), 3–pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3–methyl–2–butanyl (C_5), tertiary amyl (C_5), and n–hexyl (C_6). 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. In certain embodiments, the alkyl group is an unsubstituted C_{1-10} alkyl (*e.g.,* $–CH_3$). In certain embodiments, the alkyl group is a substituted C_{1-10} alkyl.

[0023] The term "haloalkyl" is a substituted alkyl group as described 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 some embodiments, the haloalkyl moiety has 1 to 8 carbon atoms ("C_{1-8} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 6 carbon atoms ("C_{1-6} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 4 carbon atoms ("C_{1-4} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 3 carbon atoms ("C_{1-3} haloalkyl"). In some embodiments, the haloalkyl moiety has 1 to 2 carbon atoms ("C_{1-2} haloalkyl"). In some embodiments, all of the haloalkyl hydrogen atoms are replaced with fluoro to provide a perfluoroalkyl group. In some 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.

[0024] The term "heteroalkyl" refers to an alkyl group as described 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, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{1-10} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{1-9} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{1-8} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{1-7} alkyl"). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms within the parent chain ("heteroC_{1-6} alkyl"). In some 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 some 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 some 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 some 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 some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom ("heteroC_1 alkyl"). In some 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.

[0025] The term "alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more double bonds (*e.g.,* 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms ("C_{2-9} alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C_{2-8} alkenyl"). In some embodiments, an alkenyl group has 2 to 7 carbon atoms ("C_{2-7} alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C_{2-6} alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C_{2-5} alkenyl"). In some

embodiments, an alkenyl group has 2 to 4 carbon atoms ("C_{2-4} alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C_{2-3} alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C_2 alkenyl"). The one or more carbon–carbon double bonds can be internal (such as in 2–butenyl) or terminal (such as in 1–butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1–propenyl (C_3), 2–propenyl (C_3), 1–butenyl (C_4), 2–butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups 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.

[0026] The term "heteroalkenyl" refers to an alkenyl group as described 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, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-10} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-9} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-8} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-7} alkenyl"). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms within the parent chain ("heteroC_{2-6} alkenyl"). In some 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 some 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 some 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 some 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.

[0027] The term "alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more triple bonds (*e.g.,* 1, 2, 3, or 4 triple bonds) and optionally one or more double bonds (*e.g.,* 1, 2, 3, or 4 double bonds) ("C_{2-10} alkynyl"). In some embodiments, an alkynyl group has 2 to 9 carbon atoms ("C_{2-9} alkynyl"). In some embodiments, an alkynyl group has 2 to 8 carbon atoms ("C_{2-8} alkynyl"). In some embodiments, an alkynyl group has 2 to 7 carbon atoms ("C_{2-7} alkynyl"). In some embodiments, an alkynyl group has 2 to 6 carbon atoms ("C_{2-6} alkynyl"). In some embodiments, an alkynyl group has 2 to 5 carbon atoms ("C_{2-5} alkynyl"). In some embodiments, an alkynyl group has 2 to 4 carbon atoms ("C_{2-4} alkynyl"). In some embodiments, an alkynyl group has 2 to 3 carbon atoms ("C_{2-3} alkynyl"). In some embodiments, an alkynyl group has 2 carbon atoms ("C_2 alkynyl"). The one or more carbon–carbon triple bonds can be internal (such as in 2–butynyl) or terminal (such as in 1–butynyl). Examples of C_{2-4} alkynyl groups include, without limitation, ethynyl (C_2), 1–propynyl (C_3), 2–propynyl (C_3), 1–butynyl (C_4), 2–butynyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkynyl groups as well as pentynyl (C_5), hexynyl (C_6), and the like. Additional examples of alkynyl include heptynyl (C_7), octynyl (C_8), and the like. Unless otherwise specified, each instance of an alkynyl group is independently 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.

[0028] The term "heteroalkynyl" refers to an alkynyl group as described 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, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-10} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-9} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4

heteroatoms within the parent chain ("heteroC_{2-8} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms within the parent chain ("heteroC_{2-7} alkynyl"). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms within the parent chain ("heteroC_{2-6} alkynyl"). In some 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 some 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 some 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 some 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.

[0029] The term "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 some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms ("C_{3-10} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 9 ring carbon atoms ("C_{3-9} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms ("C_{3-8} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms ("C_{3-7} carbocyclyl"). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms ("C_{3-6} carbocyclyl"). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C_{5-10} carbocyclyl"). Exemplary C_{3-6} carbocyclyl groups include, without limitation, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), and the like. Exemplary C_{3-8} carbocyclyl groups include, without limitation, the aforementioned C_{3-6} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), and the like. Exemplary C_{3-10} carbocyclyl groups include, without limitation, the aforementioned C_{3-8} carbocyclyl groups as well as cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}),

cyclodecenyl (C_{10}), octahydro–1*H*–indenyl (C_9), decahydronaphthalenyl (C_{10}), spiro[4.5]decanyl (C_{10}), and the like. In certain embodiments, the carbocyclyl group is either monocyclic ("monocyclic carbocyclyl") or polycyclic (*e.g.,* containing a fused, bridged or spiro–fused 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. Exemplary fused bicyclic systems include, but are not limited to, decalin (cis or trans decalin). Exemplary fused tricyclic systems include, but are not limited to, fluorenyl. Exemplary spiro–fused bicyclic systems include, but are not limited to, spiropentane. Exemplary bridged bicyclic systems include, but are not limited to, norbornane, norbornene, bicyclo[2.2.2]octane, bicyclo[2.2.2]oct–2–ene, bicyclo[3.2.1]octane, and bicyclo[2.2.1]heptan–2–one. Exemplary bridged tricyclic systems include, but are not limited to adamantane. "Carbocyclyl" 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.

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

[0031] The term "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. In certain embodiments, the heterocyclyl group is either monocyclic ("monocyclic heterocyclyl") or polycyclic (*e.g.,* containing a fused, bridged or spiro–fused 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" 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.

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

[0033] 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, dioxanyl. Exemplary 6–membered heterocyclyl groups containing 3 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.

[0034] "Heterocyclylalkyl" is a subset of "alkyl" and refers to an alkyl group, as described herein, substituted by one or more heterocyclyl groups, as described herein, wherein the point of attachment is on the alkyl moiety.

[0035] The term "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 some embodiments, an aryl group has 6 ring carbon atoms ("C_6 aryl"; *e.g.,* phenyl). In some embodiments, an aryl group has 10 ring carbon atoms ("C_{10} aryl"; *e.g.,* naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms ("C_{14} aryl"; *e.g.,* anthracenyl). "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.

[0036] "Aralkyl" or "arylalkyl" is a subset of "alkyl" and refers to an alkyl group, as described herein, substituted by one or more aryl groups, as described herein, wherein the point of attachment is on the alkyl moiety.

[0037] The term "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).

[0038] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and

sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently 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.

[0039] 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.

[0040] "Heteroaralkyl" or "heteroarylalkyl" is a subset of "alkyl" and refers to an alkyl group, as described herein, substituted by one or more heteroaryl groups, as described herein, wherein the point of attachment is on the alkyl moiety.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] As understood from the above, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as described 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", whether preceded by the term "optionally" or not, means that at least one hydrogen present on a group (*e.g.,* a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.,* a substituent which upon substitution results in a stable compound, *e.g.,* a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a "substituted" group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term "substituted" is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present invention contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this invention, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0045] 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, $C_{1–10}$ heteroalkyl, $C_{2–10}$ heteroalkenyl, $C_{2–10}$heteroalkynyl, $C_{3–14}$ 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, $C_{1–10}$ heteroalkyl, $C_{2–10}$ heteroalkenyl, $C_{2–10}$heteroalkynyl, $C_{3–14}$ 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, $C_{1–10}$ heteroalkyl, $C_{2–10}$ heteroalkenyl, $C_{2–10}$heteroalkynyl, $C_{3–14}$ 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, C_{1-10} heteroalkyl, C_{2-10} heteroalkenyl, C_{2-10}heteroalkynyl, C_{3-14} 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, C_{1-6} heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6}heteroalkynyl, 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, C_{1-6} heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6}heteroalkynyl, 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, C_{1-6} heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6}heteroalkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, 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, C_{1-6}heteroalkyl, C_{2-6} heteroalkenyl, C_{2-6}heteroalkynyl, 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.

[0046] In certain embodiments, one or more carbon atom substituents are selected from the group consisting of halogen, –CN, –NO_2, –N_3, –SO_2H, –SO_3H, –OH, –OR^{aa}, –N(R^{bb})$_2$, –SH, –SR^{aa}, –C(=O)R^{aa}, –CO_2H, –CHO, –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(=O)$NR^{bb}SO_2R^{aa}$, –$NR^{bb}SO_2R^{aa}$, –SO_2N(R^{bb})$_2$, –SO_2R^{aa}, –S(=O)R^{aa}, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} heteroalkyl, C_{2-10} heteroalkenyl, C_{2-10}heteroalkynyl, C_{3-14} 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.

[0047] The term "halo" or "halogen" refers to fluorine (fluoro, –F), chlorine (chloro, –Cl), bromine (bromo, –Br), or iodine (iodo, –I).

[0048] The term "counterion" is a negatively charged group associated with a positively charged quarternary amine in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.,* F^-, Cl^-, Br^-, I^-), NO_3^-, ClO_4^-, OH^-, $H_2PO_4^-$, HSO_4^-, sulfonate ions (*e.g.,* methansulfonate, trifluoromethanesulfonate, p–toluenesulfonate, benzenesulfonate, 10–camphor sulfonate, naphthalene–2–sulfonate, naphthalene–1–sulfonic acid–5–sulfonate, ethan–1–sulfonic acid–2–sulfonate, and the like), and carboxylate ions (*e.g.,* acetate,

ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0049] The term "hydroxyl" or "hydroxy" refers to the group –OH. The term "substituted hydroxyl" or "substituted hydroxy," by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-OR^{aa}$, $-ON(R^{bb})_2$, $-OC(=O)SR^{aa}$, $-OC(=O)R^{aa}$, $-OCO_2R^{aa}$, $-OC(=O)N(R^{bb})_2$, $-OC(=NR^{bb})R^{aa}$, $-OC(=NR^{bb})OR^{aa}$, $-OC(=NR^{bb})N(R^{bb})_2$, $-OS(=O)R^{aa}$, $-OSO_2R^{aa}$, $-OSi(R^{aa})_3$, $-OP(R^{cc})_2$, $-OP(R^{cc})_3$, $-OP(=O)_2R^{aa}$, $-OP(=O)(R^{aa})_2$, $-OP(=O)(OR^{cc})_2$, $-OP(=O)_2N(R^{bb})_2$, and $-OP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as described herein.

[0050] The term "thiol" or "thio" refers to the group –SH. The term "substituted thiol" or "substituted thio," by extension, refers to a thiol group wherein the sulfur atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from $-SR^{aa}$, $-S=SR^{cc}$, $-SC(=S)SR^{aa}$, $-SC(=O)SR^{aa}$, $-SC(=O)OR^{aa}$, and $-SC(=O)R^{aa}$, wherein R^{aa} and R^{cc} are as described herein.

[0051] The term "amino" refers to the group $-NH_2$. The term "substituted amino," by extension, refers to a monosubstituted amino, a disubstituted amino, or a trisubstituted amino, as described herein. In certain embodiments, the "substituted amino" is a monosubstituted amino or a disubstituted amino group.

[0052] The term "monosubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-NH(R^{bb})$, $-NHC(=O)R^{aa}$, $-NHCO_2R^{aa}$, $-NHC(=O)N(R^{bb})_2$, $-NHC(=NR^{bb})N(R^{bb})_2$, $-NHSO_2R^{aa}$, $-NHP(=O)(OR^{cc})_2$, and $-NHP(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb} and R^{cc} are as described herein, and wherein R^{bb} of the group $-NH(R^{bb})$ is not hydrogen.

[0053] The term "disubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with two groups other than hydrogen, and includes groups selected from $-N(R^{bb})_2$, $-NR^{bb}C(=O)R^{aa}$, $-NR^{bb}CO_2R^{aa}$, $-NR^{bb}C(=O)N(R^{bb})_2$, $-NR^{bb}C(=NR^{bb})N(R^{bb})_2$, $-NR^{bb}SO_2R^{aa}$, $-NR^{bb}P(=O)(OR^{cc})_2$, and $-NR^{bb}P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, and R^{cc} are as described herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[0054] The term "trisubstituted amino" refers to an amino group wherein the nitrogen atom directly attached to the parent molecule is substituted with three groups, and includes groups selected from $-N(R^{bb})_3$ and $-N(R^{bb})_3^+X^-$, wherein R^{bb} and X^- are as described herein.

[0055] The term "oxo" refers to the group =O, and the term "thiooxo" refers to the group =S.

[0056] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substitutents include, but are not limited to, hydrogen, –OH, $–OR^{aa}$, $–N(R^{cc})_2$, –CN, $–C(=O)R^{aa}$, $–C(=O)N(R^{cc})_2$, $–CO_2R^{aa}$, $–SO_2R^{aa}$, $–C(=NR^{bb})R^{aa}$, $–C(=NR^{cc})OR^{aa}$, $–C(=NR^{cc})N(R^{cc})_2$, $–SO_2N(R^{cc})_2$, $–SO_2R^{cc}$, $–SO_2OR^{cc}$, $–SOR^{aa}$, $–C(=S)N(R^{cc})_2$, $–C(=O)SR^{cc}$, $–C(=S)SR^{cc}$, $–P(=O)_2R^{aa}$, $–P(=O)(R^{aa})_2$, $–P(=O)_2N(R^{cc})_2$, $–P(=O)(NR^{cc})_2$, $C_{1–10}$ alkyl, $C_{1–10}$ perhaloalkyl, $C_{2–10}$ alkenyl, $C_{2–10}$ alkynyl, $C_{1–10}$ 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, or two R^{cc} groups attached to an N atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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).

[0062] 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.

[0063] 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).

[0064] 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, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, –

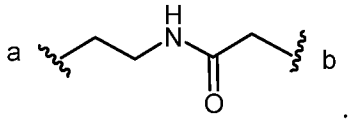
$C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa}, R^{bb}, 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.

[0065] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

[0066] 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.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used 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. Pharmaceutically acceptable 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.

[0067] It understood that divalent moieties depicted herein are interpreted to be read left ("a") to right ("b"), *e.g.,* as provided below, and that the attachment of the divalent moiety into the reference Formula is also interpreted to be attached left to right:



Other definitions

[0068] A "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.,* a male or female of any age group, *e.g.,* a pediatric subject (*e.g,* infant, child, adolescent) or adult subject (*e.g.,* young adult, middle–aged adult or senior adult)) and/or other non–human animals, for example, mammals (*e.g.*, primates (*e.g.,* cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), reptiles, amphibians, and fish. In certain embodiments, the non–human animal is a mammal. The non–human animal may be a male or female and at any stage of development. A non–human animal may be a transgenic animal.

[0069] A "condition," "disease," and "disorder" are used interchangeably herein.

[0070] The term "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease, disorder or condition, which reduces the severity of the disease, disorder or condition, or retards or slows the progression of the disease, disorder or condition ("therapeutic treatment"), and also contemplates an action that occurs before a subject begins to suffer from the specified disease, disorder or condition ("prophylactic treatment").

[0071] In general, the "effective amount" of a compound refers to an amount sufficient to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated, the mode of administration, and the age, health, and condition of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0072] The term "therapeutically effective amount" of a compound refers to an amount sufficient to provide a therapeutic benefit in the treatment of a disease, disorder or condition, or to delay or minimize one or more symptoms associated with the disease, disorder or condition. A therapeutically effective amount of a compound means an amount of therapeutic

agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the disease, disorder or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutic agent. In certain embodiments, the condition is associated with aberrant activity of a kinase (*e.g.*, JAK3). In certain embodiments, a therapeutically effective amount is an amount sufficient to reduce the activity or expression of a kinase (*e.g.*, JAK3)and/or inhibit cell proliferation.

[0073] A "prophylactically effective amount" of a compound is an amount sufficient to prevent a disease, disorder or condition, or one or more symptoms associated with the disease, disorder or condition, or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the disease, disorder or condition. The term "prophylactically effective amount" can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0074] The term "inhibitor" refers to the ability of a compound to reduce (*e.g.,* slow, halt) or prevent activity of a particular biological process (kinase activity) in a cell relative to vehicle.

[0075] Use of the phrase "at least one" instance refers to 1, 2, 3, 4, or more instances, but also encompasses a range, *e.g.*, for example, from 1 to 4, from 1 to 3, from 1 to 2, from 2 to 4, from 2 to 3, or from 3 to 4 instances, inclusive.

[0076] A "kinase" is a type of enzyme that transfers phosphate groups from high energy donor molecules, such as ATP, to specific substrates, referred to as phosphorylation. Kinases are part of the larger family of phosphotransferases. One of the largest groups of kinases are protein kinases, which act on and modify the activity of specific proteins. Kinases are used extensively to transmit signals and control complex processes in cells. Various other kinases act on small molecules such as lipids, carbohydrates, amino acids, and nucleotides, either for signaling or to prime them for metabolic pathways. Kinases are often named after their substrates. More than 500 different protein kinases have been identified in humans. These exemplary human protein kinases include, but are not limited to, AAK1, ABL, ACK, ACTR2, ACTR2B, AKT1, AKT2, AKT3, ALK, ALK1, ALK2, ALK4, ALK7, AMPKa1, AMPKa2, ANKRD3, ANPa, ANPb, ARAF, ARAFps, ARG, AurA, AurAps1, AurAps2, AurB, AurBps1, AurC, AXL, BARK1, BARK2, BIKE, BLK, BMPR1A, BMPR1Aps1, BMPR1Aps2, BMPR1B, BMPR2, BMX, BRAF, BRAFps, BRK, BRSK1, BRSK2, BTK,

BUB1, BUBR1, CaMK1a, CaMK1b, CaMK1d, CaMK1g, CaMK2a, CaMK2b, CaMK2d, CaMK2g, CaMK4, CaMKK1, CaMKK2, caMLCK, CASK, CCK4, CCRK, CDC2, CDC7, CDK10, CDK11, CDK2, CDK3, CDK4, CDK4ps, CDK5, CDK5ps, CDK6, CDK7, CDK7ps, CDK8, CDK8ps, CDK9, CDKL1, CDKL2, CDKL3, CDKL4, CDKL5, CGDps, CHED, CHK1, CHK2, CHK2ps1, CHK2ps2, CK1a, CK1a2, CK1aps1, CK1aps2, CK1aps3, CK1d, CK1e, CK1g1, CK1g2, CK1g2ps, CK1g3, CK2a1, CK2a1–rs, CK2a2, CLIK1, CLIK1L, CLK1, CLK2, CLK2ps, CLK3, CLK3ps, CLK4, COT, CRIK, CRK7, CSK, CTK, CYGD, CYGF, DAPK1, DAPK2, DAPK3, DCAMKL1, DCAMKL2, DCAMKL3, DDR1, DDR2, DLK, DMPK1, DMPK2, DRAK1, DRAK2, DYRK1A, DYRK1B, DYRK2, DYRK3, DYRK4, EGFR, EphA1, EphA10, EphA2, EphA3, EphA4, EphA5, EphA6, EphA7, EphA8, EphB1, EphB2, EphB3, EphB4, EphB6, Erk1, Erk2, Erk3, Erk3ps1, Erk3ps2, Erk3ps3, Erk3ps4, Erk4, Erk5, Erk7, FAK, FER, FERps, FES, FGFR1, FGFR2, FGFR3, FGFR4, FGR, FLT1, FLT1ps, FLT3, FLT4, FMS, FRK, Fused, FYN, GAK, GCK, GCN2, GCN22, GPRK4, GPRK5, GPRK6, GPRK6ps, GPRK7, GSK3A, GSK3B, Haspin, HCK, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4, HH498, HIPK1, HIPK2, HIPK3, HIPK4, HPK1, HRI, HRIps, HSER, HUNK, ICK, IGF1R, IKKa, IKKb, IKKe, ILK, INSR, IRAK1, IRAK2, IRAK3, IRAK4, IRE1, IRE2, IRR, ITK, JAK1, JAK2, JAK3, JNK1, JNK2, JNK3, KDR, KHS1, KHS2, KIS, KIT, KSGCps, KSR1, KSR2, LATS1, LATS2, LCK, LIMK1, LIMK2, LIMK2ps, LKB1, LMR1, LMR2, LMR3, LOK, LRRK1, LRRK2, LTK, LYN, LZK, MAK, MAP2K1, MAP2K1ps, MAP2K2, MAP2K2ps, MAP2K3, MAP2K4, MAP2K5, MAP2K6, MAP2K7, MAP3K1, MAP3K2, MAP3K3, MAP3K4, MAP3K5, MAP3K6, MAP3K7, MAP3K8, MAPKAPK2, MAPKAPK3, MAPKAPK5, MAPKAPKps1, MARK1, MARK2, MARK3, MARK4, MARKps01, MARKps02, MARKps03, MARKps04, MARKps05, MARKps07, MARKps08, MARKps09, MARKps10, MARKps11, MARKps12, MARKps13, MARKps15, MARKps16, MARKps17, MARKps18, MARKps19, MARKps20, MARKps21, MARKps22, MARKps23, MARKps24, MARKps25, MARKps26, MARKps27, MARKps28, MARKps29, MARKps30, MAST1, MAST2, MAST3, MAST4, MASTL, MELK, MER, MET, MISR2, MLK1, MLK2, MLK3, MLK4, MLKL, MNK1, MNK1ps, MNK2, MOK, MOS, MPSK1, MPSK1ps, MRCKa, MRCKb, MRCKps, MSK1, MSK12, MSK2, MSK22, MSSK1, MST1, MST2, MST3, MST3ps, MST4, MUSK, MYO3A, MYO3B, MYT1, NDR1, NDR2, NEK1, NEK10, NEK11, NEK2, NEK2ps1, NEK2ps2, NEK2ps3, NEK3, NEK4, NEK4ps, NEK5, NEK6, NEK7, NEK8, NEK9, NIK, NIM1, NLK, NRBP1, NRBP2, NuaK1, NuaK2, Obscn, Obscn2, OSR1, p38a, p38b, p38d, p38g, p70S6K, p70S6Kb, p70S6Kps1, p70S6Kps2, PAK1, PAK2, PAK2ps, PAK3, PAK4, PAK5, PAK6, PASK, PBK, PCTAIRE1,

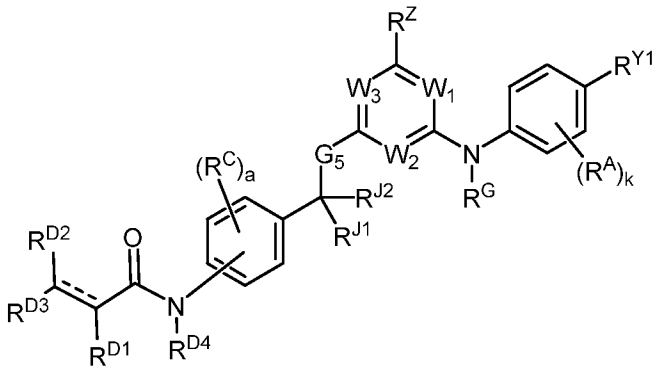
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DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS OF THE INVENTION

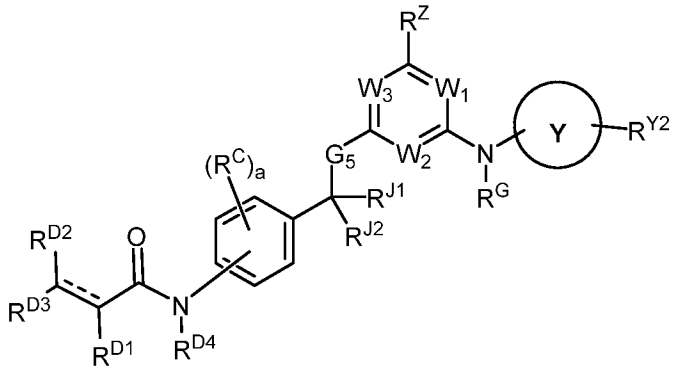
[0077] Previous efforts have led to the development of an ATP-site directed library of acrylamide modified kinase inhibitors that have the potential to form covalent bonds with cysteine residues situated in and around the ATP binding site. These libraries have been used successfully to develop covalent inhibitors of numerous kinases, including EGFR, BTK, BMX, JNK and FGFR. Current estimates suggest 180 kinases may represent attractive targets for the development of new therapeutics. To-date, there exist only 11 kinases that are targeted by FDA approved kinase inhibitors, suggesting that there exists considerable opportunity for new covalent inhibitor drugs. The advantage of covalent inhibitors from a therapeutic standpoint is the potential to achieve durable target suppression without the necessity of maintaining high continuous drug exposure. Given the potential advantages of these agents

and the considerable interest in developing inhibitors of JAK3 in the pharmaceutical field, inhibitors possessing the ability to covalently modify JAK3 developed which include a hydrophobic tag moiety (R^H) to enhance the bioactivity of the JAK3 inhibitors. While the precise function of these hydrophobic moeties are unknown, it has been observed that such functionality can lead to improved bioactivity through mechanisms not directly associated with enzymatic inhibition. In addition to the covalent inhibitors, non-covalent analogs were also discovered (*e.g.*, reduced acrylamide moiety) and likewise modified with hydrophobic tags. These non-covalent derivatives could serve as complementary therapeutics that exhibit alternate modes of inhibition and pharmacokinetic/pharmacodynamic profiles.

[0078] As generally described herein, provided are compounds of Formula (**I**) and (**II**) designed as hydrophobically tagged kinase inhibitors, *e.g.*, JAK inhibitors, *e.g.,* which may inhibit JAK (*e.g.,* JAK3) selectively:



(**I**)

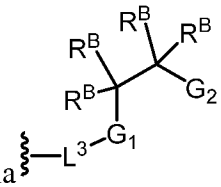


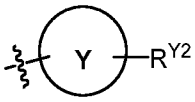
(**II**)

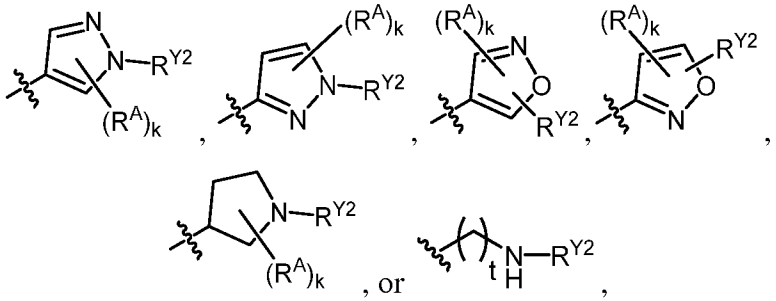
and pharmaceutically acceptable salts thereof,

wherein:

W_1 is N, W_2 is N and W_3 is CR^X, or W_1 is N, W_2 is CH, and W_3 is N;

R^{Y1} and R^{Y2} are each a group of formula  or $-L^1$-R^H;


is selected from the group consisting of:



wherein t is 2, 3, 4, 5, or 6;

L^3 is a bond or a linker selected from the group consisting of substituted and unsubstituted C_{1-6}alkylene, substituted and unsubstituted C_{2-6}alkenylene, substituted and unsubstituted C_{2-6}alkynylene, substituted and unsubstituted heteroC_{1-6}alkylene, substituted and unsubstituted heteroC_{2-6}alkenylene, and substituted and unsubstituted heteroC_{2-6}alkynylene;

G_1 is NR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H, O-L^1-R^H, or $C(R^{G2a})$-L^1-R^H; or G_1 is CHR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H or O-L^1-R^H;

each instance of R^{G1a} and R^{G2a} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or R^{G1a} and one instance of R^{G2a} are joined to form the group $–C(R^B)_2$-$C(R^B)_2$-;

L^1 is a linker selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, substituted and unsubstituted heterocyclylene, substituted and unsubstituted carbocyclylene, substituted and unsubstituted arylene, substituted and unsubstituted heteroarylene, and combinations thereof;

R^H is a hydrophobic group selected from the group consisting of substituted and unsubstituted aryl, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heteroarylalkyl, substituted and unsubstituted carbocycylalkyl, and substituted and unsubstituted heterocyclylalkyl;

---- represents a single or double bond;

each instance of R^{D1}, R^{D2}, and R^{D3} is independently hydrogen or substituted or

unsubstituted alkyl;

R^{D4} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

G^5 is O, S, or NR^E;

each instance of R^E and R^G is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

each instance of R^{J1} and R^{J2} is independently hydrogen, halogen, or substituted or unsubstituted alkyl;

each instance of R^A and R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$;

each instance of R^B is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$; or two R^B groups attached to the same carbon atom are joined to form an oxo (=O) group;

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

a and k are each independently 0, 1, or 2, provided when k is 0 then R^A is absent, and when a is 0 then R^C is absent; and

each instance of R^X and R^Z is independently hydrogen, halogen, substituted or unsubstituted alkyl, cyclopropyl, -CN, $–OR^{X1}$, or $–NHR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to an oxygen, or a nitrogen protecting group when attached to a nitrogen, or R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring;

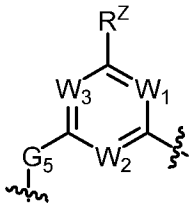
or R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered

heterocyclic ring.

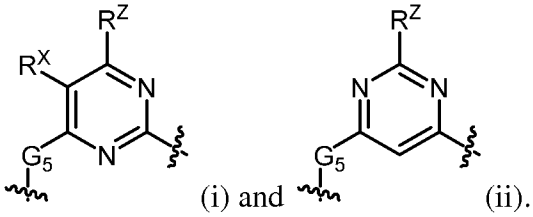
[0079] As generally described herein, compounds of Formula (**I**) and (**II**), and pharmaceutically acceptable salts thereof, are contemplated useful as kinase inhibitors (*e.g.*, JAK inhibitors, *e.g.,* JAK3 inhibitors). The compounds may covalently or non-covalently bind to the kinase. The compounds including a hydrophobic moiety R^H may signal to the intracellular protein homeostasis machinery to induce degradation of the targeted kinase. Also provided are pharmaceutical compositions and kits comprising such compounds, and methods of their use and treatment, *e.g.,* for reducing the activity of a kinase. and/or treating and/or preventing a condition associated with aberrant activity of a kinase (*e.g.*, a proliferative disease, inflammatory disorder, autoimmune disorder, painful condition, or viral infection), in a subject in need thereof.

Core Ring System comprising W_1, W_2, W_3, R^X, and R^Z

[0080] As generally described herein, W_1 is N, W_2 is N and W_3 is CR^X, or W_1 is N, W_2 is CH, and W_3 is N. Thus, the following two core ring systems corresponding to the group:



are contemplated herein:



(i) and (ii).

wherein:

G_5 is O, S, or NR^E;

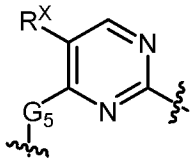
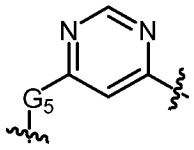
each instance of R^E is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

each instance of R^X and R^Z is independently hydrogen, halogen, substituted or unsubstituted alkyl, cyclopropyl, -CN, $–OR^{X1}$, or $–NHR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to an oxygen, or a nitrogen protecting group when attached to a nitrogen, or R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring;

or R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered heterocyclic ring.

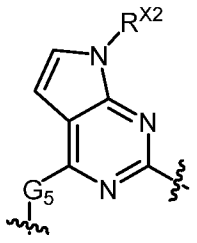
[0081] In certain embodiments, R^Z is hydrogen or $-NHR^{X1}$ (*e.g.*, $-NH_2$).

[0082] In certain embodiments, R^Z is hydrogen to provide a ring system of formula:


(i-a) and

(ii-a).

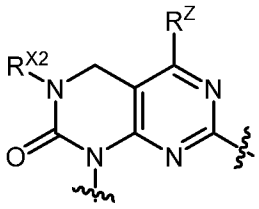
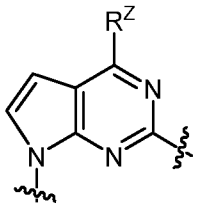
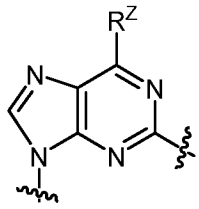
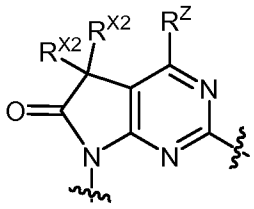
[0083] In certain embodiments, various bicyclic ring systems are contemplated.

[0084] For example, in certain embodiments, R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring. For example, in certain embodiments, wherein R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring, provided is a group of formula:


(i-b)

wherein R^{X2} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group.

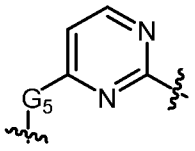
[0085] Alternatively, in certain embodiments, R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered heterocyclic ring. For example, in certain embodiments, wherein R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered heterocyclic ring, provided is a group of formula:


,

,

, or

.

wherein R^{X2} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group when attached to a nitrogen atom.

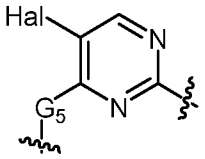
[0086] Furthermore, alternatively, R^X is not joined to form a ring with either R^Z or R^E. In certain embodiments, R^X is hydrogen, halogen, substituted or unsubstituted alkyl, cyclopropyl, -CN, $-OR^{X1}$, or $-NHR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to an oxygen, or a nitrogen protecting group when attached to a nitrogen.

[0087] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is hydrogen. In certain embodiments, both R^X and R^Z are hydrogen, *e.g.,* to provide a ring system of formula:



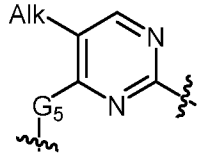
(i-c)

[0088] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is F. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is Cl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is Br. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is I (iodine). In certain embodiments, R^X is halogen ("Hal") and R^Z is hydrogen, *e.g.,* to provide a ring system of formula:



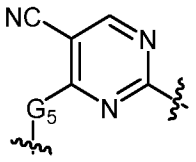
(i-d).

[0089] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is cyclopropyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is unsubstituted $C_{1\text{-}6}$ alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted $C_{1\text{-}6}$ alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $C_{1\text{-}6}$ alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $-CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $-CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $-CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $-CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted hexyl. In certain embodiments, R^X is alkyl or cyclopropyl ("Alk") and R^Z is hydrogen, *e.g.,* to provide a ring system of formula:



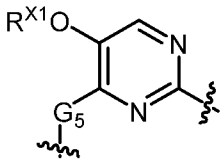
(i-e).

[0090] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is –CN. In certain embodiments, R^X is -CN and R^Z is hydrogen, *e.g.,* to provide a ring system of formula:



(i-f).

[0091] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$. In certain embodiments, R^X is $–OR^{X1}$ and R^Z is hydrogen, *e.g.,* to provide a ring system of formula:



(i-g).

[0092] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$ wherein R^{X1} is hydrogen (*i.e.,* to provide –OH).

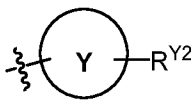
[0093] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$, wherein R^{X1} is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted hexyl.

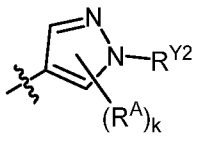
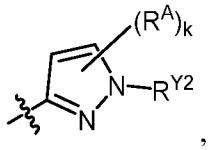
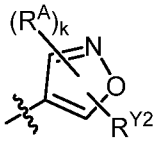
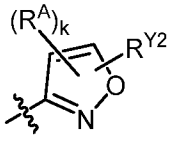
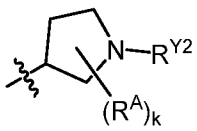
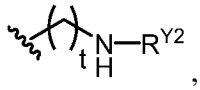
[0094] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$, wherein R^{X1} is an oxygen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[0095] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–NHR^{X1}$.

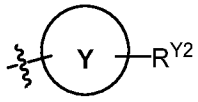
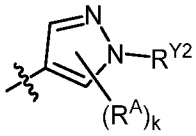
Group Y

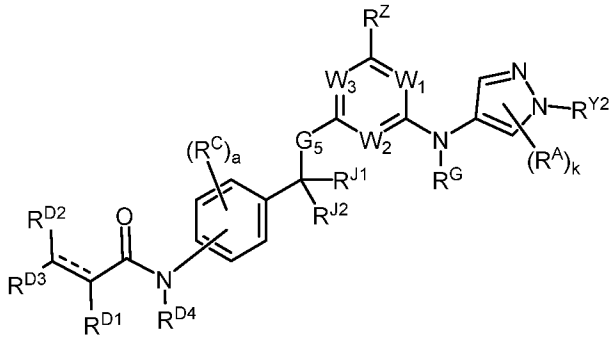
[0096] As generally described herein, Formula (**II**) comprises a group of formula:



is selected from the group consisting of , , , , , and ,

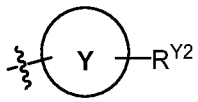
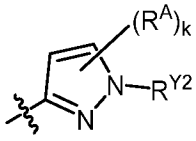
wherein t is 2, 3, 4, 5, or 6.

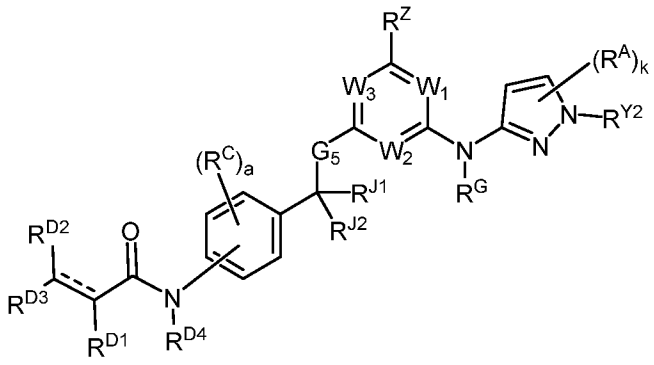
[0097] In certain embodiments of Formula (**II**), the group  is , to provide a compound of Formula:



(**II-C**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, W_1 is N, W_2 is N and W_3 is CR^X. In certain embodiments, G_5 is NR^E. In certain embodiments, R^Z is hydrogen.

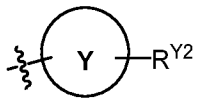
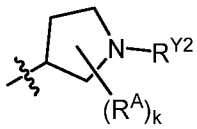
[0098] In certain embodiments of Formula (**II**), the group  is , to provide a compound of Formula:

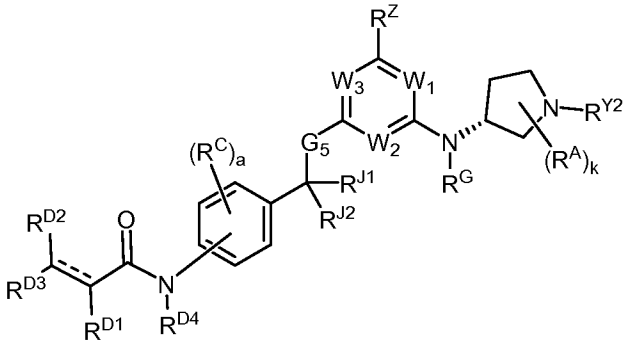


(**II-D**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, W_1 is N, W_2 is N and

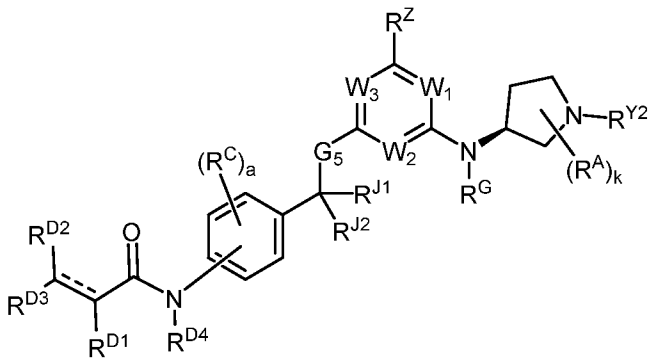
W_3 is CR^X. In certain embodiments, G_5 is NR^E. In certain embodiments, R^Z is hydrogen.

[0099] In certain embodiments of Formula (**II**), the group  is  to provide a compound of Formula:



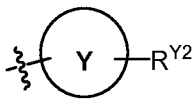
(**II-F**)

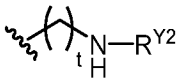
or

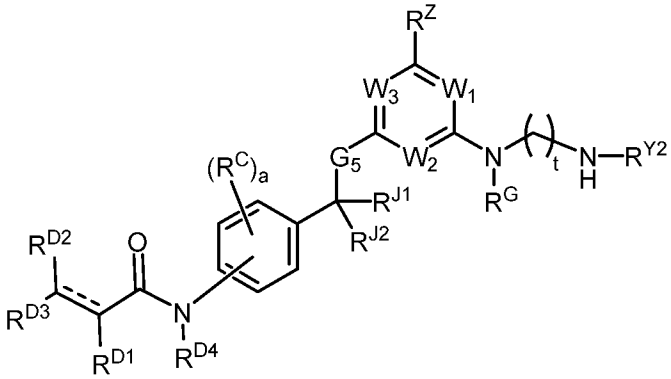


(**II-G**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, W_1 is N, W_2 is N and W_3 is CR^X. In certain embodiments, G_5 is NR^E. In certain embodiments, R^Z is hydrogen.

[00100] In certain embodiments of Formula (**II**), the group  is:

, wherein t is 2, 3, 4, 5, or 6, to provide a compound of formula:



(**II-H**)

or a pharmaceutically acceptable salt thereof. In certain embodiments, W_1 is N, W_2 is N and W_3 is CR^X. In certain embodiments, G_5 is NR^E. In certain embodiments, R^Z is hydrogen. In certain embodiments, t is 4.

Group R^A and k

[00101] As generally described herein, each instance of R^A is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$, and k is 0, 1, or 2, provided when k is 0 then R^A is absent.

[00102] In certain embodiments of Formula (**I**) or (**II**), k is 0 and R^A is absent.

[00103] In certain embodiments of Formula (**I**) or (**II**), k is 1. In certain embodiments of Formula (**I**), k is 1 and R^A is a group as described herein attached *ortho* to the point of attachment to $–N(R^G)$-. In certain embodiments of Formula (**I**), k is 1 and R^A is a group as described herein attached *meta* to the point of attachment to $–N(R^G)$-.

[00104] In certain embodiments of Formula (**I**) or (**II**), k is 2. In certain embodiments of Formula (**I**), k is 2, and each R^A is independently a group as described herein, wherein one R^A is attached *ortho* and one R^A is attached *meta* to the point of attachment to $–N(R^G)$-. In certain embodiments of Formula (**I**), k is 2, and each R^A is independently a group as described herein, both R^A groups are attached *ortho* to the point of attachment to $–N(R^G)$-. In certain embodiments of Formula (**I**), k is 2, and each R^A is independently a group as described herein, both R^A groups are attached *meta* to the point of attachment to $–N(R^G)$-.

[00105] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is halogen. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is F. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is Cl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is Br. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is I (iodine). In certain embodiments of Formula (**I**) or (**II**), k is 2 and both instances of R^A are independently halogen. In certain embodiments of Formula (**I**) or (**II**), k is 2 and both instances of R^A are F. In certain embodiments of Formula (**I**) or (**II**), k is 2 and both instances of R^A are Cl.

[00106] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted alkyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2

and at least one instance of R^A is unsubstituted alkyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–CH_3$. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted methyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–CH_2F$. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–CHF_2$. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–CF_3$. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted hexyl.

[00107] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-5}alkenyl, substituted or unsubstituted C_{2-4}alkenyl, or substituted or unsubstituted C_{2-3}alkenyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is unsubstituted alkenyl.

[00108] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is substituted alkynyl, *e.g.,* substituted or unsubstituted C_{2-6}alkynyl, substituted or unsubstituted C_{2-5}alkynyl, substituted or unsubstituted C_{2-4}alkynyl, or substituted or unsubstituted C_{2-3}alkynyl. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is unsubstituted alkynyl.

[00109] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OH), or a non-hydrogen group.

[00110] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–SR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –SH), or a non-hydrogen group.

[00111] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one

instance of R^A is —$N(R^{A1})_2$, wherein at least one R^{A1} is hydrogen (*e.g.,* to provide –NH_2 or NHR^{A1}), each R^{A1} is a non-hydrogen group, or wherein two R^{A1} groups are joined to form a substituted or unsubstitued heterocyclic or heteroaryl ring.

[00112] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is –CN. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–NO_2$.

[00113] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=NR^{A1})R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)H), or a non-hydrogen group.

[00114] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=NR^{A1})OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)OH), or a non-hydrogen group.

[00115] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=NR^{A1})N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide –$C(=NH)NH_2$), or a non-hydrogen group.

[00116] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)H), or a non-hydrogen group.

[00117] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)OH), or a non-hydrogen group.

[00118] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide –$C(=O)NH_2$), or a non-hydrogen group.

[00119] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide –$C(=O)NH_2$), or a non-hydrogen group. In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–C(=O)NMe_2$, or –C(=O)NHMe.

[00120] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–NR^{A1}C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)H), or a non-hydrogen group.

[00121] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–NR^{A1}C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)OH), or a non-hydrogen group.

[00122] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–NR^{A1}C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–NHC(=O)NH_2$), or a non-hydrogen group.

[00123] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–OC(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OC(=O)H), or a non-hydrogen group.

[00124] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–OC(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OC(=O)OH), or a non-hydrogen group.

[00125] In certain embodiments of Formula (**I**) or (**II**), k is 1 or 2 and at least one instance of R^A is $–OC(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–OC(=O)NH_2$), or a non-hydrogen group.

[00126] Furthermore, as generally described herein, in any of the above described embodiments of group R^A comprising a group R^{A1}, each instance of R^{A1} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

[00127] For example, in any of the above described embodiments of R^A comprising a group R^{A1}, at least one instance of R^{A1} is hydrogen.

[00128] In any of the above described embodiments of R^A comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted alkyl, *e.g.*, substituted or unsubstituted C_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_1alkyl, substituted or unsubstituted C_2alkyl, substituted or unsubstituted C_3alkyl, substituted or unsubstituted C_4alkyl, substituted or unsubstituted C_5alkyl, or substituted or unsubstituted C_6alkyl.

[00129] In any of the above described embodiments of R^A comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkenyl, *e.g.,* substituted or unsubstituted C_2alkenyl, substituted or unsubstituted C_3alkenyl, substituted or unsubstituted C_4alkenyl, substituted or unsubstituted C_5alkenyl, or substituted or unsubstituted C_6alkenyl.

[00130] In any of the above described embodiments of R^A comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkynyl, *e.g.,* substituted or

unsubstituted C_2alkynyl, substituted or unsubstituted C_3alkynyl, substituted or unsubstituted C_4alkynyl, substituted or unsubstituted C_5alkynyl, or substituted or unsubstituted C_6alkynyl.

[00131] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is substituted or unsubstituted carbocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is saturated carbocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is unsaturated carbocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is monocyclic C_{3-7} carbocyclyl.

[00132] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is substituted or unsubstituted heterocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is saturated heterocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is unsaturated heterocyclyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is 3- to 7-membered, monocyclic heterocyclyl.

[00133] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is substituted or unsubstituted aryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is C_{6-10} aryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is monocyclic aryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is substituted phenyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is unsubstituted phenyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is bicyclic aryl.

[00134] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is substituted or unsubstituted heteroaryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is monocyclic heteroaryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is 5- or 6-membered, monocyclic heteroaryl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is bicyclic heteroaryl, wherein the point of attachment may be on any atom of the bicyclic heteroaryl

ring system, as valency permits.

[00135] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is a nitrogen protecting group when attached to a nitrogen atom. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^{A1} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts when attached to a nitrogen atom.

[00136] In certain embodiments of Formula (**I**) or Formula (**II**), R^{A1} is an oxygen protecting group when attached to an oxygen atom. In certain embodiments of Formula (**I**) or Formula (**II**), 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.

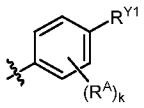
[00137] In certain embodiments of Formula (**I**) or Formula (**II**), R^{A1} is a sulfur protecting group when attached to a sulfur atom. In certain embodiments of Formula (**I**) or Formula (**II**), R^{A1} is acetamidomethyl, *t*-Bu, 3-nitro-2-pyridine sulfenyl, 2-pyridine-sulfenyl, or triphenylmethyl when attached to a sulfur atom.

[00138] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^A is $-N(R^{A1})_2$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)N(R^{A1})_2$, or $-OC(=O)N(R^{A1})_2$, two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom, are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a saturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form an unsaturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring.

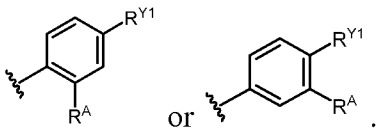
[00139] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^A is $-N(R^{A1})_2$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)N(R^{A1})_2$, or $-OC(=O)N(R^{A1})_2$, two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom, are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 9- to 10-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

[00140] In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^A is independently hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{A1}$, wherein R^{A1} is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^A is independently hydrogen, halogen, unsubstituted C_{1-6} alkyl, C_{1-6} alkyl substituted with at least one halogen, or $-OR^{A1}$, wherein R^{A1} is unsubstituted C_{1-6} alkyl.

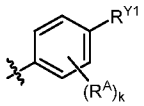
[00141] In certain embodiments of Formula (**I**), k is 1; and the group:



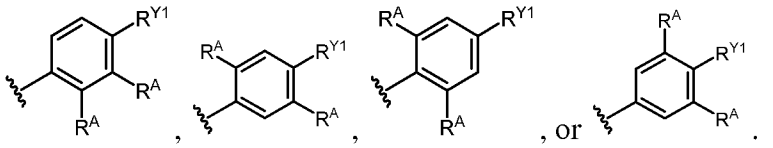
corresponds to any one of formula:



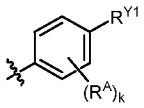
[00142] In certain embodiments of Formula (**I**), k is 2 and the group:



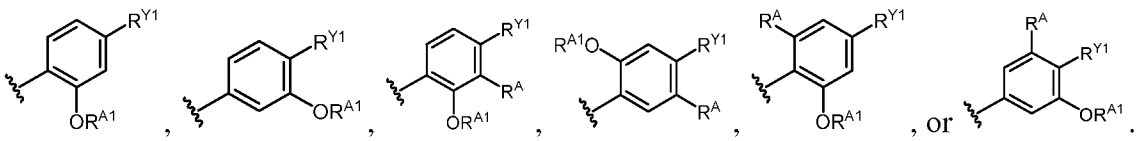
corresponds to any one of formula:



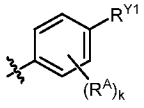
[00143] In certain embodiments of Formula (**I**), at least one instance of R^A is $-OR^{A1}$, and and the group:



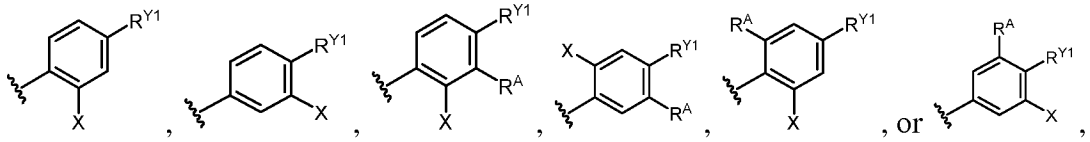
corresponds to any one of formula:



[00144] In certain embodiments of Formula (**I**), at least one instance of R^A is halogen, and and the group:



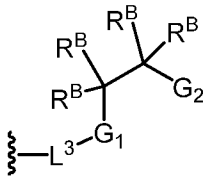
corresponds to any one of formula:



wherein X is halogen.

Linker L^3 and Groups R^{Y1}, R^{Y2}, G_1, G_2, R^{G1a}, R^{G2a}, and R^B

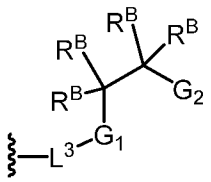
[00145] As generally described herein, R^{Y1}, which is attached to a compound of Formula (**I**), is a group of formula:



or $-L^1$-R^H,

wherein G_1, G_2, L^1, L^3, R^H, and R^B are as defined herein.

[00146] Furthermore, as generally described herein, R^{Y2}, attached to a compound of Formula (**II**), is a group of formula:



or $-L^1$-R^H,

wherein G_1, G_2, L^1, L^3, R^H, and R^B are as defined herein.

[00147] As generally described herein, each instance of R^B, provided in Formula (**I**) or (**II**), is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $-OR^{A1}$, $-N(R^{A1})_2$, $-SR^{A1}$, $-CN$, $-SCN$, $-C(=NR^{A1})R^{A1}$, $-C(=NR^{A1})OR^{A1}$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)R^{A1}$, $-C(=O)OR^{A1}$, $-C(=O)N(R^{A1})_2$, $-NO_2$, $-NR^{A1}C(=O)R^{A1}$, $-NR^{A1}C(=O)OR^{A1}$, $-NR^{A1}C(=O)N(R^{A1})_2$, $-OC(=O)R^{A1}$, $-OC(=O)OR^{A1}$, or $-OC(=O)N(R^{A1})_2$; or two R^B groups attached to the same carbon atom are joined to form a =O group.

[00148] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least two instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least three instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least four instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least five instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least six instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or

Formula (**II**), at least seven instances of R^B are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), all instances of R^B are hydrogen.

[00149] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is halogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is F. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is Cl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is Br. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is I (iodine). In certain embodiments of Formula (**I**) or Formula (**II**), at least two instances of R^B are independently halogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least two instances of R^B are F. In certain embodiments of Formula (**I**) or Formula (**II**), at least two instances of R^B are Cl.

[00150] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted or unsubstituted hexyl.

[00151] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted alkenyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is unsubstituted alkenyl.

[00152] In certain embodiments of Formula (**I**) or Formula (**II**), at least one instance of R^B is substituted alkynyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one

instance of R^B is unsubstituted alkynyl.

[00153] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –OR^{A1}, wherein R^{A1} is hydrogen (*i.e.,* to provide –OH), or a non-hydrogen group.

[00154] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –SR^{A1}, wherein R^{A1} is hydrogen (*i.e.,* to provide –SH), or a non-hydrogen group.

[00155] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is —$N(R^{A1})_2$, wherein at least one R^{A1} is hydrogen (*e.g.,* to provide $–NH_2$ or NHR^{A1}), each R^{A1} is a non-hydrogen group, or wherein two R^{A1} groups are joined to form a substituted or unsubstitued heterocyclic or heteroaryl ring.

[00156] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –CN. In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B $–NO_2$.

[00157] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=NR^{A1})R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)H), or a non-hydrogen group.

[00158] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=NR^{A1})OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)OH), or a non-hydrogen group.

[00159] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=NR^{A1})N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=NH)NH_2$), or a non-hydrogen group.

[00160] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)H), or a non-hydrogen group.

[00161] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)OH), or a non-hydrogen group.

[00162] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=O)NH_2$), or a non-hydrogen group.

[00163] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=O)NH_2$), or a non-hydrogen group. In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$C(=O)NMe_2$, or –C(=O)NHMe.

[00164] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is –$NR^{A1}C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)H), or a non-hydrogen group.

[00165] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is $-NR^{A1}C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)OH), or a non-hydrogen group.

[00166] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is $-NR^{A1}C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $-NHC(=O)NH_2$), or a non-hydrogen group.

[00167] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is $-OC(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OC(=O)H), or a non-hydrogen group.

[00168] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is $-OC(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OC(=O)OH), or a non-hydrogen group.

[00169] In certain embodiments of Formula (**I**) or (**II**), at least one instance of R^B is $-OC(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $-OC(=O)NH_2$), or a non-hydrogen group.

[00170] Furthermore, as generally described herein, in any of the above described embodiments of group R^B comprising a group R^{A1}, each instance of R^{A1} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

[00171] For example, in any of the above described embodiments of R^B comprising a group R^{A1}, at least one instance of R^{A1} is hydrogen.

[00172] In any of the above described embodiments of R^B comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstitutedC_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_1alkyl, substituted or unsubstituted C_2alkyl, substituted or unsubstituted C_3alkyl, substituted or unsubstituted C_4alkyl, substituted or unsubstituted C_5alkyl, or substituted or unsubstituted C_6alkyl.

[00173] In any of the above described embodiments of R^B comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkenyl, *e.g.,* substituted or unsubstituted C_2alkenyl, substituted or unsubstituted C_3alkenyl, substituted or unsubstituted C_4alkenyl, substituted or unsubstituted C_5alkenyl, or substituted or unsubstituted C_6alkenyl

[00174] In any of the above described embodiments of R^B comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkynyl, *e.g.,* substituted or unsubstituted C_2alkynyl, substituted or unsubstituted C_3alkynyl, substituted or unsubstituted C_4alkynyl, substituted or unsubstituted C_5alkynyl, or substituted or unsubstituted C_6alkynyl.

[00175] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^B is $-N(R^{A1})_2$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)N(R^{A1})_2$, or $-OC(=O)N(R^{A1})_2$, two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom,are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a saturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form an unsaturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring.

[00176] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^B is $-N(R^{A1})_2$, $-C(=NR^{A1})N(R^{A1})_2$, $-C(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)N(R^{A1})_2$, or $-OC(=O)N(R^{A1})_2$, two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom, are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 9- to 10-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

[00177] In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^B is independently hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, or $-OR^{A1}$, wherein R^{A1} is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^B is independently hydrogen, halogen, unsubstituted C_{1-6} alkyl, C_{1-6} alkyl substituted with at least one halogen, or $-OR^{A1}$, wherein R^{A1} is unsubstituted C_{1-6} alkyl.

[00178] Furthermore, in certain embodiments of Formula (**I**) or Formula (**II**), two R^B groups attached to the same carbon atom are joined to form a =O group.

[00179] As generally described herein, L^3, provided in a compound of Formula (**I**) or

(**II**), is a bond or a linker selected from the group consisting of substituted and unsubstituted C_{1-6}alkylene, substituted and unsubstituted C_{2-6}alkenylene, substituted and unsubstituted C_{2-6}alkynylene, substituted and unsubstituted heteroC_{1-6}alkylene, substituted and unsubstituted heteroC_{2-6}alkenylene, and substituted and unsubstituted heteroC_{2-6}alkynylene.

[00180] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a bond, *i.e.,* a direct, covalent single bond.

[00181] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted C_{1-6}alkylene, *e.g.,* substituted or unsubstituted C_{2-6}alkylene, substituted or unsubstituted C_{3-6}alkylene, substituted or unsubstituted C_{4-6}alkylene, substituted or unsubstituted C_{5-6}alkylene, substituted or unsubstituted C_{2-5}alkylene, substituted or unsubstituted C_{2-4}alkylene, substituted or unsubstituted C_{2-3}alkylene, substituted or unsubstituted C_1alkylene, substituted or unsubstituted C_2alkylene, substituted or unsubstituted C_3alkylene, substituted or unsubstituted C_4alkylene, substituted or unsubstituted C_5alkylene, or substituted or unsubstituted C_6alkylene. In certain embodiments, L^3 is unsubstituted C_{1-6}alkylene.

[00182] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted C_{2-6}alkenylene, *e.g.,* substituted or unsubstituted C_{3-6}alkenylene, substituted or unsubstituted C_{4-6}alkenylene, substituted or unsubstituted C_{5-6}alkenylene, substituted or unsubstituted C_{2-5}alkenylene, substituted or unsubstituted C_{2-4}alkenylene, substituted or unsubstituted C_{2-3}alkenylene, substituted or unsubstituted C_2alkenylene, substituted or unsubstituted C_3alkenylene, substituted or unsubstituted C_4alkenylene, substituted or unsubstituted C_5alkenylene, or substituted or unsubstituted C_6alkenylene. In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is unsubstituted C_{2-6}alkenylene.

[00183] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted C_{2-6}alkynylene, *e.g.,* substituted or unsubstituted C_{3-6}alkynylene, substituted or unsubstituted C_{4-6}alkynylene, substituted or unsubstituted C_{5-6}alkynylene, substituted or unsubstituted C_{2-5}alkynylene, substituted or unsubstituted C_{2-}4alkynylene, substituted or unsubstituted C_{2-3}alkynylene, substituted or unsubstituted C_2alkynylene, substituted or unsubstituted C_3alkynylene, substituted or unsubstituted C_4alkynylene, substituted or unsubstituted C_5alkynylene, or substituted or unsubstituted C_6alkynylene. In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is unsubstituted C_{2-6}alkynylene.

[00184] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted heteroC_{1-6}alkylene, *e.g.,* substituted or unsubstituted heteroC_{2-6}alkylene, substituted or unsubstituted heteroC_{3-6}alkylene, substituted or unsubstituted heteroC_{4-}

$_6$alkylene, substituted or unsubstituted heteroC_{5-6}alkylene, substituted or unsubstituted heteroC_{2-5}alkylene, substituted or unsubstituted heteroC_{2-4}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_1alkylene, substituted or unsubstituted heteroC_2alkylene, substituted or unsubstituted heteroC_3alkylene, substituted or unsubstituted heteroC_4alkylene, substituted or unsubstituted heteroC_5alkylene, or substituted or unsubstituted heteroC_6alkylene. In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is unsubstituted heteroC_{1-6}alkylene. In certain embodiments of Formula (**I**) or Formula (**II**), wherein L^3 is a substituted or unsubstituted heteroC_{1-6}alkylene, the heteroC_{2-6}alkylene comprises includes one, two, or three heteroatoms in the heteroalkylene chain, wherein the heteroatoms are independently nitrogen, oxygen, or sulfur.

[00185] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted heteroC_{2-6}alkenylene, *e.g.,* substituted or unsubstituted heteroC_{3-6}alkenylene, substituted or unsubstituted heteroC_{4-6}alkenylene, substituted or unsubstituted heteroC_{5-6}alkenylene, substituted or unsubstituted heteroC_{2-5}alkenylene, substituted or unsubstituted heteroC_{2-4}alkenylene, substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_2alkenylene, substituted or unsubstituted heteroC_3alkenylene, substituted or unsubstituted heteroC_4alkenylene, substituted or unsubstituted heteroC_5alkenylene, or substituted or unsubstituted heteroC_6alkenylene. In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is unsubstituted heteroC_{2-6}alkenylene. In certain embodiments of Formula (**I**) or Formula (**II**), wherein L^3 is a substituted or unsubstituted heteroC_{2-6}alkenylene, the heteroC_{2-6}alkenylene comprises one, two, or three heteroatoms in the heteroalkenylene chain, wherein the heteroatoms are independently nitrogen, oxygen, or sulfur.

[00186] In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is a substituted or unsubstituted heteroC_{2-6}alkynylene, *e.g.,* substituted or unsubstituted heteroC_{2-6}alkynylene, substituted or unsubstituted heteroC_{3-6}alkynylene, substituted or unsubstituted heteroC_{4-6}alkynylene, substituted or unsubstituted heteroC_{5-6}alkynylene, substituted or unsubstituted heteroC_{2-5}alkynylene, substituted or unsubstituted heteroC_{2-4}alkynylene, substituted or unsubstituted heteroC_{2-3}alkynylene, substituted or unsubstituted heteroC_2alkynylene, substituted or unsubstituted heteroC_3alkynylene, substituted or unsubstituted heteroC_4alkynylene, substituted or unsubstituted heteroC_5alkynylene, or substituted or unsubstituted heteroC_6alkynylene. In certain embodiments of Formula (**I**) or Formula (**II**), L^3 is unsubstituted heteroalkynylene. In certain embodiments of Formula (**I**) or Formula (**II**), wherein L^3 is a substituted or unsubstituted heteroC_{2-6}alkynylene, L^3 includes one, two, or

three heteroatoms in the heteroalkynylene chain, wherein the heteroatoms are independently nitrogen, oxygen, or sulfur.

[00187] As generally described herein, as provided in a compound of Formula (**I**) or (**II**), G_1 is NR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H, O-L^1-R^H, or $C(R^{G2a})$-L^1-R^H; or G_1 is CHR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H or O-L^1-R^H; and each instance of R^{G1a} and R^{G2a} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or R^{G1a} and one instance of R^{G2a} are joined to form the group –$C(R^B)_2$-$C(R^B)_2$-.

[00188] In certain embodiments of Formula (**I**) or Formula (**II**), G_1 is NR^{G1a}. In certain embodiments of Formula (**I**) or Formula (**II**), G_1 is CHR^{G1a}.

[00189] In certain embodiments of Formula (**I**) or Formula (**II**), G_2 is $N(R^{G2a})$-L^1-R^H. In certain embodiments of Formula (**I**) or Formula (**II**), G_2 is O-L^1-R^H.

[00190] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a} or CHR^{G1a}, R^{G1a} is hydrogen.

[00191] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a} or CHR^{G1a}, R^{G1a} is substituted or unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G1a} is substituted or unsubstituted hexyl.

[00192] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a}, R^{G1a} is a nitrogen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a}, R^{G1a} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or

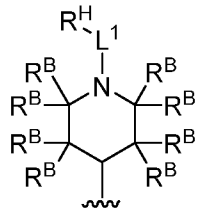
Ts.

[00193] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_2 is $N(R^{G2a})$-L^1-R^H, R^{G2a} is hydrogen.

[00194] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_2 is $N(R^{G2a})$-L^1-R^H, R^{G2a} is substituted or unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{G2a} is substituted or unsubstituted hexyl.

[00195] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_2 is $N(R^{G2a})$-L^1-R^H, R^{G2a} is a nitrogen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_2 is $N(R^{G2a})$-L^1-R^H, R^{G2a} is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

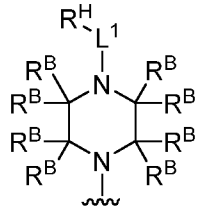
[00196] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is CHR^{G1a}, and G_2 is $N(R^{G2a})$-L^1-R^H, R^{G1a} and one instance of R^{G2a} are joined to form the group $–C(R^B)_2$-$C(R^B)_2–$, *i.e.,* to provide a group of the formula:



wherein L^1, R^H, and R^B are as defined herein. In certain embodiments, each instance of R^B is hydrogen.

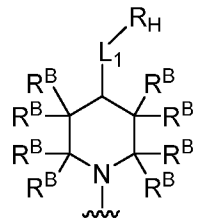
[00197] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a}

and G_2 is $N(R^{G2a})$-L^1-R^H, R^{G1a} and one instance of R^{G2a} are joined to form the group $–C(R^B)_2$-$C(R^B)_2–$, *i.e.,* to provide a group of the formula:



wherein L^1, R^H, and R^B are as defined herein. In certain embodiments, each instance of R^B is hydrogen.

[00198] In certain embodiments of Formula (**I**) or Formula (**II**), wherein G_1 is NR^{G1a} and G_2 is $C(R^{G2a})$-L^1-R^H, R^{G1a} and R^{G2a} are joined to form the group $–C(R^B)_2$-$C(R^B)_2–$, *i.e.,* to provide a group of the formula:



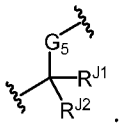
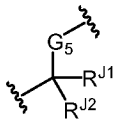
wherein R^{G2a} and R^B are as defined herein. In certain embodiments, each instance of R^B is hydrogen. In certain embodiments, R^{G2a} is substituted or unsubstituted alkyl, *e.g.*, $-CH_3$, or substituted or unsubstituted hydroxyl, *e.g.*, -OH or $–OCH_3$.

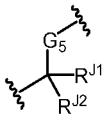
[00199] In certain embodiments of Formula (**I**), R^{Y1} is $–L^1$-R^H wherein L^1 and R^H are as defined herein. In certain embodiments of Formula (**II**), R^{Y2} is $–L^1$-R^H wherein L^1 and R^H are as defined herein.

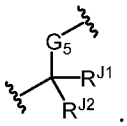
Group R^C and a

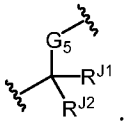
[00200] As generally described herein, each instance of R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$, and a is 0, 1, or 2, provided when a is 0 then R^C is absent.

[00201] In certain embodiments of Formula (**I**) or (**II**), a is 1. In certain embodiments of Formula (**I**) or (**II**), a is 1 and R^C is a group as described herein attached *ortho* to the point

of attachment to . In certain embodiments of Formula (**I**) or (**II**), a is 1 and R^C is a group as described herein attached *meta* to the point of attachment to .

[00202] In certain embodiments of Formula (**I**) or (**II**), a is 2. In certain embodiments of Formula (**I**) or (**II**), a is 2, and each R^C is independently a group as described herein, wherein one R^C is attached *ortho* and one R^C is attached *meta* to the point of attachment to .

[00203] In certain embodiments of Formula (**I**) or (**II**), a is 2, and each R^C is independently a group as described herein, both R^C groups are attached *ortho* to the point of attachment to .

[00204] In certain embodiments of Formula (**I**) or (**II**), a is 2, and each R^C is independently a group as described herein, both R^C groups are attached *meta* to the point of attachment to .

[00205] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is halogen. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is F. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is Cl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is Br. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is I (iodine). In certain embodiments of Formula (**I**) or (**II**), a is 2 and both instances of R^C are independently halogen. In certain embodiments of Formula (**I**) or (**II**), a is 2 and both instances of R^C are F. In certain embodiments of Formula (**I**) or (**II**), a is 2 and both instances of R^C are Cl.

[00206] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted alkyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is unsubstituted alkyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is unsubstituted $C_{1\text{-}6}$ alkyl. In certain

embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–CH_3$. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted methyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–CH_2F$. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–CHF_2$. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–CF_3$. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted hexyl.

[00207] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted alkenyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-5}alkenyl, substituted or unsubstituted C_{2-4}alkenyl, or substituted or unsubstituted C_{2-3}alkenyl.

[00208] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is substituted or unsubstituted alkynyl, *e.g.,* substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-5}alkenyl, substituted or unsubstituted C_{2-4}alkenyl, or substituted or unsubstituted C_{2-3}alkenyl.

[00209] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –OH), or a non-hydrogen group.

[00210] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–SR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –SH), or a non-hydrogen group.

[00211] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $—N(R^{A1})_2$, wherein at least one R^{A1} is hydrogen (*e.g.,* to provide $–NH_2$ or NHR^{A1}), each R^{A1} is a non-hydrogen group, or wherein two R^{A1} groups are joined to form a substituted or unsubstitued heterocyclic or heteroaryl ring.

[00212] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one

instance of R^C is –CN. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–NO_2$.

[00213] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=NR^{A1})R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)H), or a non-hydrogen group.

[00214] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=NR^{A1})OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=NH)OH), or a non-hydrogen group.

[00215] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=NR^{A1})N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=NH)NH_2$), or a non-hydrogen group.

[00216] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)H), or a non-hydrogen group.

[00217] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –C(=O)OH), or a non-hydrogen group.

[00218] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=O)NH_2$), or a non-hydrogen group.

[00219] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–C(=O)NH_2$), or a non-hydrogen group. In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–C(=O)NMe_2$, or –C(=O)NHMe.

[00220] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–NR^{A1}C(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)H), or a non-hydrogen group.

[00221] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–NR^{A1}C(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide –NHC(=O)OH), or a non-hydrogen group.

[00222] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $–NR^{A1}C(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $–NHC(=O)NH_2$), or a non-hydrogen group.

[00223] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one

instance of R^C is $-OC(=O)R^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide $-OC(=O)H$), or a non-hydrogen group.

[00224] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $-OC(=O)OR^{A1}$, wherein R^{A1} is hydrogen (*i.e.,* to provide $-OC(=O)OH$), or a non-hydrogen group.

[00225] In certain embodiments of Formula (**I**) or (**II**), a is 1 or 2 and at least one instance of R^C is $-OC(=O)N(R^{A1})_2$, wherein R^{A1} is hydrogen (*i.e.,* to provide $-OC(=O)NH_2$), or a non-hydrogen group.

[00226] Furthermore, as generally described herein, in any of the above described embodiments of group R^C comprising a group R^{A1}, each instance of R^{A1} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring.

[00227] For example, in any of the above described embodiments of R^C comprising a group R^{A1}, at least one instance of R^{A1} is hydrogen.

[00228] In any of the above described embodiments of R^C comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted alkyl, *e.g.,* substituted or unsubstitutedC_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_1alkyl, substituted or unsubstituted C_2alkyl, substituted or unsubstituted C_3alkyl, substituted or unsubstituted C_4alkyl, substituted or unsubstituted C_5alkyl, or substituted or unsubstituted C_6alkyl.

[00229] In any of the above described embodiments of R^C comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkenyl, *e.g.,* substituted or unsubstituted C_2alkenyl, substituted or unsubstituted C_3alkenyl, substituted or unsubstituted C_4alkenyl, substituted or unsubstituted C_5alkenyl, or substituted or unsubstituted C_6alkenyl

[00230] In any of the above described embodiments of R^C comprising a group R^{A1}, at least one instance of R^{A1} is substituted or unsubstituted C_{2-6}alkynyl, *e.g.,* substituted or unsubstituted C_2alkynyl, substituted or unsubstituted C_3alkynyl, substituted or unsubstituted C_4alkynyl, substituted or unsubstituted C_5alkynyl, or substituted or unsubstituted C_6alkynyl.

[00231] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^C is– $N(R^{A1})_2$, $-C(=NR^{A1})N(R^{A1})_2$,$-C(=O)N(R^{A1})_2$, $-NR^{A1}C(=O)N(R^{A1})_2$, or $-OC(=O)N(R^{A1})_2$,

two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom,are joined to form a substituted or unsubstituted heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a saturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form an unsaturated heterocyclic ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a heterocyclic ring, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a 3- to 7-membered, monocyclic heterocyclic ring.

[00232] In certain embodiments of Formula (**I**) or Formula (**II**), *e.g.,* wherein R^C is–$N(R^{A1})_2$, –$C(=NR^{A1})N(R^{A1})_2$,–$C(=O)N(R^{A1})_2$, –$NR^{A1}C(=O)N(R^{A1})_2$, or –$OC(=O)N(R^{A1})_2$, two instances of R^{A1}, *e.g.,* attached to the same nitrogen (N) atom, are joined to form a substituted or unsubstituted heteroaryl ring. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur. In certain embodiments of Formula (**I**) or Formula (**II**), two instances of R^{A1} are joined to form a substituted or unsubstituted, 9- to 10-membered, monocyclic heteroaryl ring, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur.

[00233] In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^C is independently hydrogen, halogen, substituted or unsubstituted C_{1-6} alkyl, or –OR^{A1}, wherein R^{A1} is substituted or unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), each instance of R^C is independently hydrogen, halogen, unsubstituted C_{1-6} alkyl, C_{1-6} alkyl substituted with at least one halogen, or –OR^{A1}, wherein R^{A1} is unsubstituted C_{1-6} alkyl.

Group G^5 and R^E

[00234] As generally described herein, G^5 is O, S, or NR^E.

[00235] As generally described herein, R^E is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group.

[00236] In certain embodiments of Formula (**I**) or Formula (**II**), G^5 is O. In certain embodiments of Formula (**I**) or Formula (**II**), G^5 is S. In certain embodiments of Formula (**I**) or Formula (**II**), G^5 is NR^E.

[00237] In certain embodiments of Formula (**I**) or Formula (**II**), R^E is hydrogen.

[00238] In certain embodiments of Formula (**I**) or Formula (**II**), R^E is substituted or unsubstituted C_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_{1-2} alkyl, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted C_{1-4} alkyl, or substituted or unsubstituted C_{1-5} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is substituted or unsubstituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is a nitrogen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), R^E is a nitrogen protecting group selected from the group consisting of Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, and Ts.

[00239] In certain embodiments of Formula (**I**) or Formula (**II**), G^5 is NR^E and R^E is hydrogen or substituted or unsubstituted C_{1-2} alkyl (*e.g.,* $-CH_3$, $-CF_3$).

Group R^G

[00240] As generally described herein, R^G is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group.

[00241] In certain embodiments of Formula (**I**) or Formula (**II**), R^G is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is substituted or unsubstituted C_{1-6} alkyl, *e.g.,* substituted or unsubstituted C_{1-2} alkyl, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted C_{1-4} alkyl, or substituted or unsubstituted C_{1-5} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is substituted or unsubstituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is a nitrogen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), R^G is a nitrogen protecting group selected from the group consisting of Bn, BOC, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00242] In certain embodiments of Formula (**I**) or Formula (**II**), R^G is hydrogen or substituted or unsubstituted C_{1-2} alkyl (*e.g.,* $-CH_3$, $-CF_3$).

Groups R^{J1} and R^{J2}

[00243] As generally described herein, each instance of R^{J1} and R^{J2} is independently

hydrogen, halogen, or substituted or unsubstituted alkyl.

[00244] In certain embodiments of Formula (**I**) or Formula (**II**), R^{J1} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J2} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), both R^{J1} and R^{J2} are hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), neither R^{J1} nor R^{J2} are hydrogen.

[00245] In certain embodiments of Formula (**I**) or Formula (**II**), R^{J1} is halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J2} is halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J1} is F. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J2} is F. In certain embodiments of Formula (**I**) or Formula (**II**), both R^{J1} and R^{J2} are F. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J1} is Cl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{J2} is Cl. In certain embodiments of Formula (**I**) or Formula (**II**), both R^{J1} and R^{J2} are Cl.

[00246] In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), at least one of R^{J1} and R^{J2} is substituted or unsubstituted hexyl.

Group R^X and R^{X1}

[00247] As generally described herein, R^X is hydrogen, halogen, substituted or unsubstituted alkyl, –CN, or $–OR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted

alkyl, or an oxygen protecting group.

[00248] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is hydrogen.

[00249] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is F. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is Cl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is Br. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is I (iodine).

[00250] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–CF_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^X is substituted or unsubstituted hexyl.

[00251] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is –CN.

[00252] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$, wherein R^{X1} is hydrogen (*i.e.,* to provide –OH).

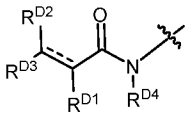
[00253] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $–OR^{X1}$, wherein R^{X1} is substituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is unsubstituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted C_{1-6} alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted methyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CH_2F$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CHF_2$. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is $–CF_3$. In certain embodiments of Formula (**I**) or Formula

(**II**), R^{X1} is substituted or unsubstituted ethyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted propyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted butyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted pentyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is substituted or unsubstituted hexyl.

[00254] In certain embodiments of Formula (**I**) or Formula (**II**), R^X is $-OR^{X1}$, wherein R^{X1} is an oxygen protecting group. In certain embodiments of Formula (**I**) or Formula (**II**), R^{X1} is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

R^{D1}, R^{D2}, R^{D3}, and R^{D4}

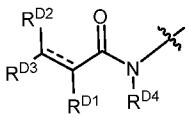
[00255] As generally described herein, for the group as provided in Formula (**I**) and (**II**) having the structure:

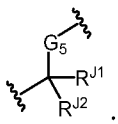


each instance of R^{D1}, R^{D2}, and R^{D3} is independently hydrogen or substituted or unsubstituted alkyl, and R^{D4} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group, and ==== represents a single bond or a double bond.

[00256] In certain embodiments of Formula (**I**) or Formula (**II**), ==== represents a double bond. In certain embodiments of Formula (**I**) or Formula (**II**), ==== represents a single bond.

[00257] In certain embodiments, the group of formula



is attached *meta* or *para* to the point of attachment . In certain embodiments, the group is attached *meta* to the point of attachment. In certain embodiments, the group is attached *para* to the point of attachment.

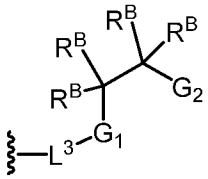
[00258] In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**),

each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2OR^{D1a}$, and R^{D1a} is methyl.

[00259] In certain embodiments of Formula (**I**) or Formula (**II**), R^{D4} is hydrogen. In certain embodiments of Formula (**I**) or Formula (**II**), R^{D4} is substituted or unsubstituted alkyl. In certain embodiments of Formula (**I**) or Formula (**II**), R^{D4} is a nitrogen protecting group.

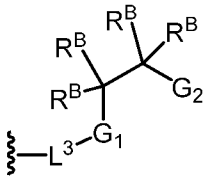
Linker L^1

[00260] In certain embodiments of Formula (**I**), R^{Y1} is $–L^1\text{-}R^H$, wherein L^1 and R^H are as defined herein, or R^{Y1} is a group of formula:



wherein L^3, G_1, and R^B is as defined herein, and G_2 is $N(R^{G2a})\text{-}L^1\text{-}R^H$, $O\text{-}L^1\text{-}R^H$, or $C(R^{G2a})\text{-}L^1\text{-}R^H$, wherein R^{G2}, L^1, and R^H are as defined herein.

[00261] Furthermore, in certain embodiments of Formula (**II**), R^{Y2} is $–L^1\text{-}R^H$, wherein L^1 and R^H are as defined herein, or R^{Y2} is a group of formula:



wherein L^3, G_1, and R^B is as defined herein, and G_2 is $N(R^{G2a})\text{-}L^1\text{-}R^H$, $O\text{-}L^1\text{-}R^H$, or $C(R^{G2a})\text{-}L^1\text{-}R^H$, wherein R^{G2}, L^1, and R^H are as defined herein.

[00262] As generally defined herein, L^1 is a linker selected from the group consisting of the following divalent moieties: substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, substituted and unsubstituted heterocyclylene, substituted and unsubstituted carbocyclylene, substituted and unsubstituted arylene, substituted and unsubstituted heteroarylene, and combinations thereof.

[00263] Reference to L^1 being a combination of at least two instances of the divalent moieties described herein refers to a linker consisting of at least one instance of a first

divalent moiety and at least one instance of a second divalent moiety, wherein the first and second divalent moieties are the same or different and are within the scope of the divalent moieties described herein, and the instances of the first and second divalent moieties are consecutive covalently attached to each other. For example, when L^1 is a combination of alkylene and heteroalkylene, linkers –alkylene– heteroalkylene–, –alkylene–(heteroalkylene)$_2$–, and –heteroalkylene–alkylene–heteroalkylene– are all within the scope of L^1, wherein each instance of alkylene in any one of the linkers may be the same or different, and each instance of heteroalkylene in any one of the linkers may be the same or different.

[00264] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted alkylene, *e.g.*, substituted or unsubstituted C_{1-6}alkylene, substituted or unsubstituted C_{1-2}alkylene, substituted or unsubstituted C_{2-3}alkylene, substituted or unsubstituted C_{3-4}alkylene, substituted or unsubstituted C_{4-5}alkylene, substituted or unsubstituted C_{5-6}alkylene, substituted or unsubstituted C_{3-6}alkylene, or substituted or unsubstituted C_{4-6}alkylene. Exemplary alkylene groups include unsubstituted alkylene groups such as methylene (–CH_2–), ethylene (–$(CH_2)_2$–), *n*-propylene (–$(CH_2)_3$–), *n*-butylene (–$(CH_2)_4$–), *n*-pentylene (–$(CH_2)_5$–), and *n*-hexylene (–$(CH_2)_6$–).

[00265] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted alkenylene, *e.g.*, substituted or unsubstituted C_{2-6}alkenylene, substituted or unsubstituted C_{2-3}alkenylene, substituted or unsubstituted C_{3-4}alkenylene, substituted or unsubstituted C_{4-5}alkenylene, or substituted or unsubstituted C_{5-6}alkenylene.

[00266] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted alkynylene, *e.g.*, substituted or unsubstituted C_{2-6}alkynylene, substituted or unsubstituted C_{2-3}alkynylene, substituted or unsubstituted C_{3-4}alkynylene, substituted or unsubstituted C_{4-5}alkynylene, or substituted or unsubstituted C_{5-6}alkynylene.

[00267] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted heteroalkylene, *e.g.*, substituted or unsubstituted heteroC_{1-6}alkylene, substituted or unsubstituted heteroC_{1-2}alkylene, substituted or unsubstituted heteroC_{2-3}alkylene, substituted or unsubstituted heteroC_{3-4}alkylene, substituted or unsubstituted heteroC_{4-5}alkylene, or substituted or unsubstituted heteroC_{5-6}alkylene. Exemplary heteroalkylene groups include unsubstituted heteroalkylene groups such as –$(CH_2)_2$–O$(CH_2)_2$–, –OCH_2–, –CH_2O–, –O$(CH_2)_2$–, –$(CH_2)_2$O–, –O$(CH_2)_3$–, –$(CH_2)_3$O–, –O$(CH_2)_4$–, –$(CH_2)_4$O–, –O$(CH_2)_5$–, –$(CH_2)_5$O–, –O$(CH_2)_6$–, and –O$(CH_2)_6$O–, and amide groups (*e.g.,* -NH-C(=O)- and -C(=O)NH-).

[00268] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted heteroalkenylene, *e.g.*, substituted or unsubstituted heteroC_{2-6}alkenylene, substituted or unsubstituted heteroC_{2-3}alkenylene, substituted or unsubstituted heteroC_{3-4}alkenylene, substituted or unsubstituted heteroC_{4-5}alkenylene, or substituted or unsubstituted heteroC_{5-6}alkenylene.

[00269] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted heteroalkynylene, *e.g.*, substituted or unsubstituted heteroC_{2-6}alkynylene, substituted or unsubstituted heteroC_{2-3}alkynylene, substituted or unsubstituted heteroC_{3-4}alkynylene, substituted or unsubstituted heteroC_{4-5}alkynylene, or substituted or unsubstituted heteroC_{5-6}alkynylene.

[00270] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted carbocyclylene, *e.g.*, substituted or unsubstituted C_{3-6}carbocyclylene, substituted or unsubstituted C_{3-4}carbocyclylene, substituted or unsubstituted C_{4-5} carbocyclylene, or substituted or unsubstituted C_{5-6} carbocyclylene.

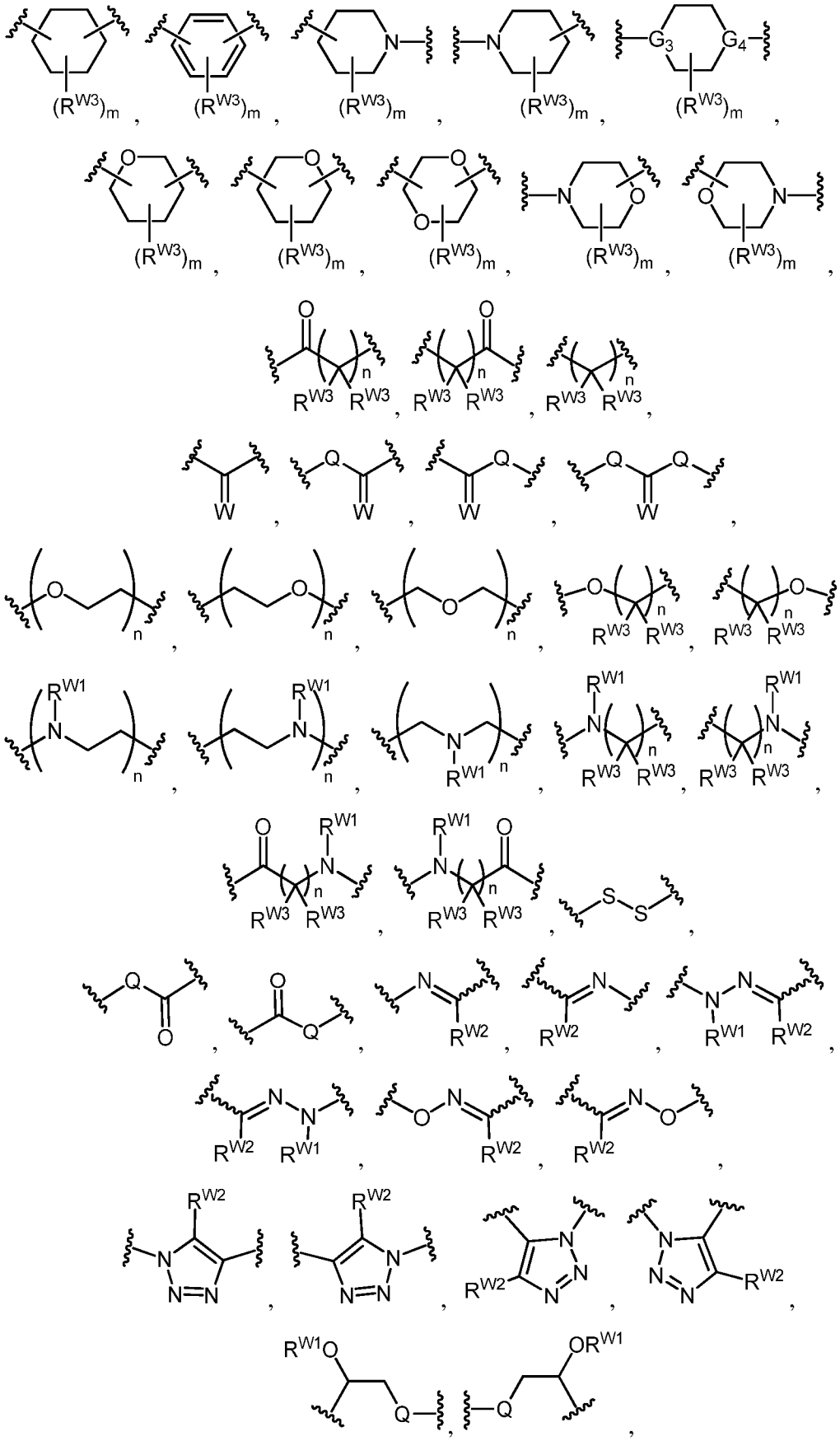
[00271] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted heterocyclylene, *e.g.*, substituted or unsubstituted 3-6 membered heterocyclylene, substituted or unsubstituted 3-4 membered heterocyclylene, substituted or unsubstituted 4-5 membered heterocyclylene, or substituted or unsubstituted 5-6 membered heterocyclylene.

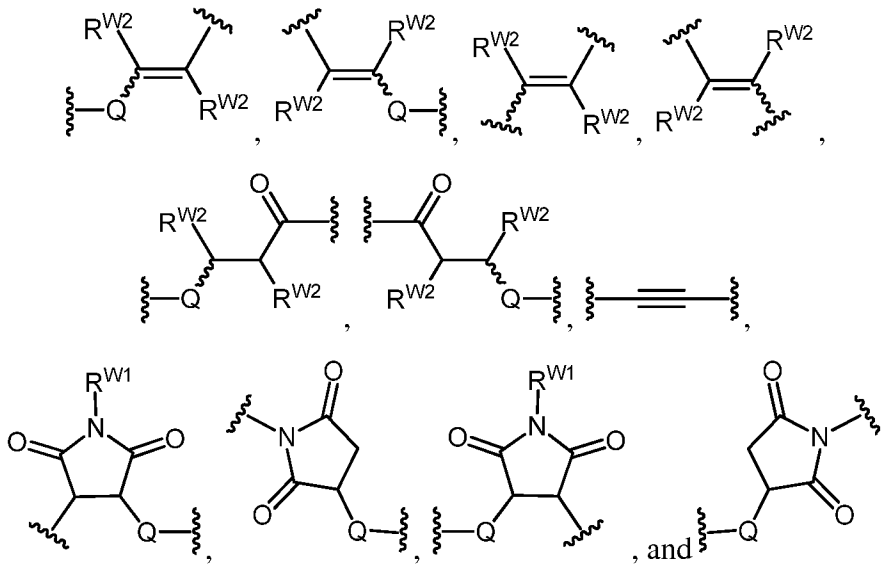
[00272] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted arylene, *e.g.*, substituted or unsubstituted phenylene.

[00273] In certain embodiments, L^1 comprises at least one instance of substituted or unsubstituted heteroarylene, *e.g.*, substituted or unsubstituted 5- to 6-membered heteroarylene.

[00274] In certain embodiments, L^1 is a linker that contains an asymmetric carbon/stereocenter, *i.e.*, an sp^3 hybridized carbon atom bearing 4 different groups attached thereto. In certain embodiments, the compound comprising such an L^1 group is enantiomerically enriched or substantially enantiomerically enriched. In certain embodiments, the compound comprising such an L^1 group is racemic.

[00275] In certain embodiments, L^1 is a linker group as defined herein comprising at least one instance of any one of the following divalent moieties:





wherein:

each instance of n is independently an integer between 1 to 10, inclusive;

each instance of m is independently 0, 1, or 2;

each instance of Q is independently $–NR^{W1}–$; $–NR^{W1}–NR^{W1}–$; $–O–NR^{W1}–$;$–NR^{W1}–O–$; –S–; or –O–;

each instance of W is independently O, S, or NR^{W1};

each instance of G_3 and G_4 are independently N or CH;

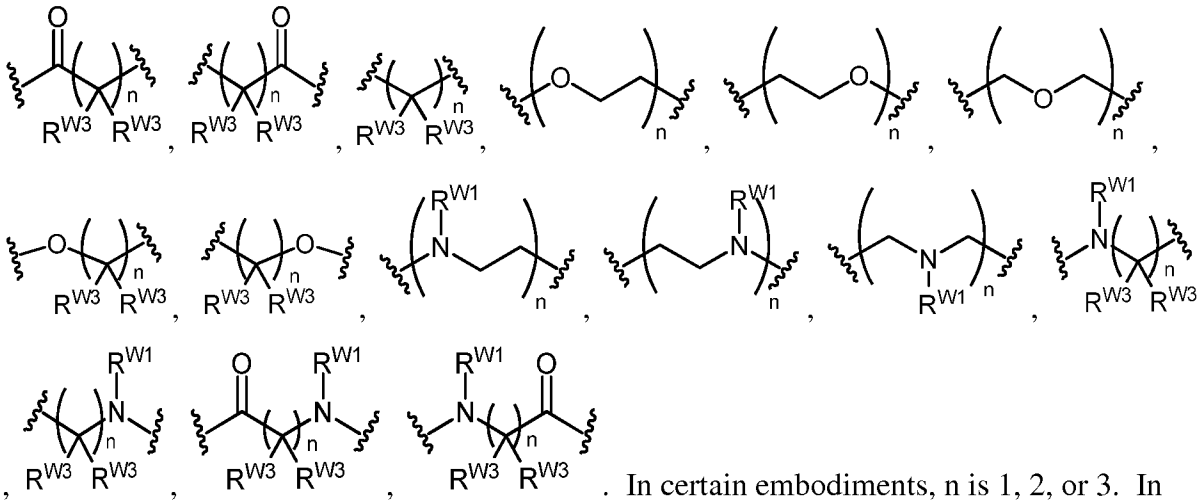
each instance of R^{W1} is independently hydrogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; a nitrogen protecting group if attached to a nitrogen atom, or an oxygen protecting group if attached to an oxygen atom;

each instance of R^{W2} is independently hydrogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or two R^{W2} groups are joined to form a 5–6 membered ring; and

each instance of R^{W3} is independently hydrogen; halogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; or substituted or unsubstituted heteroaryl, or two R^{W3} groups are joined to form a 3–6 membered ring;

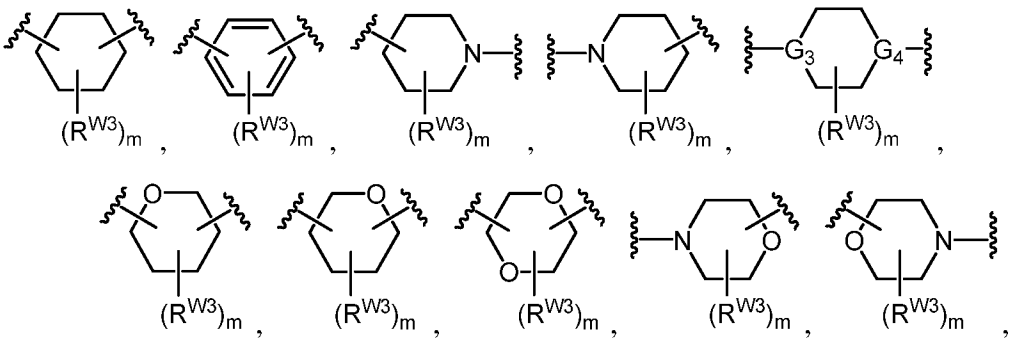
or R^{W1} and R^{W3} are joined to form a 5–6 membered heterocyclic ring.

[00276] As described herein, n of any of the below formulae is independently an integer between 1 to 10, inclusive, *e.g.,* 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10:



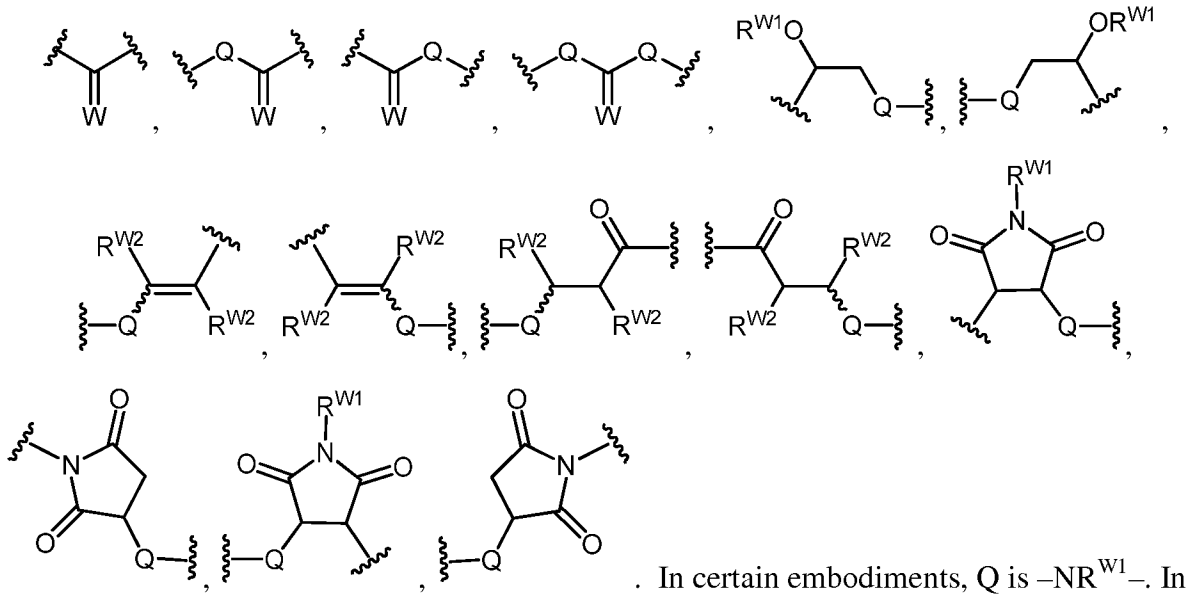
. In certain embodiments, n is 1, 2, or 3. In certain embodiments, each instance of R^{W3} is independently hydrogen; halogen; or substituted or unsubstituted alkyl (*e.g.,* methyl).

[00277] As described herein, m of any of the below formulae is independently 0, 1, or 2, and G_3 and G_4 are independently N or CH:



In certain embodiments, m is 0, and R^{W3} is absent. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, G_3 is N. In certain embodiments, G_3 is CH. In certain embodiments, G_4 is N. In certain embodiments, G_4 is CH. In certain embodiments, G_3 is N and G_4 is CH. In certain embodiments, G_3 is CH and G_4 is CH. In certain embodiments, G_3 is N and G_4 is N. In certain embodiments, G_3 is CH and G_4 is N. In certain embodiments, each instance of R^{W3} is independently hydrogen; halogen; or substituted or unsubstituted alkyl (*e.g.,* methyl).

[00278] As described herein, each instance of Q of any of the below formulae is independently $–NR^{W1}–$; $–NR^{W1}–NR^{W1}–$; $–O–NR^{W1}–$;$–NR^{W1}–O–$; –S–; or –O–, and each instance of W of any of the below formulae is independently O, S, or NR^{W1}:



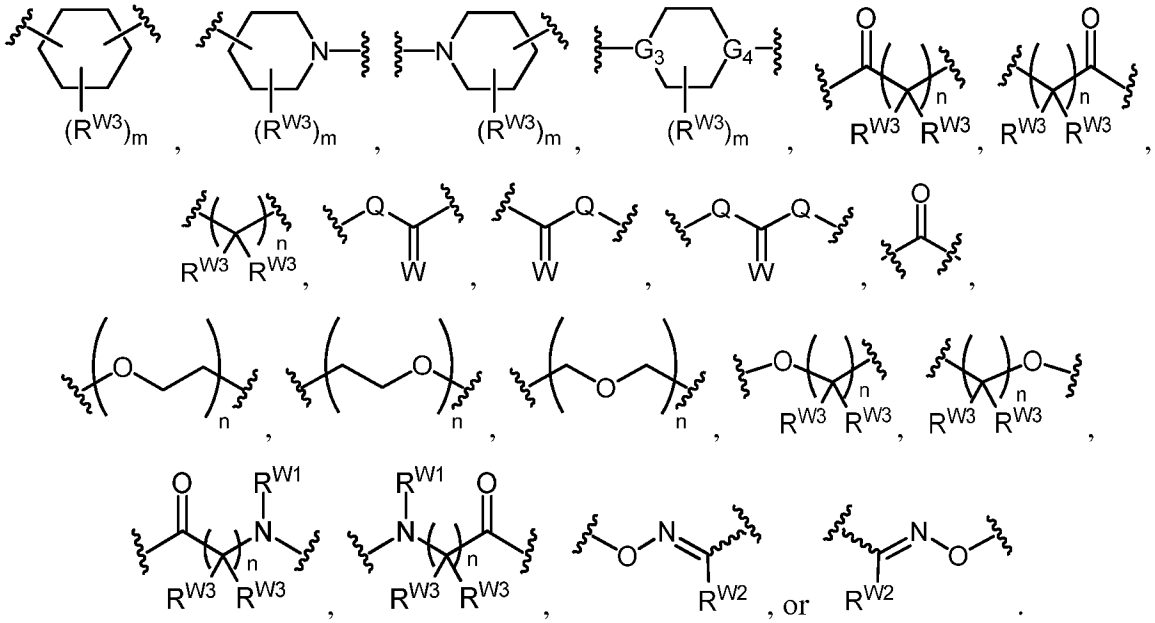
. In certain embodiments, Q is $-NR^{W1}-$. In certain embodiments, Q is $-NR^{W1}-NR^{W1}-$. In certain embodiments, Q is $-O-NR^{W1}-$. In certain embodiments, Q is $-NR^{W1}-O-$. In certain embodiments, Q is –S–. In certain embodiments, Q is –O–. In certain embodiments, W is O. In certain embodiments, W is S. In certain embodiments, W is NR^{W1}. In certain embodiments, W is O and Q is independently –S–, $-NR^{W1}-$, or –O–. In certain embodiments, R^{W1} is not hydrogen. In certain embodiments, R^{W2} is hydrogen or substituted or unsubstituted alkyl (*e.g.,* methyl).

[00279] As described herein, each instance of R^{W1} is independently hydrogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; a nitrogen protecting group if attached to a nitrogen atom, or an oxygen protecting group if attached to an oxygen atom. In any of the above formulae, as described herein, each instance of R^{W1} is independently hydrogen; substituted or unsubstituted alkyl (*e.g.,* methyl); a nitrogen protecting group if attached to a nitrogen atom, or an oxygen protecting group if attached to an oxygen atom.

[00280] As described herein, each instance of R^{W2} is independently hydrogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; substituted or unsubstituted heteroaryl; or two R^{W2} groups are joined to form a 5–6 membered ring. In any of the above formulae, as described herein, each instance of R^{W2} is independently hydrogen or substituted or unsubstituted alkyl (*e.g.,* methyl).

[00281] As described herein, each instance of R^{W3} is independently hydrogen; halogen; substituted or unsubstituted alkyl; substituted or unsubstituted alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted carbocyclyl; substituted or unsubstituted heterocyclyl; substituted or unsubstituted aryl; or substituted or unsubstituted heteroaryl, or two R^{W3} groups are joined to form a 3–6 membered ring. In any of the above formulae, as described herein, each instance of R^{W3} is independently hydrogen; halogen; substituted or unsubstituted alkyl (*e.g.,* methyl).

[00282] In certain embodiments, L^1 is a linker group as defined herein comprising one of the following divalent moieties directly (covalently) attached to the parent molecule:

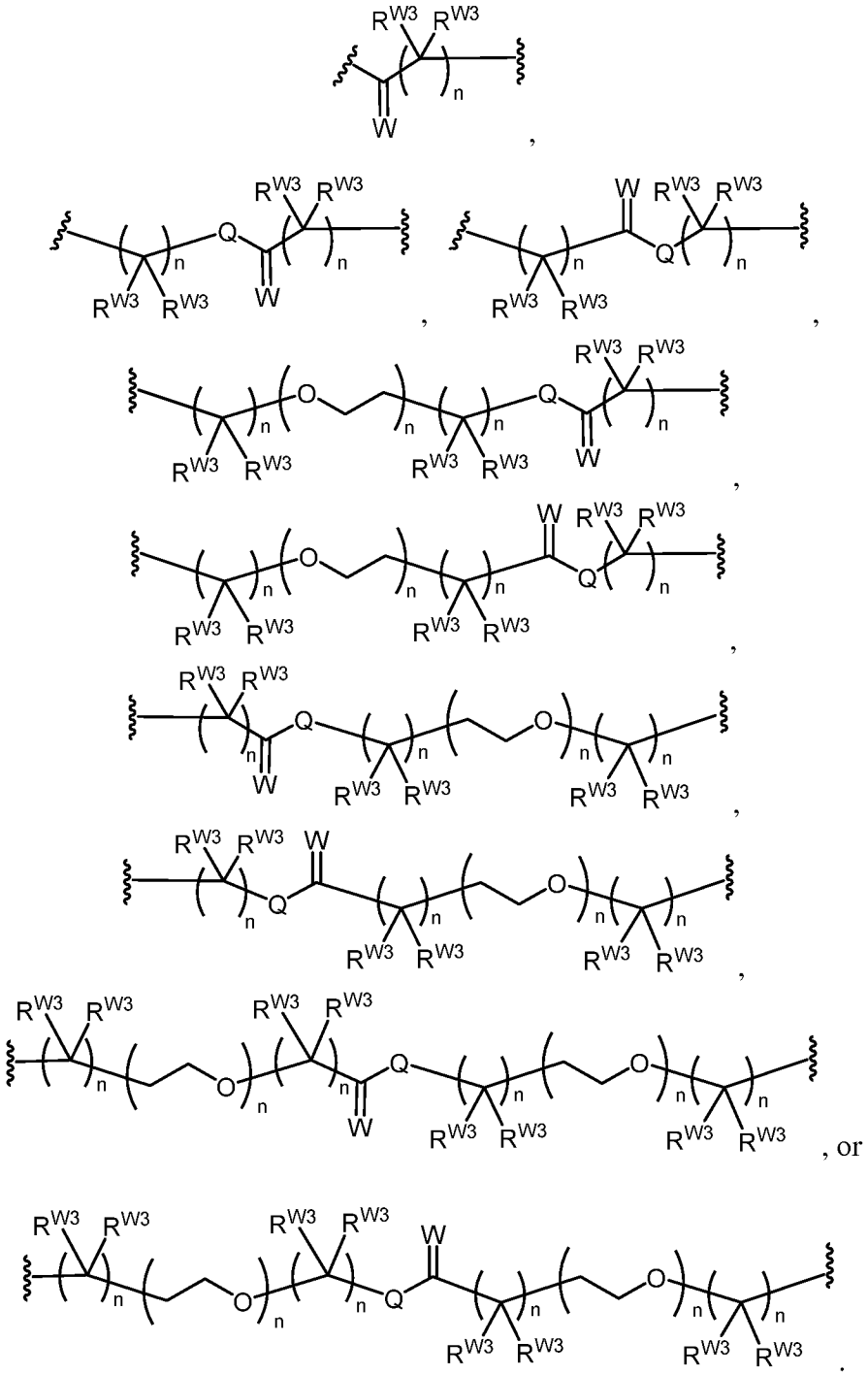


[00283] In certain embodiments, L^1 is a linker comprising a combination of 1 to 20 consecutive covalently bonded divalent moieties described herein, *e.g.*, 2 to 20, 3 to 20, 4 to 20, 5 to 20, 6 to 20, 8 to 20, 9 to 20, 10 to 20, 2 to 10, 2 to 9, 2 to 8, 2 to 7, 2 to 6, or 2 to 5 divalent moieties, inclusive. In certain embodiments, L^1 is a linker comprising a combination of 2 to 6 consecutive covalently bonded divalent moieties, inclusive. In certain embodiments, L^1 is a linker comprising a combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 consecutive covalently bonded divalent moieties. In certain embodiments, L^1 is a linker comprising a combination of 4 consecutive covalently bonded divalent moieties.

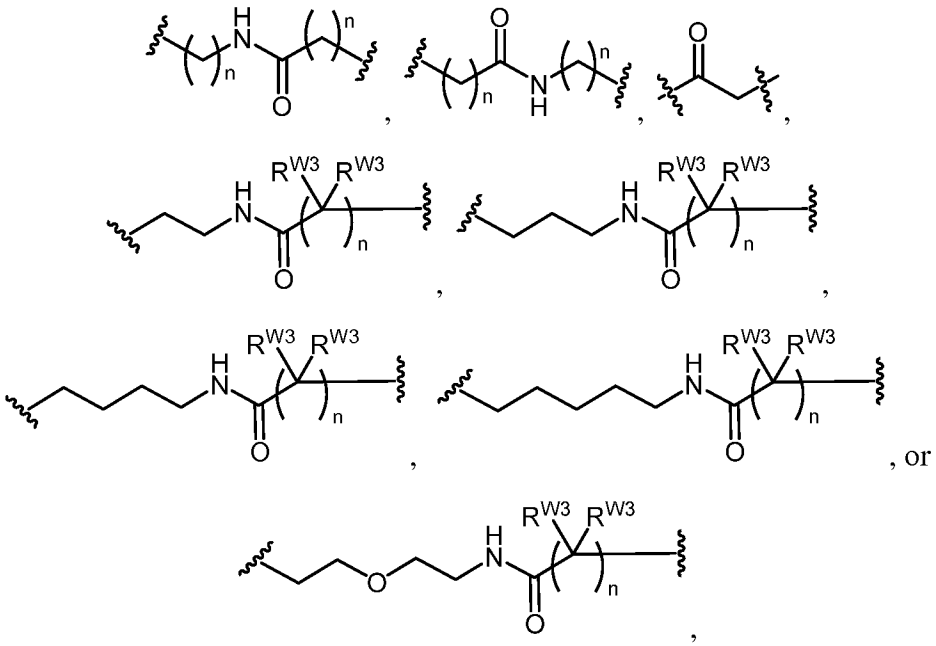
[00284] In certain embodiments, L^1 is a linker 4 to 20 consecutive covalently bonded atoms in length, inclusive, *e.g.,* 4 to 19, 4 to 18, 4 to 17, 4 to 16, 4 to 15, 4 to 14, 4 to 13, 4 to 12, 4 to 11, 4 to 10, 4 to 9, 4 to 8, 4 to 7, 4 to 6, or 5 to 11 consecutive covalently bonded atoms in length, inclusive. In certain embodiments, L^1 is a linker 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 consecutive covalently bonded atoms in length. In certain

embodiments, L^1 is a linker 5, 6, 7, 8, 9, 10, 11,12, 13, 14, or 15 consecutive covalently bonded atoms in length.

[00285] In certain embodiments, L^1 is a linker group as defined herein comprising one of the following divalent moieties directly (covalently) attached to the parent molecule:

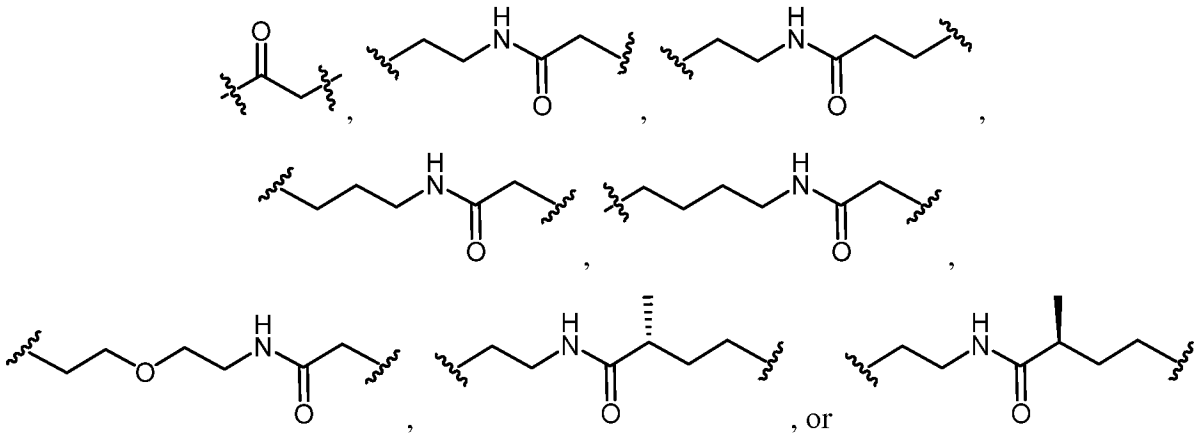


[00286] In certain embodiments, L^1 is a linker group as defined herein comprising one of the following divalent moieties directly (covalently) attached to the parent molecule:

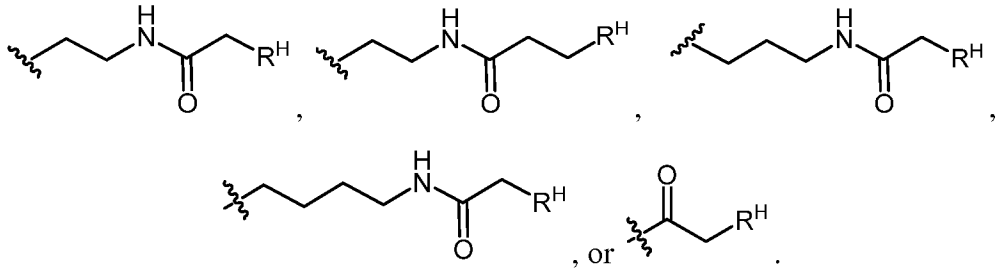


wherein n is an integer between 1 to 10, inclusive, and wherein R^{W3} is as defined herein. In certain embodiments, n is 1, 2, or 3.

[00287] In certain embodiments, L^1 is a linker group as defined herein comprising one of the following divalent moieties directly (covalently) attached to the parent molecule:



[00288] In certain embodiments, $-L^1-R^H$ represents a group of the formula:



Hydrophobic Group R^H

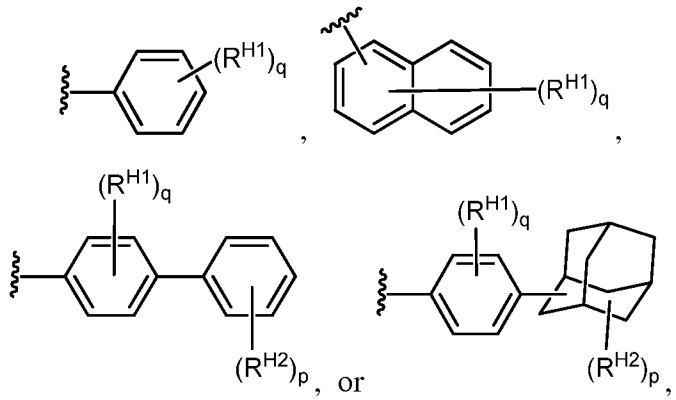
[00289] In compounds of Formula (**I**) and Formula (**II**), R^H is a hydrophobic group selected from the group consisting of substituted and unsubstituted aryl, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heteroarylalkyl, substituted and unsubstituted carbocycylalkyl, and substituted and unsubstituted heterocyclylalkyl.

[00290] The term "hydrophobic," in the context of a "hydrophobic" group $-R^H$, refers to a group $-R^H$ which comprises zero hydrogen bond donors (*e.g.,* no hydrogen attached to a nitrogen, oxygen, or sulfur, e.g., $-NH_2$, -NH-, –OH, and/or –SH) and optionally zero hydrogen bond acceptors (*e.g.,* no nitrogen, oxygen, or sulfur atoms). In certain embodiments, a hydrophobic group comprises zero hydrogen bond. In certain embodiments, a hydrophobic group comprises zero hydrogen bond acceptors. In certain embodiments, a hydrophobic group comprises zero hydrogen bond donors and zero hydrogen bond acceptors. For example, in certain embodiments, a hydrophobic group is an unsubstituted hydrocarbon (carbocyclylalkyl, carbocyclyl, aralkyl, or aryl) group, *e.g.,* comprising only carbon and hydrogen atoms. In certain embodiments, a hydrophobic group comprises at least 6 carbon atoms, *e.g.,* between 6 and 50 carbon atoms, between 6 and 40 carbon atoms, between 6 and 30 carbon atoms, between 6 and 20 carbon atoms, or between 6 and 15 carbon atoms, inclusive. In certain embodiments, a hydrophobic group comprises 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms.

[00291] In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted aryl; or a hydrophobic, substituted or unsubstituted aralkyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted aryl moiety, *e.g.,* substituted or unsubstituted phenyl, substituted or unsubstituted biphenyl, substituted or unsubstituted naphthyl, or substituted or unsubstituted anthracenyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted aralkyl, wherein each instance of the arylene portion is

independently substituted or unsubstituted 6- to 14-membered arylene. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted arylmethyl, *e.g.*, substituted or unsubstituted benzyl, substituted or unsubstituted diphenylmethyl, substituted or unsubstituted trityl, substituted or unsubstituted biphenylmethyl, substituted or unsubstituted naphthylmethyl, or substituted or unsubstituted anthracenylmethyl.

[00292] In certain embodiments, R^H is a hydrophobic moiety of the formula:



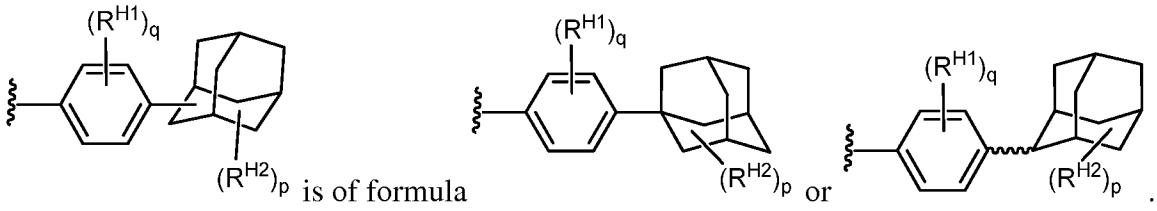
wherein:

each occurrence of R^{H1} and R^{H2} is independently halogen, –CN, substituted or unsubstituted C_{1-6} alkyl, $–OR^{H1a}$, or $–N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and

each of p and q is independently 0, 1, 2, or 3.

[00293] In certain embodiments, each occurrence of R^{H1} and R^{H2} is independently halogen (*e.g.*, fluoro, bromo, iodo, chloro), substituted or unsubstituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl, tertbutyl, difluoromethyl, perfluoromethyl), substituted hydroxyl (*e.g.*, methoxy, ethoxy, isopropoxy), or disubstituted amino (*e.g.*, dimethylamino, or diethylamino). In certain embodiments, p is 0 or 1. In certain embodiments, q is 0 or 1. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, p is 0, and q is 0.

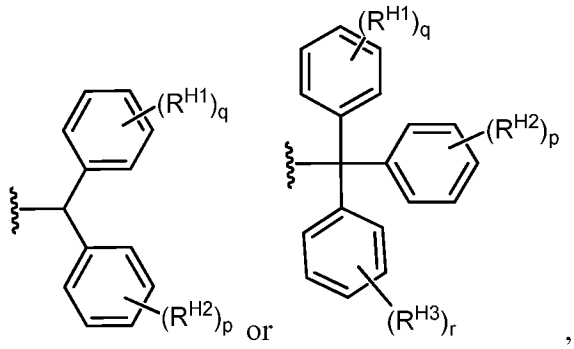
[00294] In certain embodiments, the hydrophobic moiety of formula:



is of formula

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[00295] In certain embodiments, R^H is a hydrophobic moiety of the formula:



wherein:

each occurrence of R^{H1}, R^{H2}, and R^{H3} is independently halogen, –CN, substituted or unsubstituted C_{1-6} alkyl, $–OR^{H1a}$, or $–N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and

each of p, q, and r is independently 0, 1, 2, or 3.

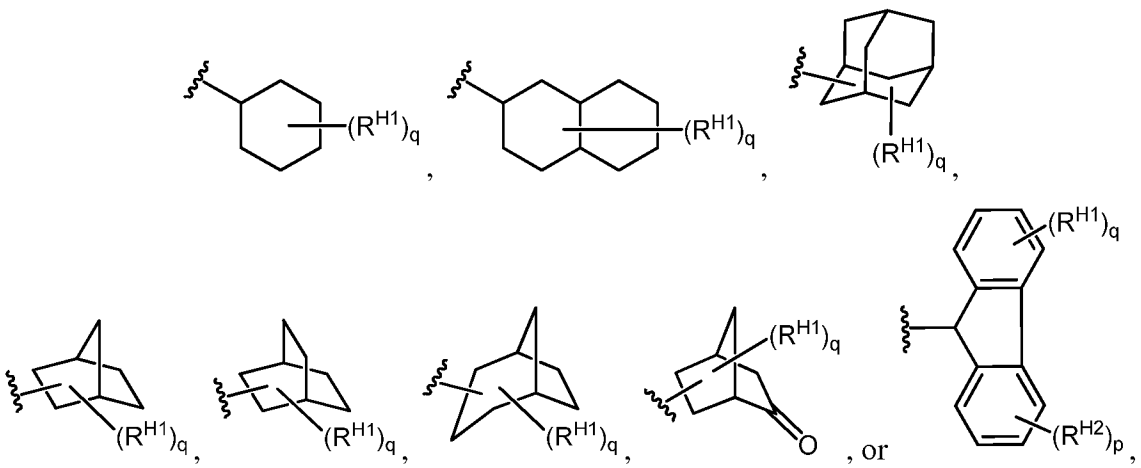
[00296] In certain embodiments, each occurrence of R^{H1}, R^{H2}, and R^{H3} is independently halogen (*e.g.,* fluoro, bromo, iodo, chloro), substituted or unsubstituted alkyl (*e.g.,* methyl, ethyl, propyl, isopropyl, tertbutyl, difluoromethyl, perfluoromethyl), substituted hydroxyl (*e.g.,* methoxy, ethoxy, isopropoxy), or disubstituted amino (*e.g.,* dimethylamino, or diethylamino). In certain embodiments, p is 0 or 1. In certain embodiments, q is 0 or 1. In certain embodiments, r is 0 or 1. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, r is 0. In certain embodiments, p is 0, q is 0, and r is 0.

[00297] In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heteroaryl; or hydrophobic, substituted or unsubstituted heteroarylalkyl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heteroaryl, *e.g.,* substituted or unsubstituted, 5- or 6-membered monocyclic heteroaryl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heteroarylaralkyl, *e.g.,* substituted or unsubstituted heteroarylmethyl, wherein each instance of the heteroarylene portion is independently a substituted or unsubstituted, 5- or 6-membered heteroarylene, wherein one, two, or three atoms in the heteroarylene ring system are independently nitrogen, oxygen, or sulfur.

[00298] In certain embodiments, R^H is hydrophobic, substituted or unsubstituted carbocyclyl; or hydrophobic, substituted or unsubstituted carbocycylalkyl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted carbocyclyl which may be monocyclic; fused, bridged, or spiro bicyclic; or fused, bridged, or spiro tricyclic. In certain embodiments, R^H is substituted or unsubstituted C_{3-9}carbocyclyl, substituted or unsubstituted C_{3-8}carbocyclyl, substituted or unsubstituted C_{3-7}carbocyclyl, substituted or unsubstituted C_{3-6}carbocyclyl, substituted or unsubstituted C_{3-5}carbocyclyl, or substituted or unsubstituted C_{3-4}

carbocyclyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted fused bicyclic carbocyclyl, *e.g.,* substituted or unsubstituted *cis*- or *trans*-decalin. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted fused tricyclic carbocyclyl, *e.g.,* substituted or unsubstituted fluorenyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted spiro bicyclic carbocyclyl, *e.g.,* substituted or unsubstituted spiropentanyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted bridged bicyclic carbocyclyl, *e.g.,* substituted or unsubstituted norbornanyl, norbornenyl, bicyclo[2.2.2]octanyl, a bicyclo[2.2.2]oct-2-ene radical, bicyclo[3.2.1]octanyl, or a bicyclo[2.2.1]heptan-2-one radical. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted, bridged, tricyclic carbocyclyl, *e.g.,* substituted or unsubstituted adamantanyl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted carbocycylalkyl, *e.g.,* hydrophobic, substituted or unsubstituted carbocycylmethyl.

[00299] In certain embodiments, R^H is a hydrophobic moiety of the formula:



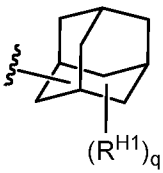
wherein:

each occurrence of R^{H1} and R^{H2} is independently halogen, –CN, substituted or unsubstituted C_{1-6} alkyl, $–OR^{H1a}$, or $–N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and

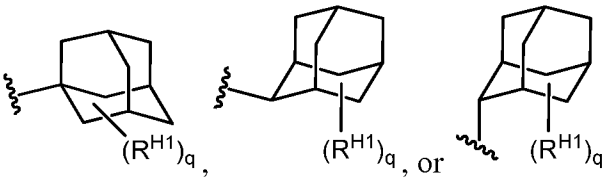
each of p and q is independently 0, 1, 2, or 3.

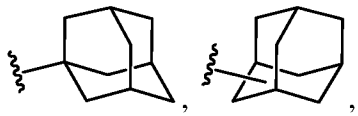
[00300] In certain embodiments, each occurrence of R^{H1} and R^{H2} is independently halogen (*e.g.,* fluoro, bromo, iodo, chloro), substituted or unsubstituted alkyl (*e.g.,* methyl, ethyl, propyl, isopropyl, tertbutyl, difluoromethyl, perfluoromethyl), substituted hydroxyl (*e.g.,* methoxy, ethoxy, isopropoxy), or disubstituted amino (*e.g.,* dimethylamino, or diethylamino). In certain embodiments, p is 0 or 1. In certain embodiments, q is 0 or 1. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, p is 0, and q is 0.

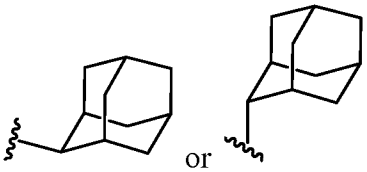
[00301] In certain embodiments, R^H is a hydrophobic moiety of the formula



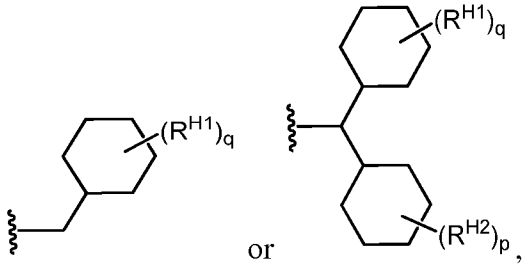
is of the formula:



[00302] In certain embodiments, R^H is of the formula: 



[00303] In certain embodiments, R^H is a hydrophobic moiety of the formula:



wherein:

each occurrence of R^{H1} and R^{H2} is independently halogen, –CN, substituted or unsubstituted C_{1-6} alkyl, $–OR^{H1a}$, or $–N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and

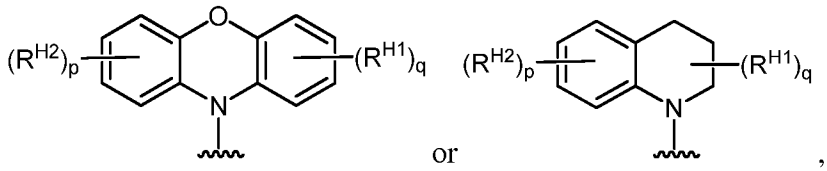
each of p and q is independently 0, 1, 2, or 3.

[00304] In certain embodiments, each occurrence of R^{H1} and R^{H2} is independently halogen (*e.g.,* fluoro, bromo, iodo, chloro), substituted or unsubstituted alkyl (*e.g.,* methyl, ethyl, propyl, isopropyl, tertbutyl, difluoromethyl, perfluoromethyl), substituted hydroxyl (*e.g.,* methoxy, ethoxy, isopropoxy), or disubstituted amino (*e.g.,* dimethylamino, or diethylamino). In certain embodiments, p is 0 or 1. In certain embodiments, q is 0 or 1. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, p is 0, and q is 0.

[00305] In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heterocyclyl or hydrophobic, substituted or unsubstituted heterocyclylalkyl. In certain embodiments, R^H is a hydrophobic, substituted or unsubstituted heterocyclyl moiety, *e.g.*, 4-14-membered heterocyclyl which may be monocyclic heterocyclyl; fused, bridged, or spiro bicyclic heterocyclyl; or fused, bridged, or spiro tricyclic heterocyclyl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted, 4- to 7-membered, monocyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted, 5- to 12-membered, bicyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted, 6- to 14-membered, tricyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur.

[00306] In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heterocyclylalkyl. In certain embodiments, the alkyl portion of the heterocyclylalkyl is C_{1-6} alkyl. In certain embodiments, R^H is hydrophobic, substituted or unsubstituted heterocyclylmethyl. In certain embodiments, the heterocyclic portion of the heterocyclylalkyl is substituted or unsubstituted, 4- to 7-membered, monocyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, the heterocyclic portion of the heterocyclylalkyl is substituted or unsubstituted, 5- to 12-membered, bicyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, the heterocyclic portion of the heterocyclylalkyl is substituted or unsubstituted, 6- to 14-membered, tricyclic heterocyclyl, wherein one, two, or three atoms in the heterocyclic ring system are independently selected from the group consisting of nitrogen, oxygen, and sulfur.

[00307] In certain embodiments, R^H is a hydrophobic moiety of the formula:



wherein each occurrence of R^{H1} and R^{H2} is independently halogen, –CN, substituted or

unsubstituted C_{1-6} alkyl, $-OR^{H1a}$, or $-N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and each of p and q is independently 0, 1, 2, or 3. In certain embodiments, each occurrence of R^{H1} and R^{H2} is independently fluoro, bromo, iodo, chloro, methyl, ethyl, propyl, isopropyl, tertbutyl, difluoromethyl, perfluoromethyl, methoxy, ethoxy, isopropoxy, dimethylamino, or diethylamino. In certain embodiments, p is 0 or 1. In certain embodiments, q is 0 or 1. In certain embodiments, p is 0. In certain embodiments, q is 0. In certain embodiments, p is 0, and q is 0.

Exemplary Physical Properties of the Compound

[00308] The term "molecular weight of a compound of Formula (**I**) or Formula (**II**)" refers to the molecular weight of a compound described herein minus the combined molecular weight of any counterions, solvents, and water included with the compound (for example, when the compound is a salt (*e.g.*, a pharmaceutically acceptable salt)).

[00309] The molecular weight of the hydrophobic group $-R^H$ may be between 50 and 300 g/mol, inclusive, *e.g.*, between 50 and 200, between 100 and 200, between 80 and 180, or between 100 and 160 g/mol, inclusive. In certain embodiments, the molecular weight of the hydrophobic moiety $-R^H$ is between 100 and 200 g/mol, inclusive. It is understood that the molecular weight of the moiety R^H is calculated by subtracting 1 from the molecular weight of the compound $H-R^H$.

[00310] The molecular weight of the group $-L^1-R^H$ may be between 50 and 600 g/mol, inclusive, *e.g.,* between 50 and 500, between 100 and 500, between 100 and 400, between 100 and 300, between 100 and 200, between 200 and 400, or between 200 and 300 g/mol, inclusive. In certain embodiments, the molecular weight of the moiety $-L^1-R^H$ is between 200 and 300 g/mol, inclusive. It is understood that the molecular weight of the moiety $-L^1-R^H$ is calculated by subtracting 1 from the molecular weight of the compound $H-L^1-R^H$.

[00311] The molecular weight of a compound of Formula (**I**) or Formula (**II**) may be between 400 and 1000 g/mol, inclusive, *e.g.,* between 400 and 900, between 400 and 800, between 400 and 700, between 400 and 600, between 400 and 500, between 500 and 1000, between 500 and 900, between 500 and 800, or between 600 and 800 g/mol, inclusive. In certain embodiments, the molecular weight of a compound of Formula (**I**) is between 500 and 900 g/mol, inclusive. In certain embodiments, the molecular weight of a compound of Formula (**I**) or Formula (**II**) is between 600 and 900 g/mol, inclusive. In certain embodiments, the molecular weight of a compound of Formula (**I**) or Formula (**II**) is between 200 and 600 g/mol, inclusive.

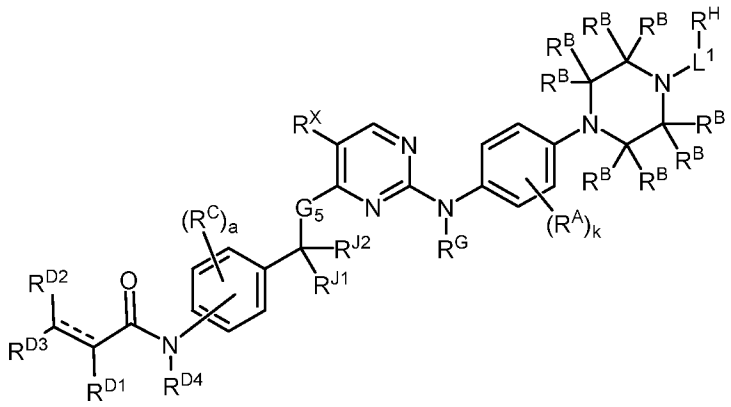
[00312] The Log(partition coefficient) (Log*P*) of a compound described herein may be less than or equal to (at most) 5, *e.g.*, between –8 to about 5, inclusive. In certain embodiments, Log*P* is determined by a shake flask (or shake tube) method using ultraviolet-visible spectroscopy.

[00313] A compound of Formula (**I**) or Formula (**II**) may consist of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hydrogen bond donors, *e.g.*, 2, 3, 4, or 5 hydrogen bond donors. A compound of Formula (**I**) or Formula (**II**) may consist of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hydrogen bond acceptors, *e.g.*, 3, 4, or 5 hydrogen bond acceptors.

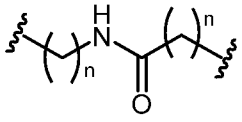
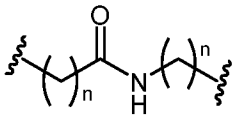
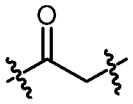
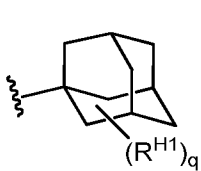
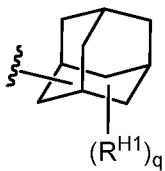
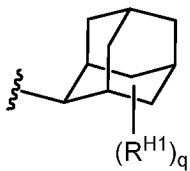
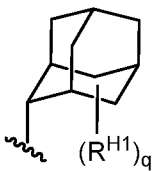
*Exemplary compounds of Formula (**I**)*

[00314] Various combinations of certain embodiments of Formula (**I**) are futher contemplated herein.

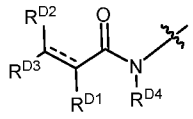
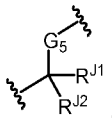
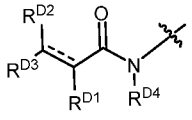
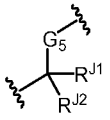
[00315] For example, in certain embodiments, a compound described herein is a compound of Formula (**Ia**):



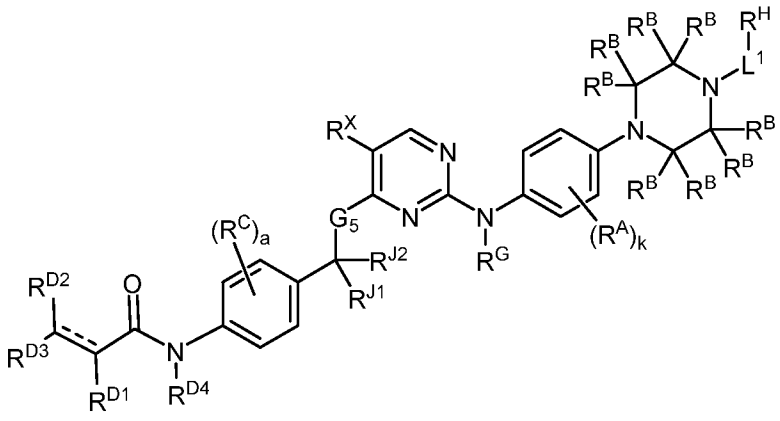
(**Ia**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0. In certain embodiments, all instances of R^B are hydrogen. In

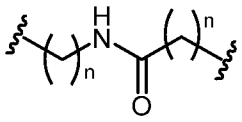
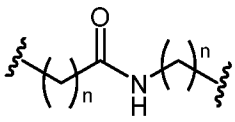
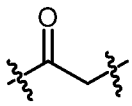
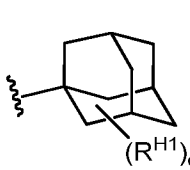
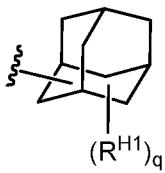
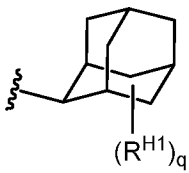
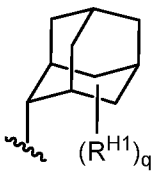
certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instance of R^A is Cl. In certain embodiments, at least two instances of R^A are independently halogen. In certain embodiments, at least two instances of R^A are F. In certain embodiments, at least two instances of R^A are Cl. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is $–CH_3$. In certain embodiments, at least one instance of R^A is $–CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $–CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $–OR^{X1}$. In certain embodiments, R^X is $–OR^{X1}$; and R^{X1} is $–CH_3$. In certain embodiments, R^X is $–OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $–CH_3$. In certain embodiments, R^X is $–CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $–CH_3$. In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is $–CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $–CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $–CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $–CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $–CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain

embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment .

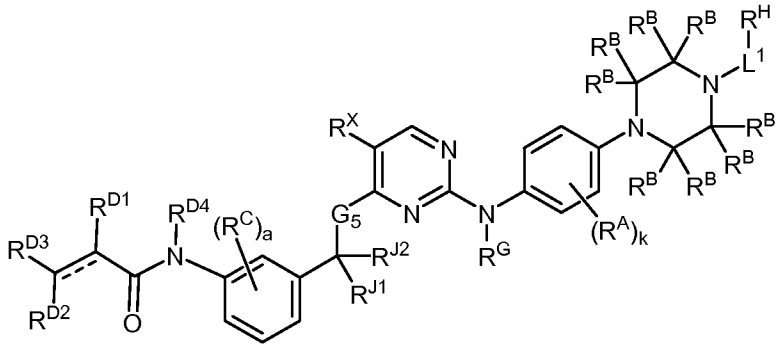
[00316] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-1**):



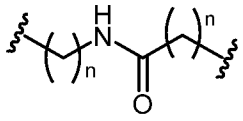
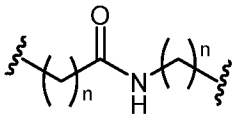
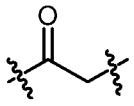
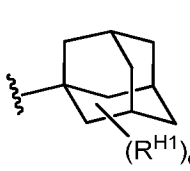
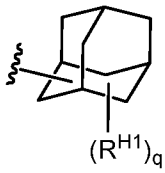
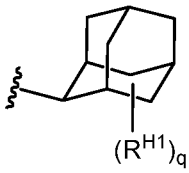
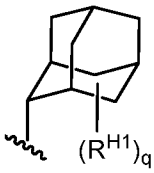
(**Ia-1**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

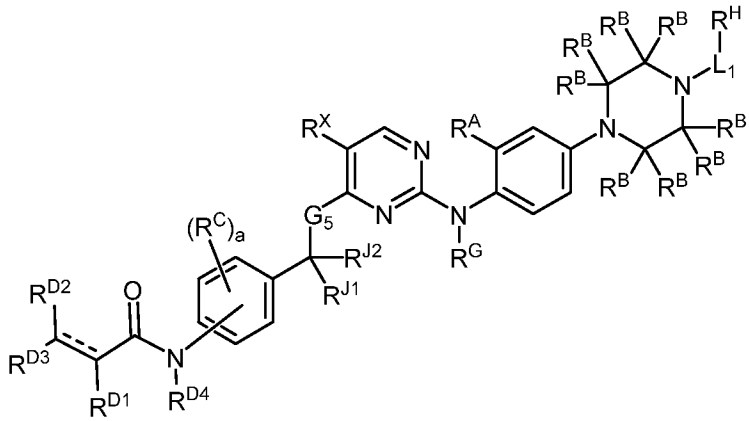
[00317] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-2**):



(**Ia-2**),

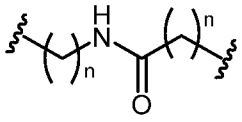
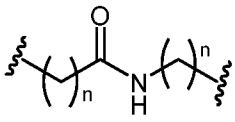
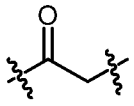
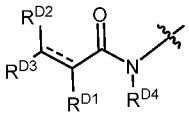
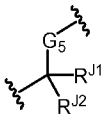
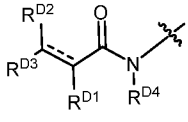
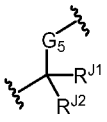
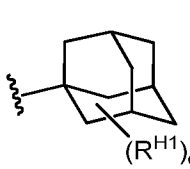
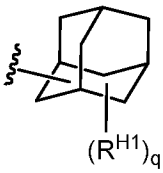
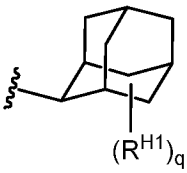
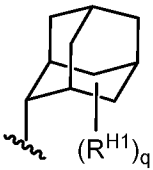
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00318] In certain embodiments, a compound of Formula (**Ia**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ia-3**):

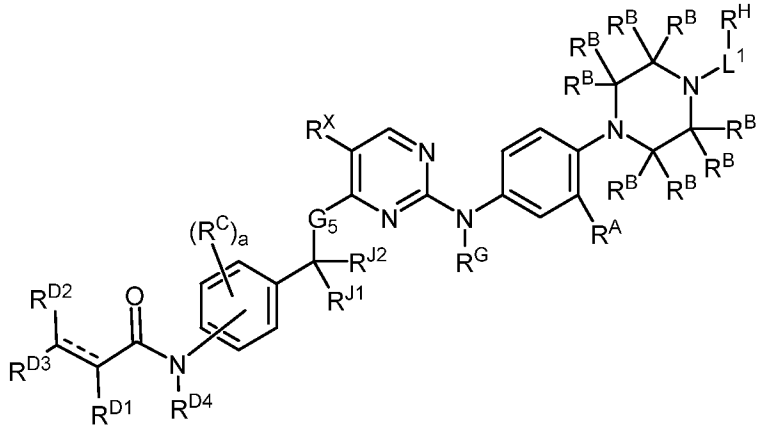


(**Ia-3**),

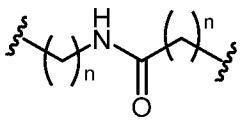
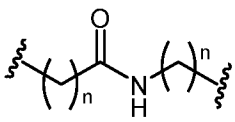
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain

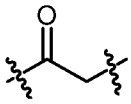
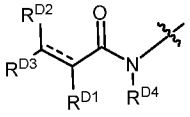
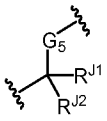
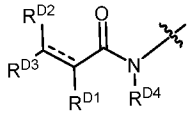
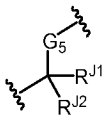
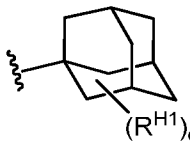
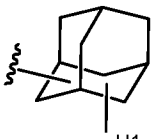
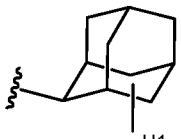
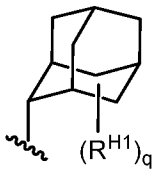
embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00319] In certain embodiments, a compound of Formula (**Ia**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ia-4**):

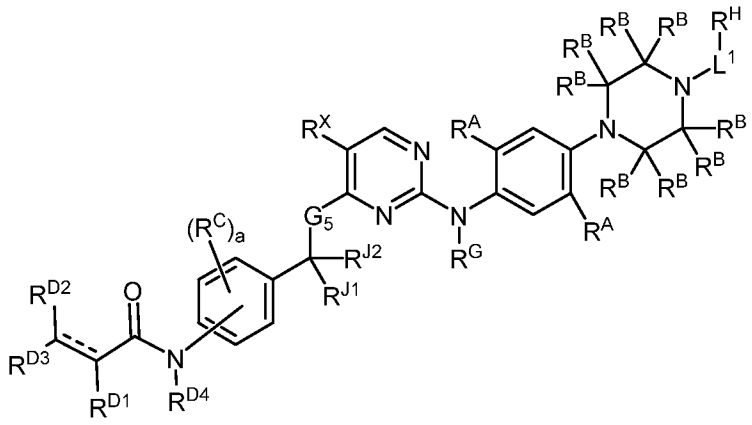


(**Ia-4**),

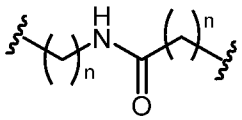
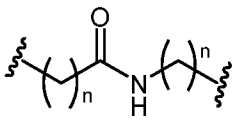
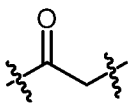
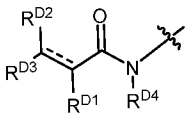
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is

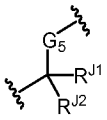
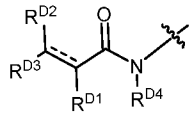
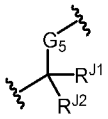
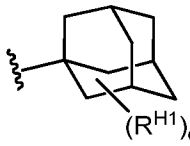
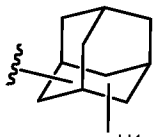
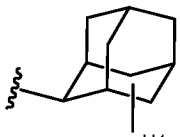
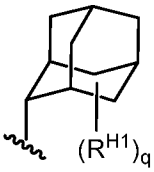
. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00320] In certain embodiments, a compound of Formula (**Ia**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ia-5**):

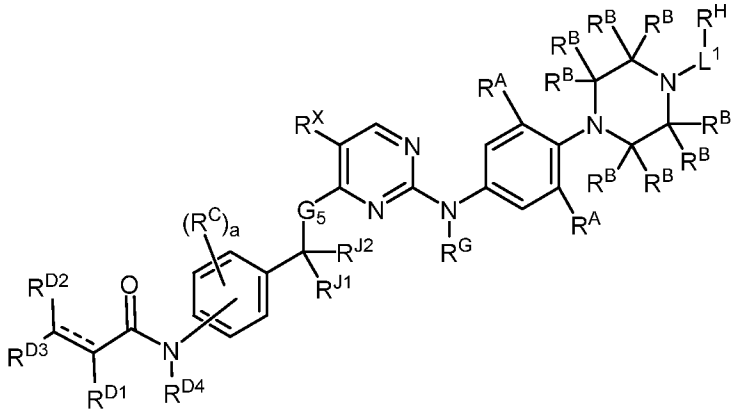


(**Ia-5**),

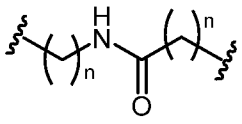
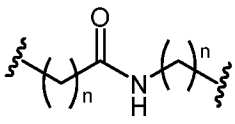
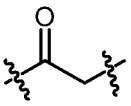
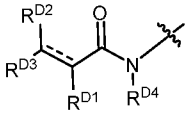
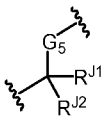
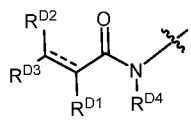
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, the group  is attached *meta* to the point of

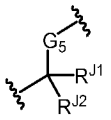
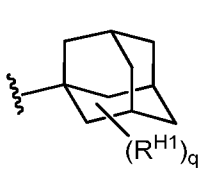
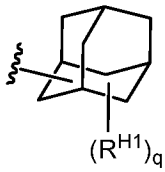
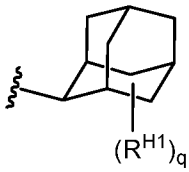
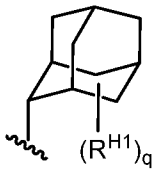
attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00321] In certain embodiments, a compound of Formula (**Ia**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ia-6**):

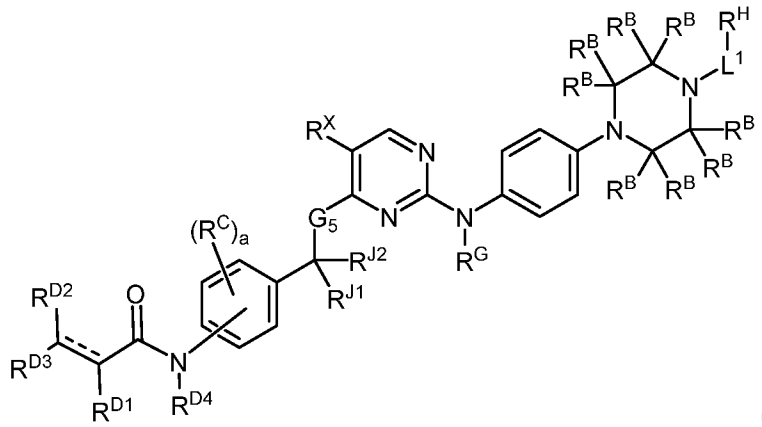


(**Ia-6**),

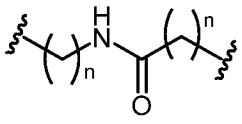
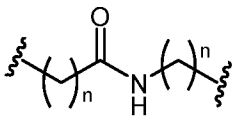
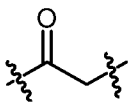
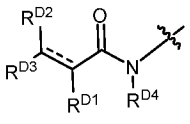
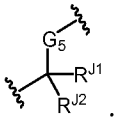
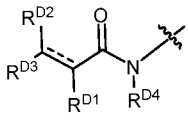
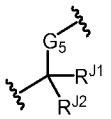
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the

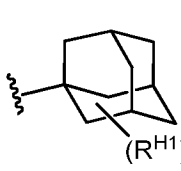
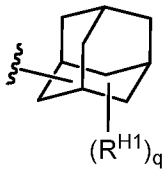
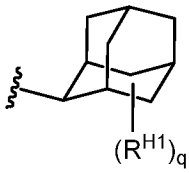
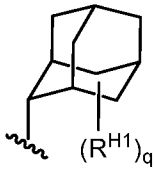
point of attachment . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00322] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-7**):

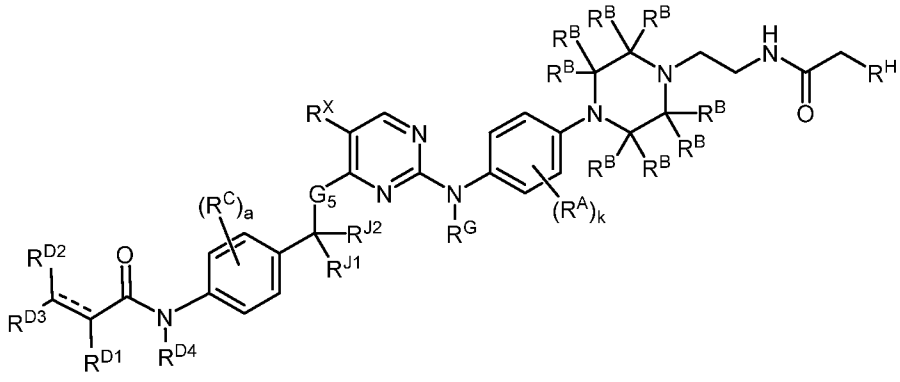


(**Ia-7**),

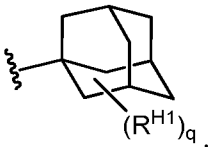
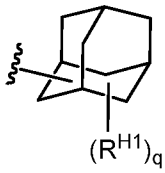
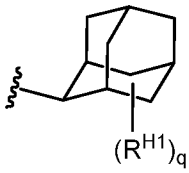
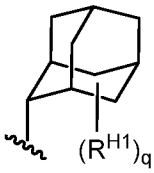
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, each instance of n is independently 1,

2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

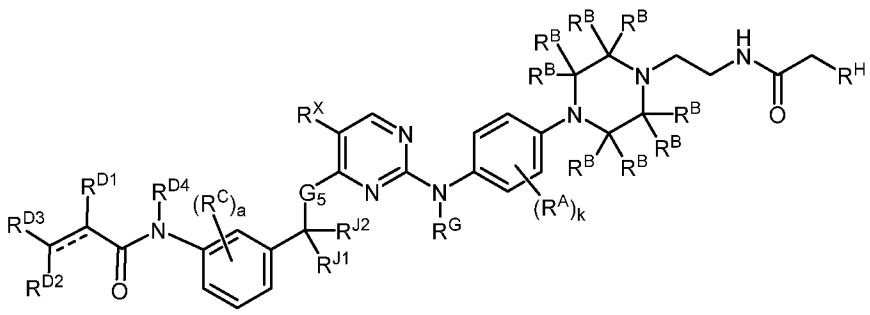
[00323] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-8**):



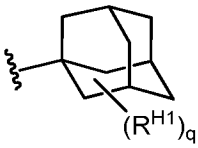
(**Ia-8**),

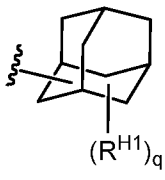
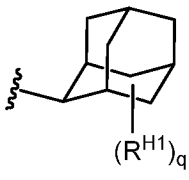
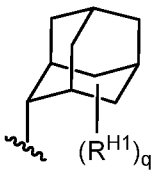
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is . , , or . In certain embodiments, q is 0.

[00324] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-9**):

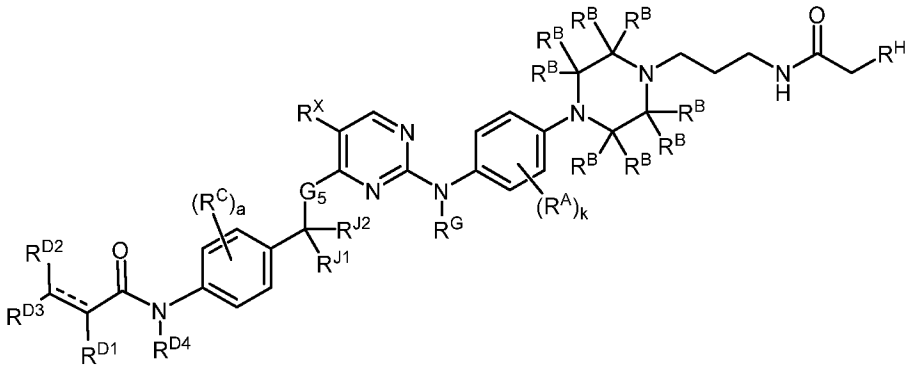


(**Ia-9**),

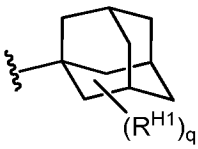
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is .

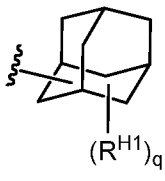
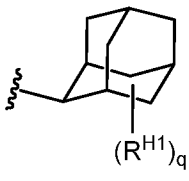
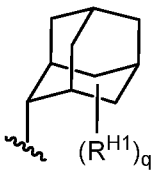
, , or . In certain embodiments, q is 0.

[00325] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-10**):

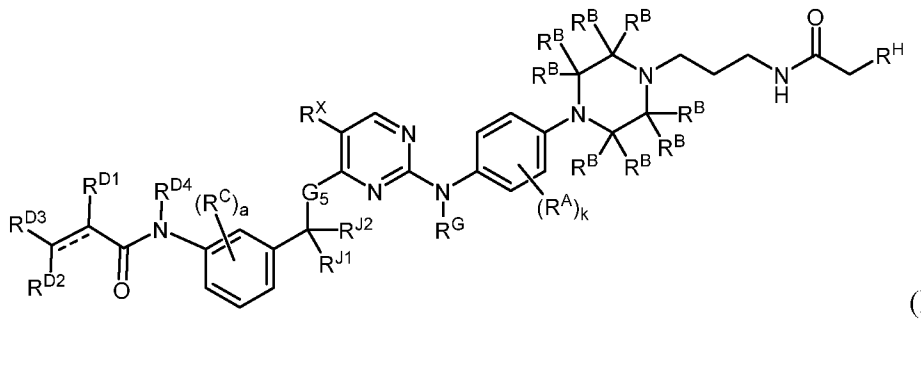


(**Ia-10**),

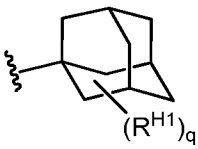
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is .

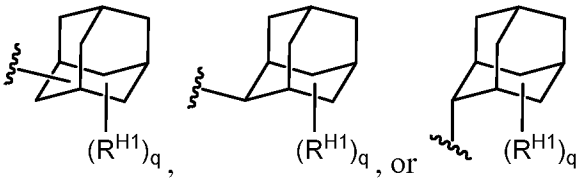
, , or . In certain embodiments, q is 0.

[00326] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-11**):



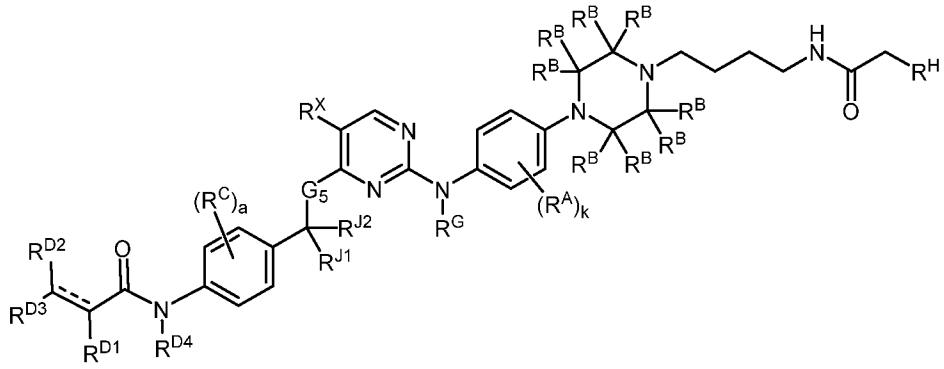
(**Ia-11**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is .

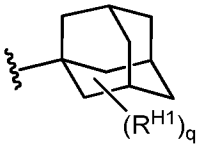


. In certain embodiments, q is 0.

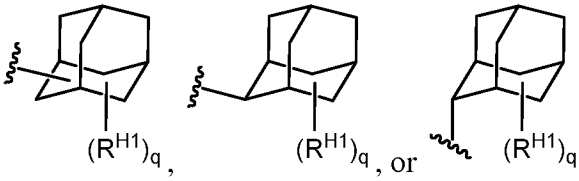
[00327] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-12**):



(**Ia-12**),

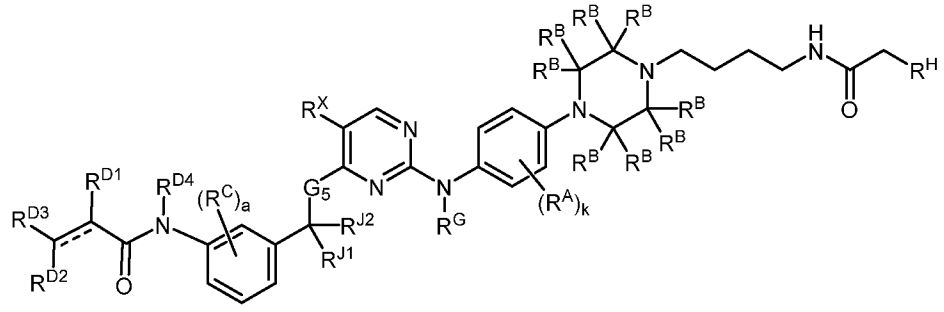


or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is

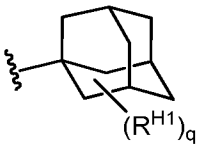


. In certain embodiments, q is 0.

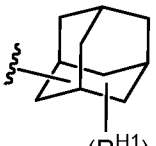
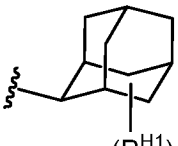
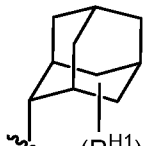
[00328] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula (**Ia-13**):



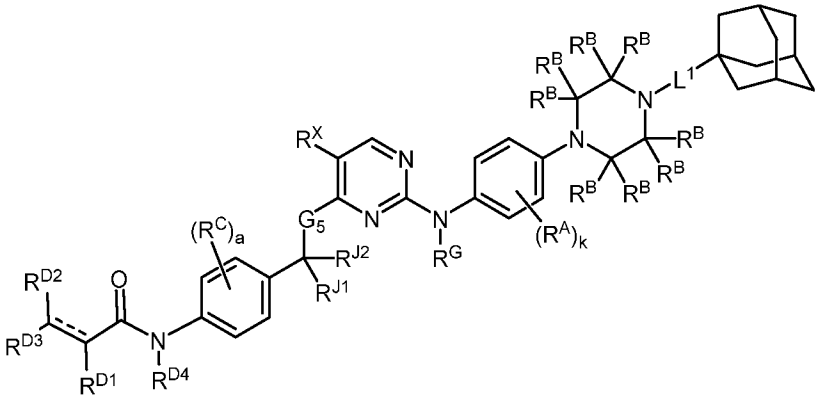
(**Ia-13**),

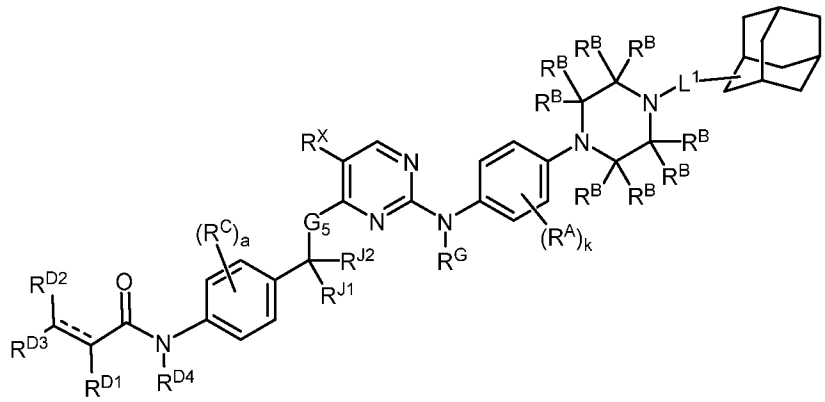


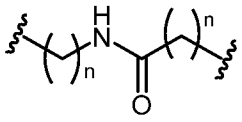
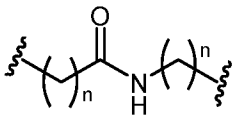
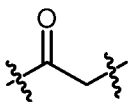
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is




. In certain embodiments, q is 0.

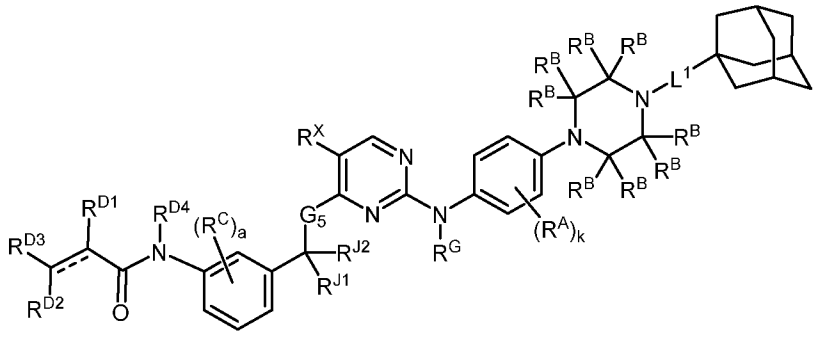
[00329] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula:


(**Ia-14**) or

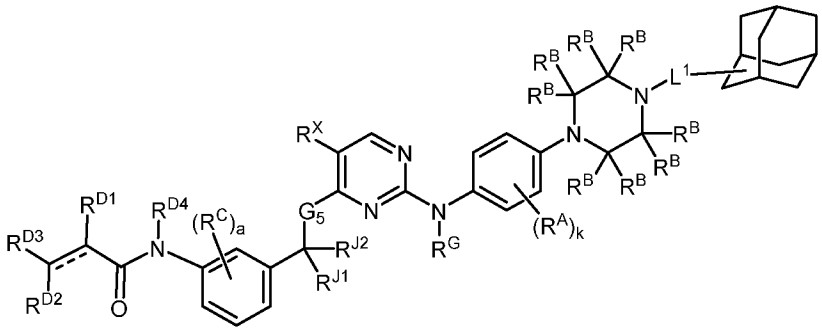

(**Ia-14a**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

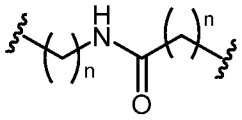
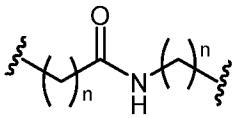
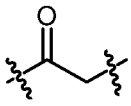
[00330] In certain embodiments, a compound of Formula (**Ia**) is a compound of Formula:



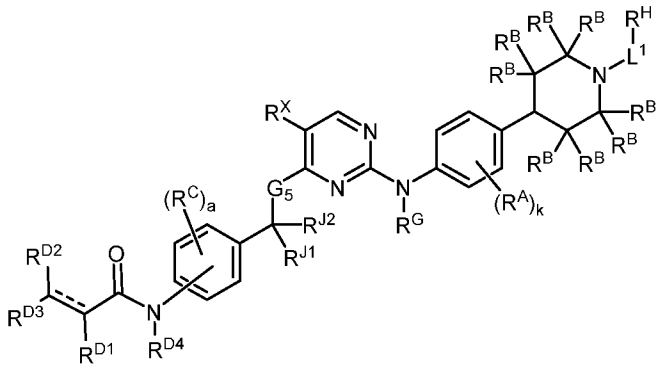
(**Ia-15**) or



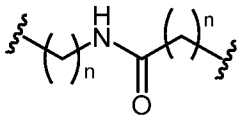
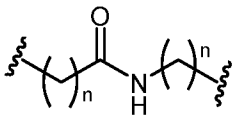
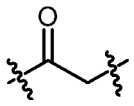
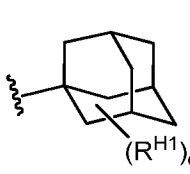
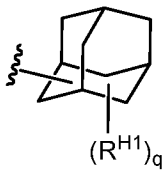
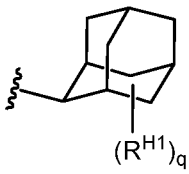
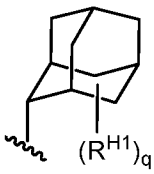
(**Ia-15a**)

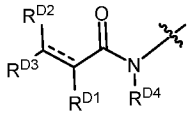
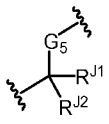
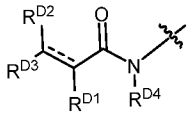
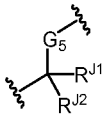
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

[00331] In certain embodiments, a compound described herein is a compound of Formula (**Ib**):

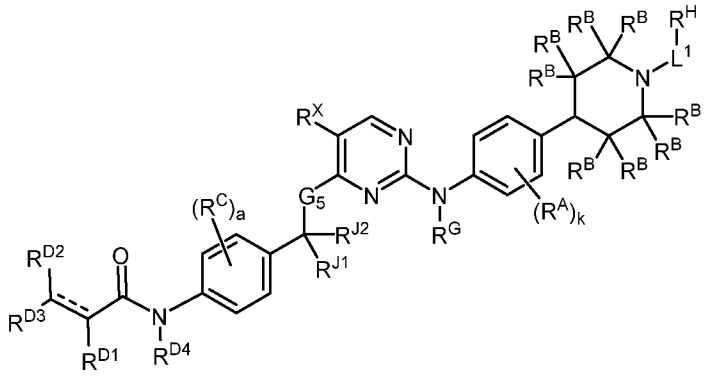


(**Ib**),

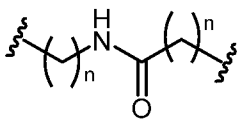
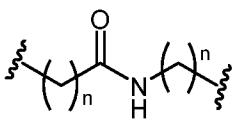
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0. In certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instance of R^A is Cl. In certain embodiments, at least two instances of R^A are independently halogen. In certain embodiments, at least two instances of R^A are F. In certain embodiments, at least two instances of R^A are Cl. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $-CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $-OR^{X1}$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is $-CH_3$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $-CH_3$. In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is $-CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain

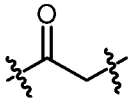
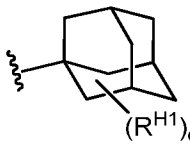
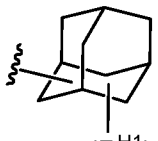
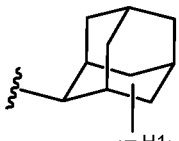
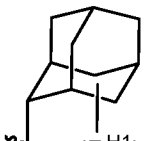
embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment .

[00332] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-1**):

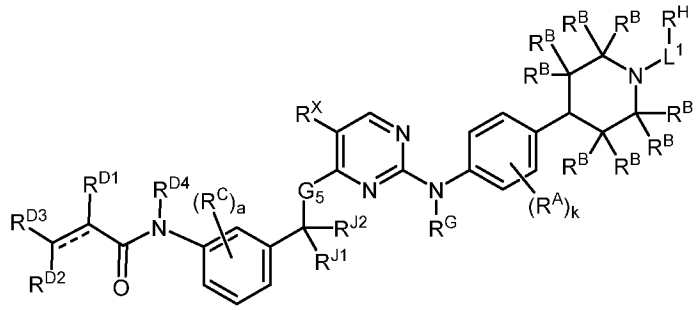


(**Ib-1**),

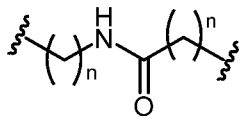
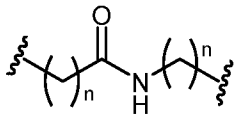
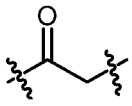
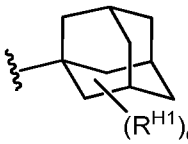
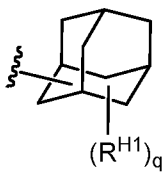
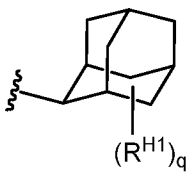
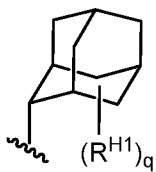
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is


.. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

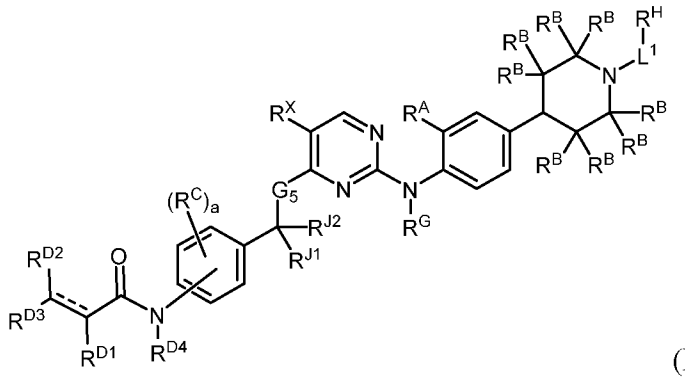
[00333] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-2**):



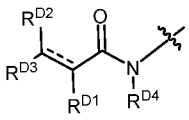
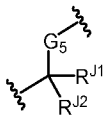
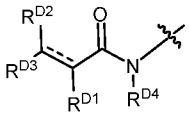
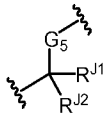
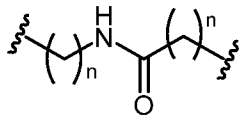
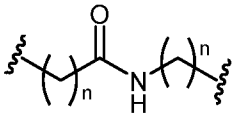
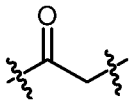
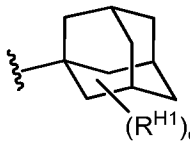
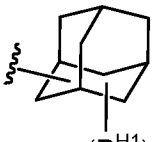
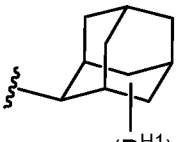
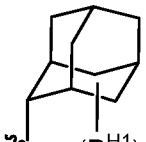
(**Ib-2**),

or a pharmaceutically acceptable salt thereof. In certain embodiments In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, R^H is , , or . In certain embodiments, q is 0.

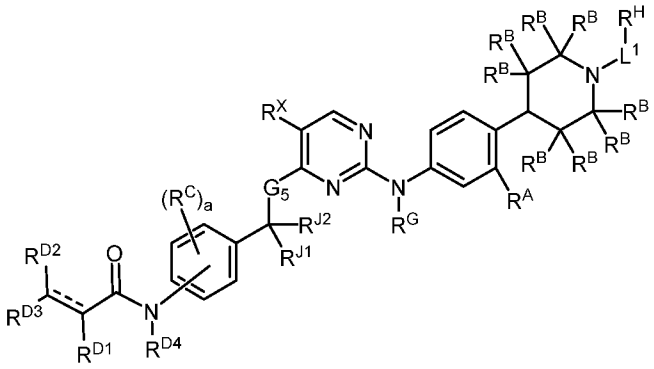
[00334] In certain embodiments, a compound of Formula (**Ib**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ib-3**):



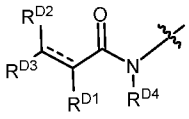
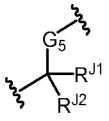
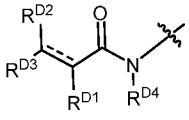
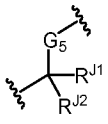
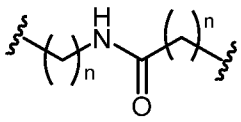
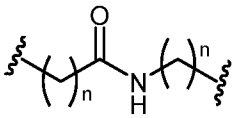
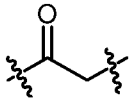
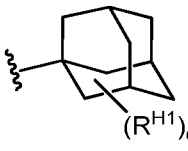
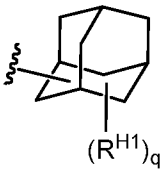
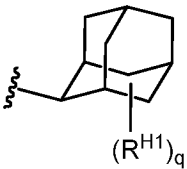
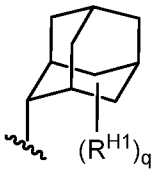
(**Ib-3**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . , , or . In certain embodiments, q is 0.

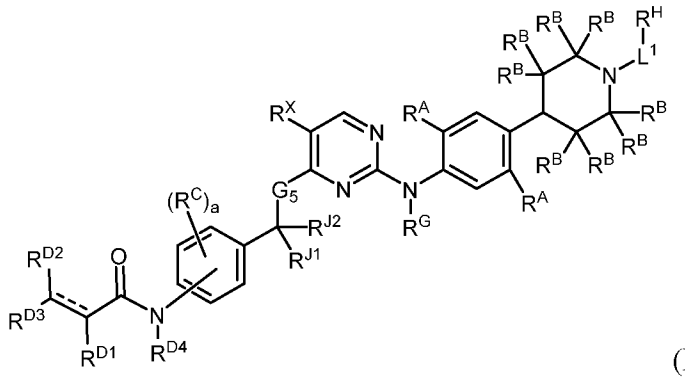
[00335] In certain embodiments, a compound of Formula (**Ib**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ib-4**):



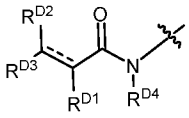
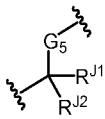
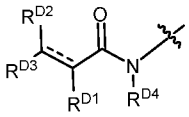
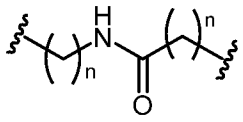
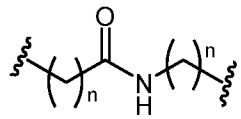
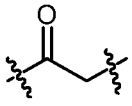
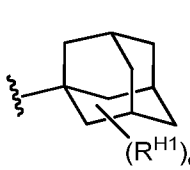
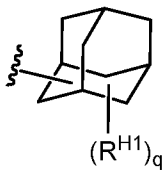
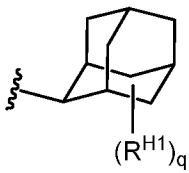
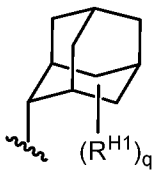
(**Ib-4**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is .  , or . In certain embodiments, q is 0.

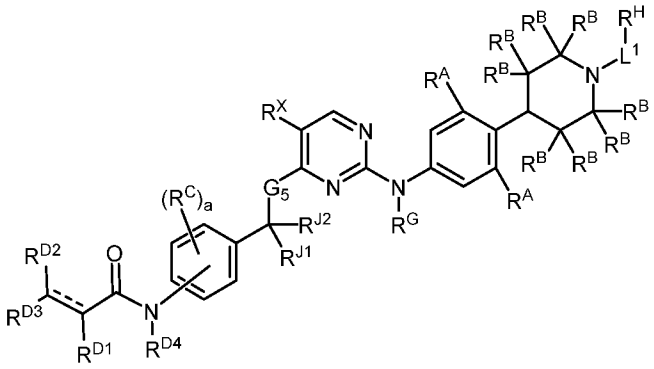
[00336] In certain embodiments, a compound of Formula (**Ib**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ib-5**):



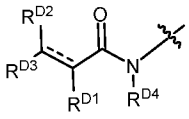
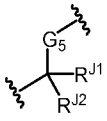
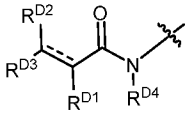
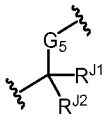
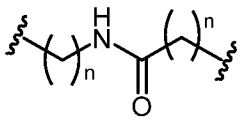
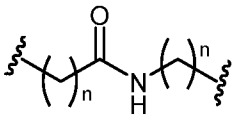
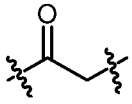
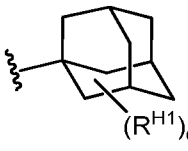
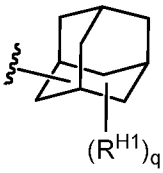
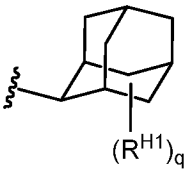
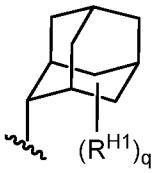
(**Ib-5**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

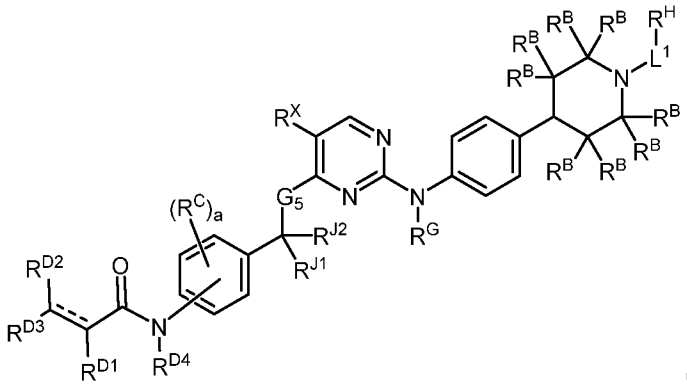
[00337] In certain embodiments, a compound of Formula (**Ib**) wherein R^A is a non-hydrogen group is a compound of Formula (**Ib-6**):



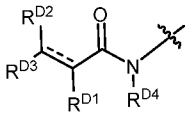
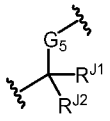
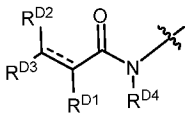
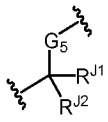
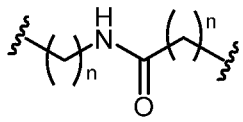
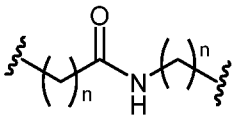
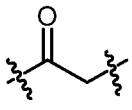
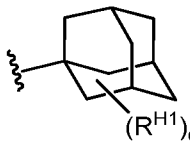
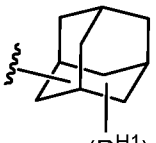
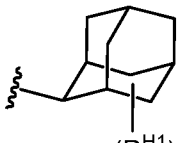
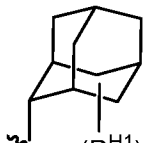
(**Ib-6**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . , , or . In certain embodiments, q is 0.

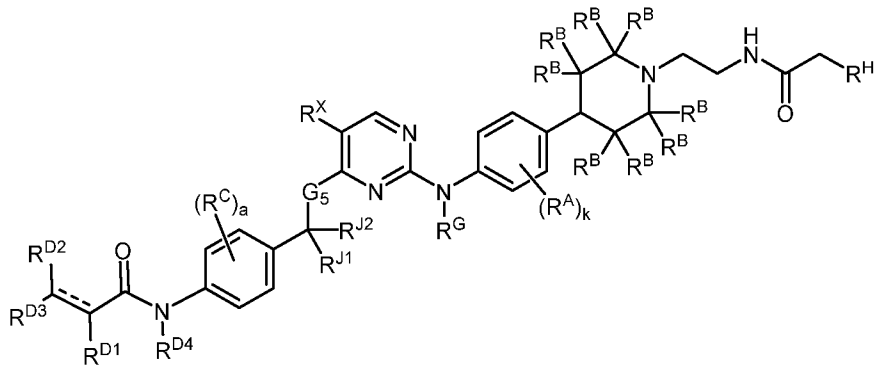
[00338] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-7**):



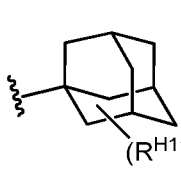
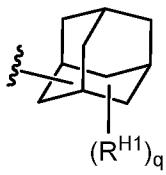
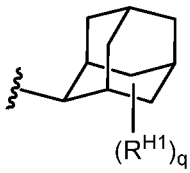
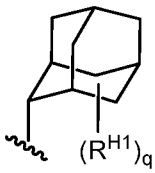
(**Ib-7**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

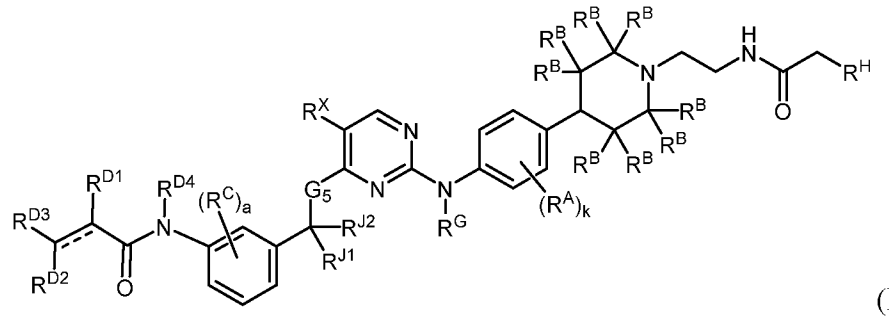
[00339] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-8**):



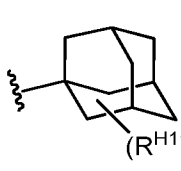
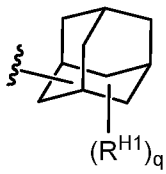
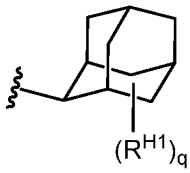
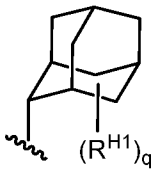
(**Ib-8**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

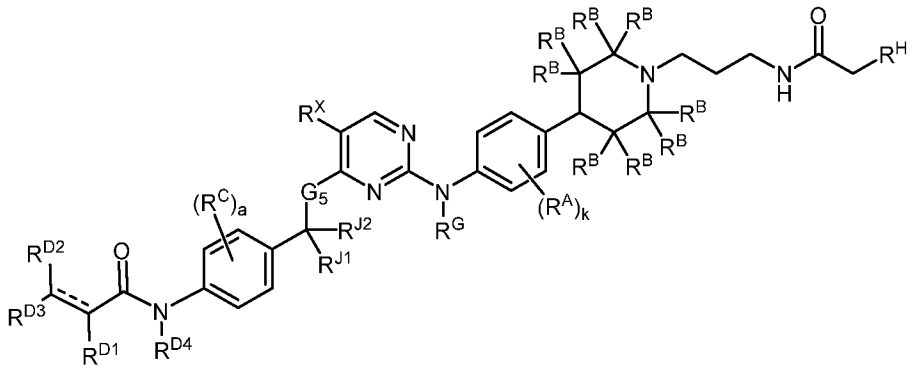
[00340] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-9**):



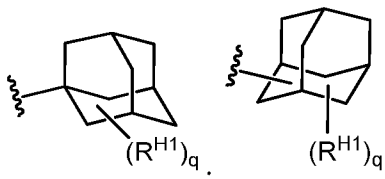
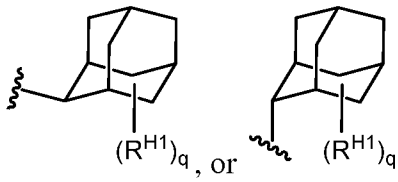
(**Ib-9**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

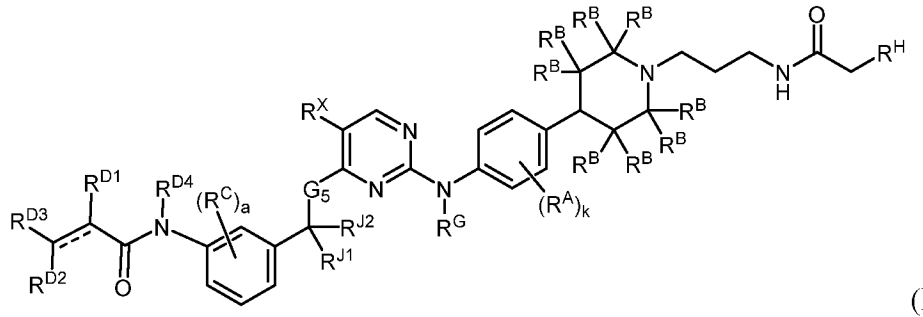
[00341] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-10**):



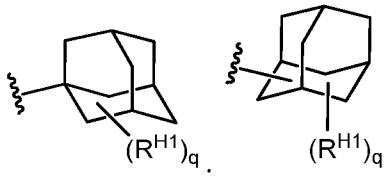
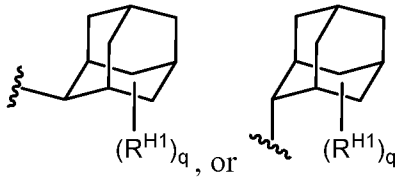
(**Ib-10**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , or . In certain embodiments, q is 0.

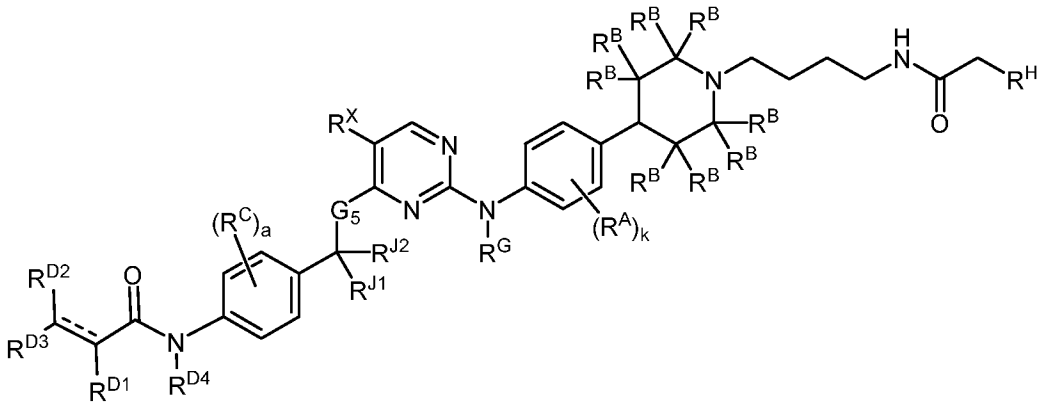
[00342] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-11**):



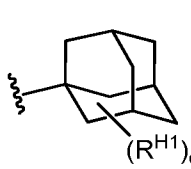
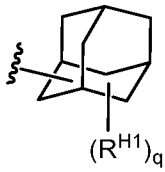
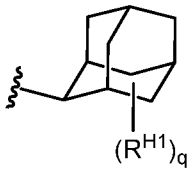
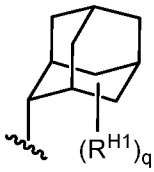
(**Ib-11**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , or . In certain embodiments, q is 0.

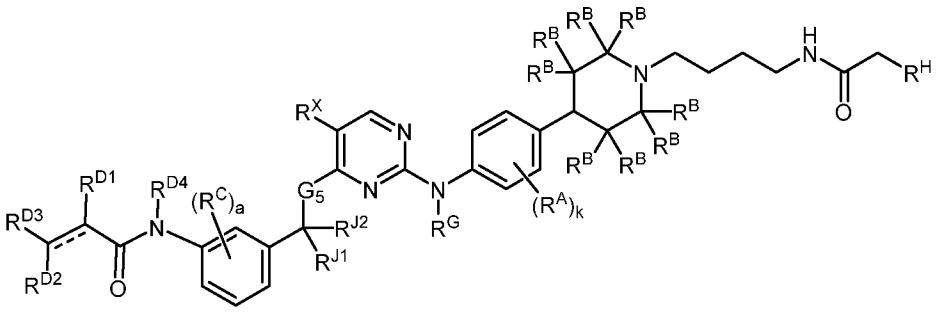
[00343] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-12**):



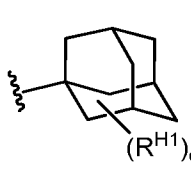
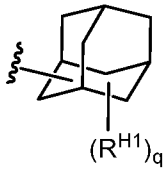
(**Ib-12**),

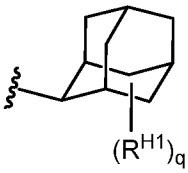
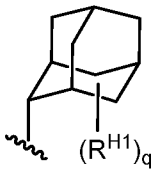
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H , , , or . In certain embodiments, q is 0.

[00344] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula (**Ib-13**):



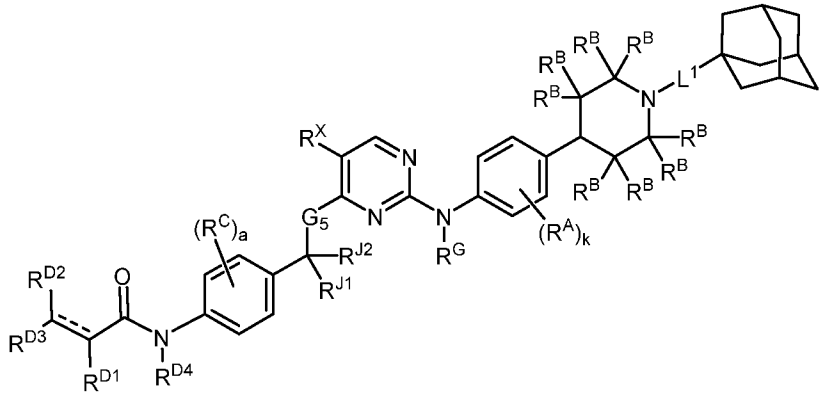
(**Ib-13**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H , ,

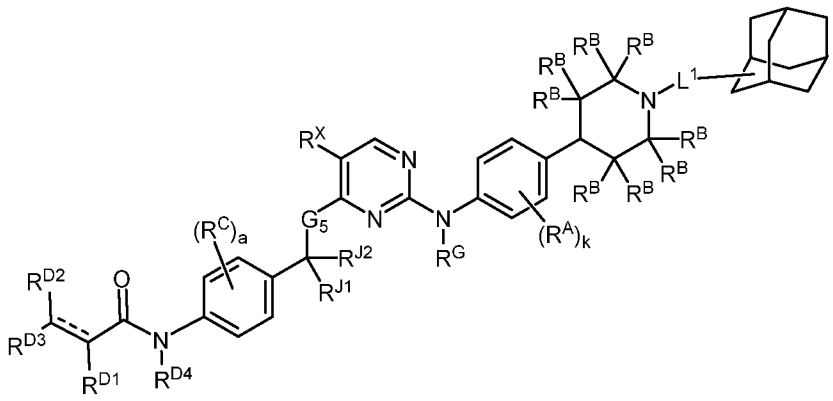



. In certain embodiments, q is 0.

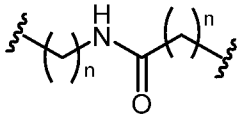
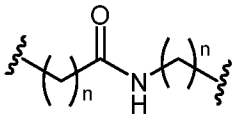
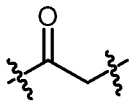
[00345] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula:



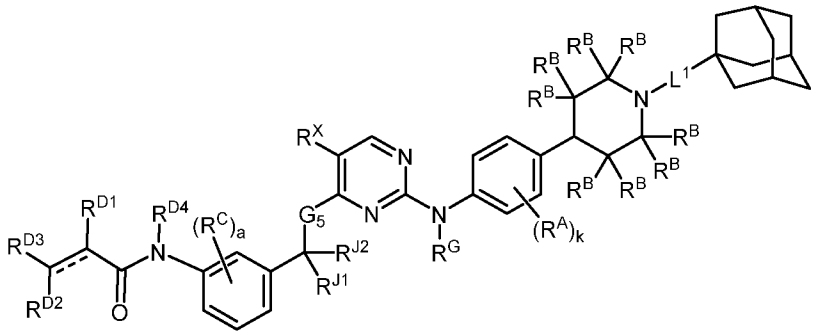
(**Ib-14**),



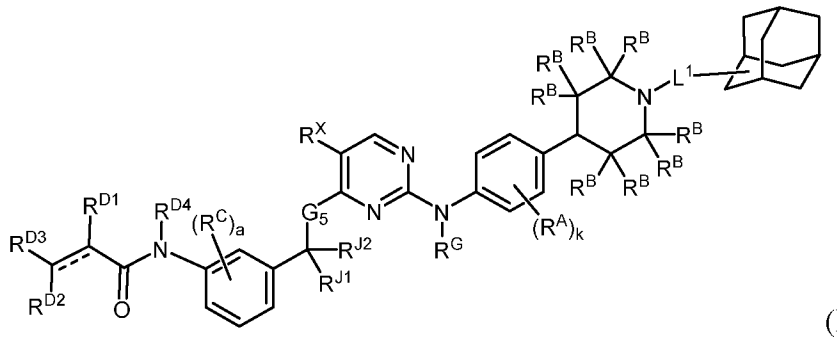
(**Ib-14a**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

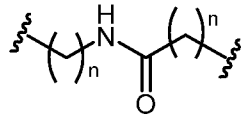
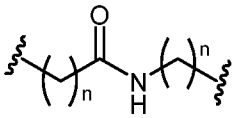
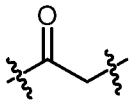
[00346] In certain embodiments, a compound of Formula (**Ib**) is a compound of Formula:



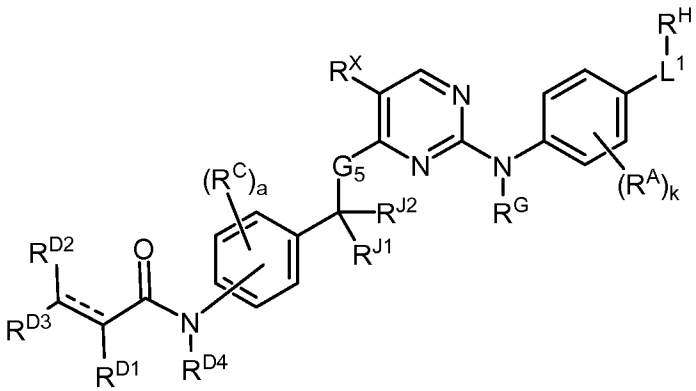
(**Ib-15**) or



(**Ib-15a**),

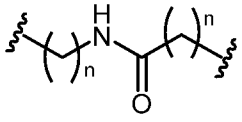
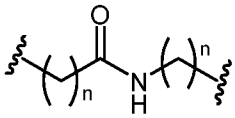
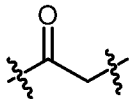
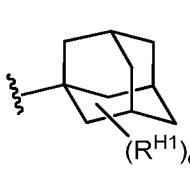
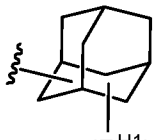
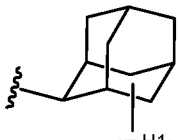
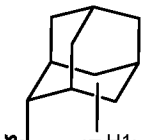
or a pharmaceutically acceptable salt thereof. In certain embodiments, In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

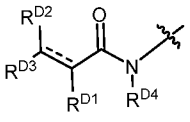
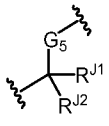
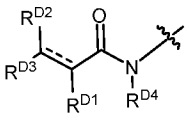
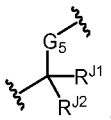
[00347] In certain embodiments, a compound described herein is a compound of Formula (**Ic**):



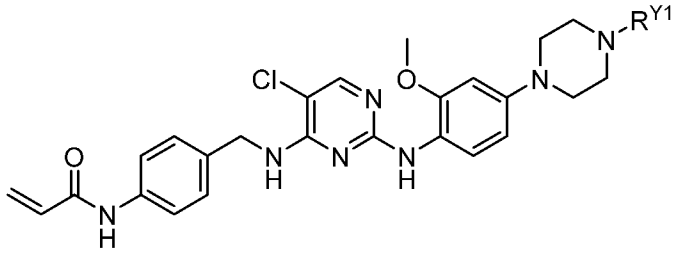
(**Ic**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or

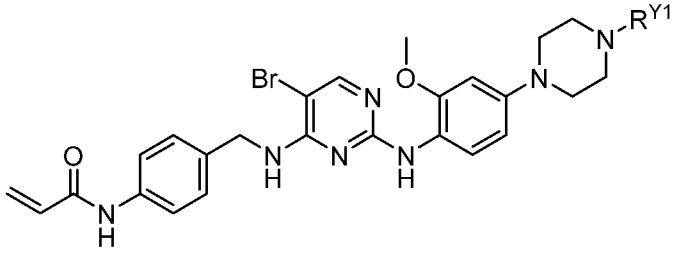
unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0. In certain embodiments, k is 0. In certain embodiments, k is 1. In certain embodiments, k is 2. In certain embodiments, at least one instance of R^A is halogen. In certain embodiments, at least one instance of R^A is F. In certain embodiments, at least one instance of R^A is Cl. In certain embodiments, at least two instances of R^A are independently halogen. In certain embodiments, at least two instances of R^A are F. In certain embodiments, at least two instances of R^A are Cl. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $-CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $-OR^{X1}$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is $-CH_3$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $-CH_3$.In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is $-CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double

bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment .

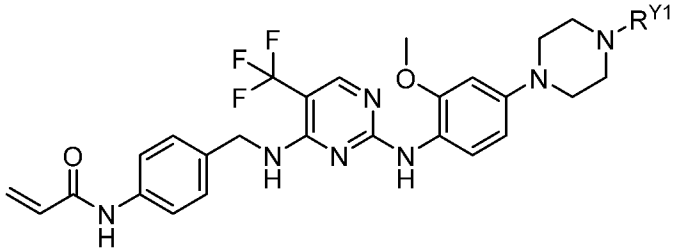
[00348] The following scaffolds are specifically contemplated for hydrophobic tagging, wherein R^{Y1} comprises a hydrophobic moiety (R^H), as defined herein:



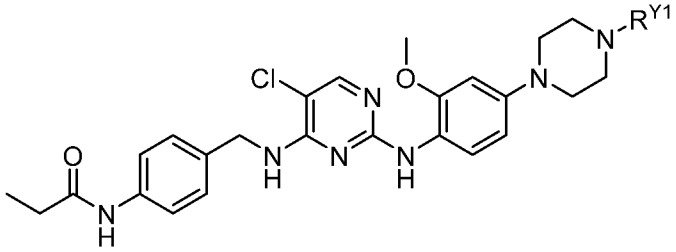
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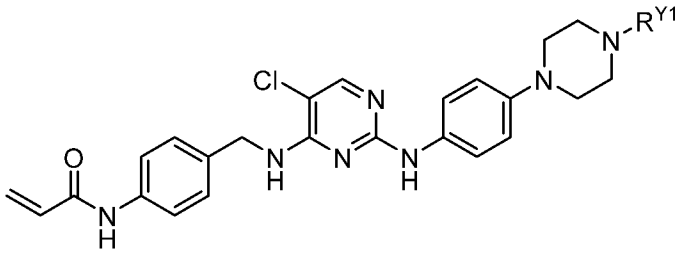
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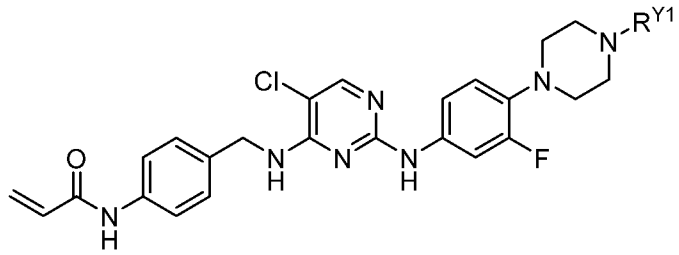
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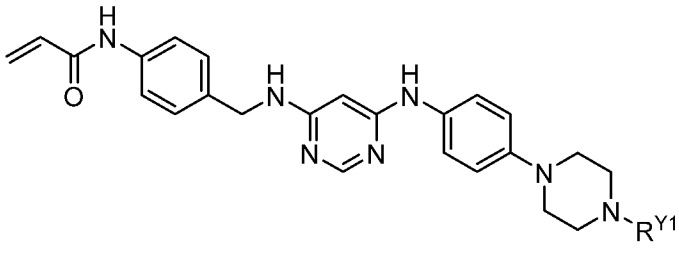
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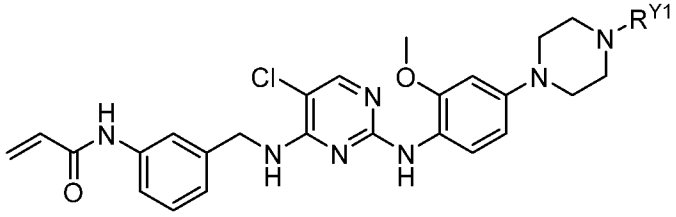
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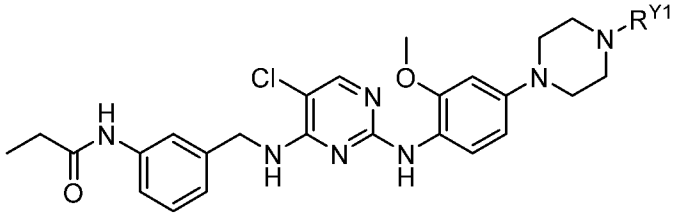
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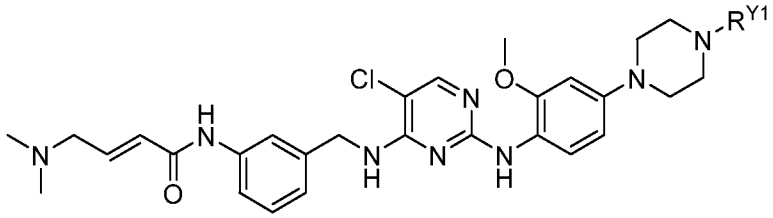
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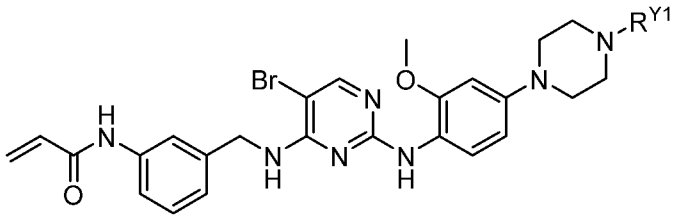
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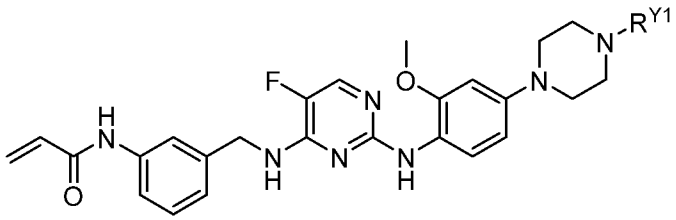
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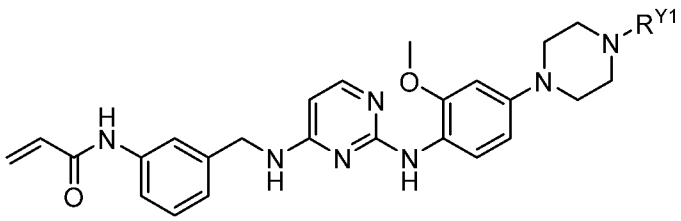
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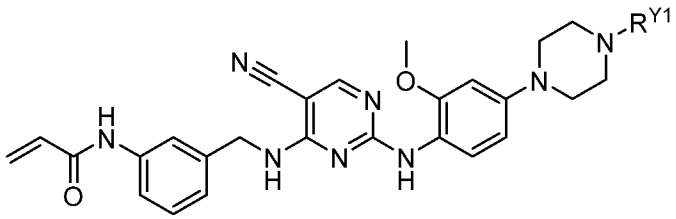
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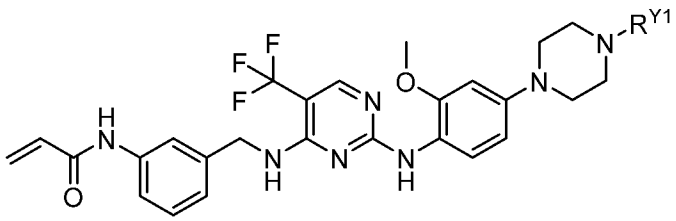
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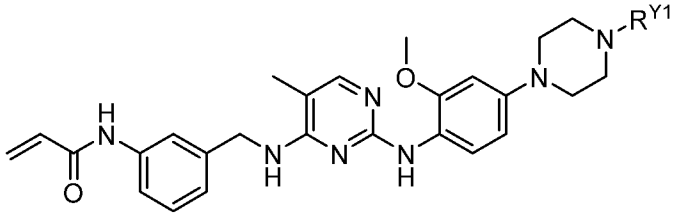
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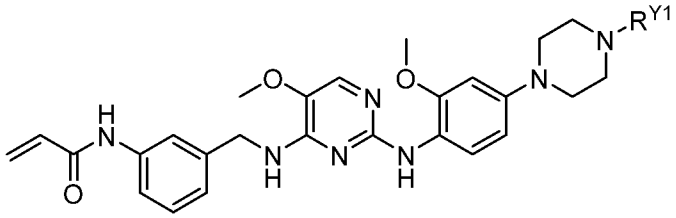
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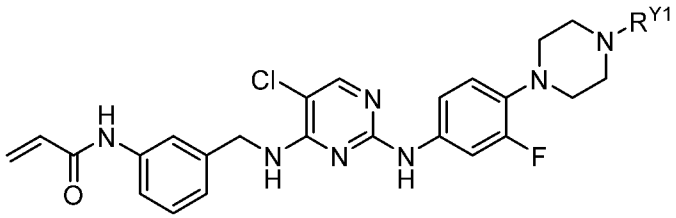
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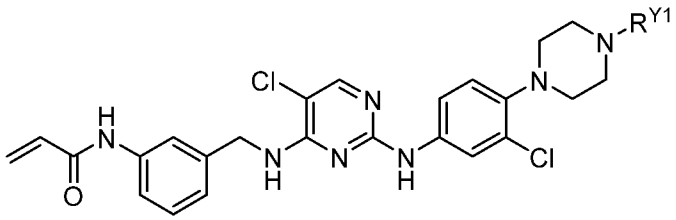
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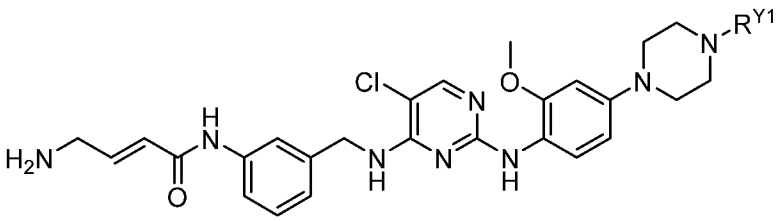
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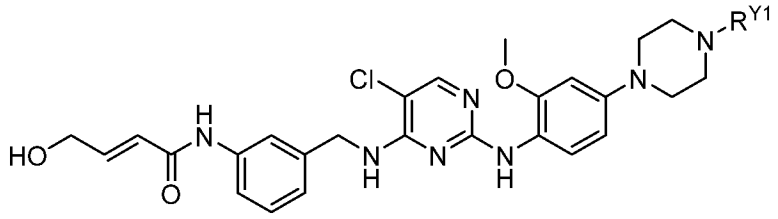
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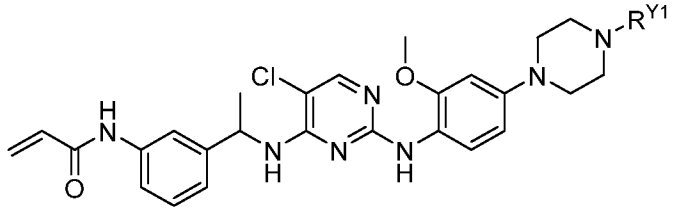
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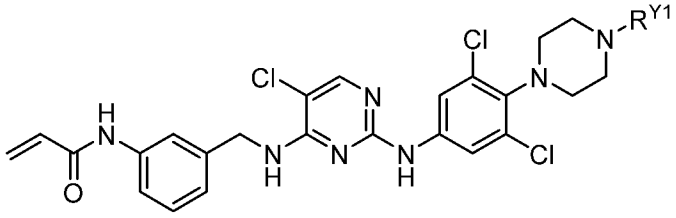
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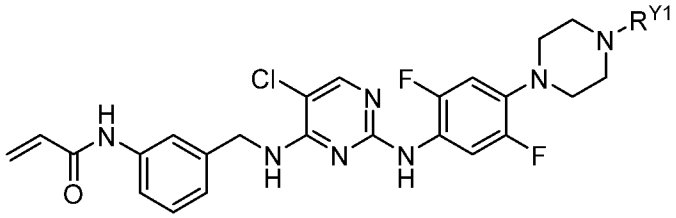
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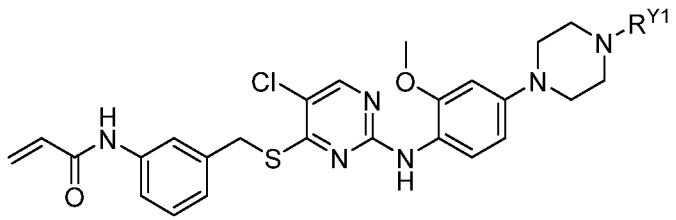
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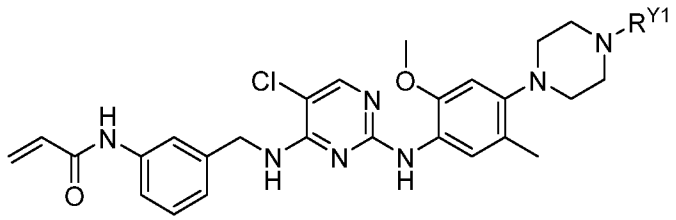
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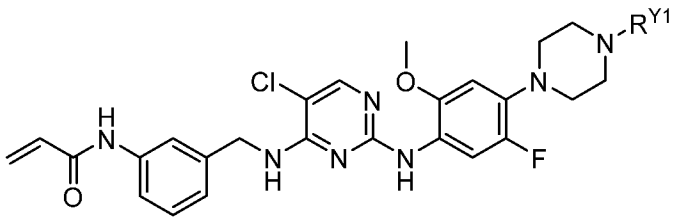
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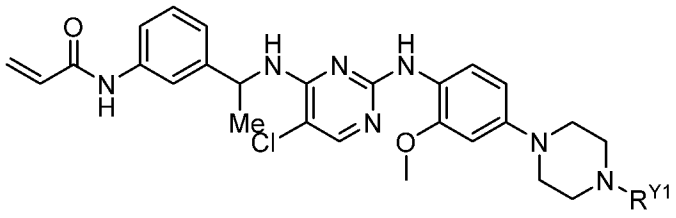
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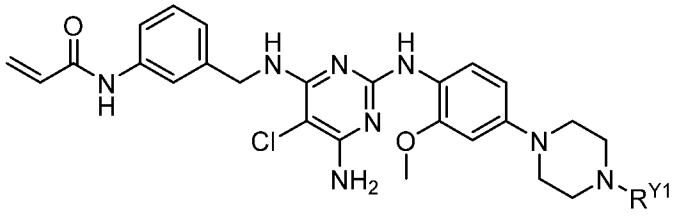
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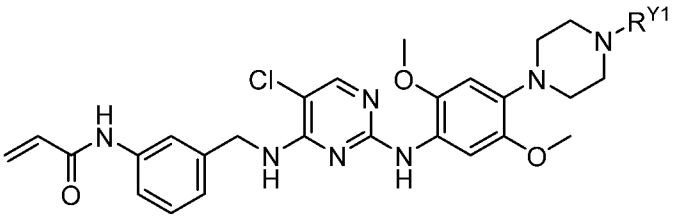
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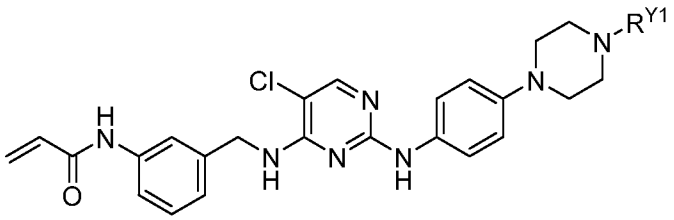
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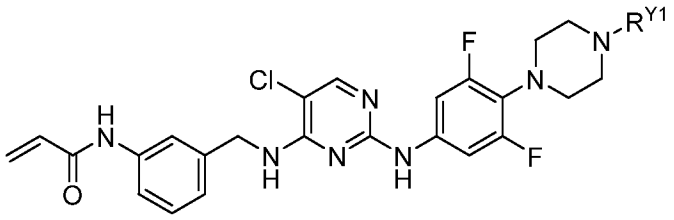
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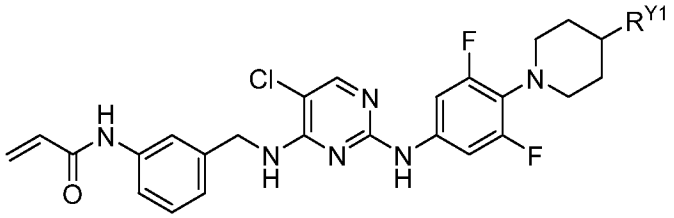
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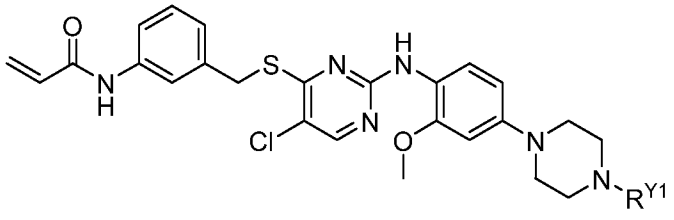
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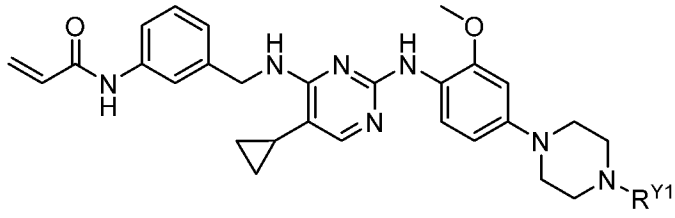
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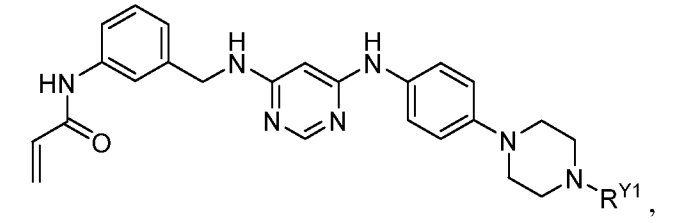
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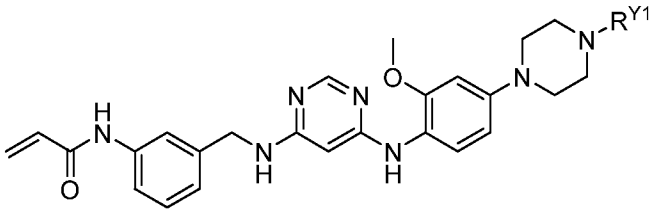
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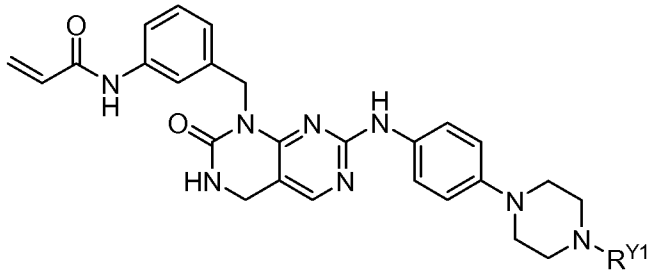
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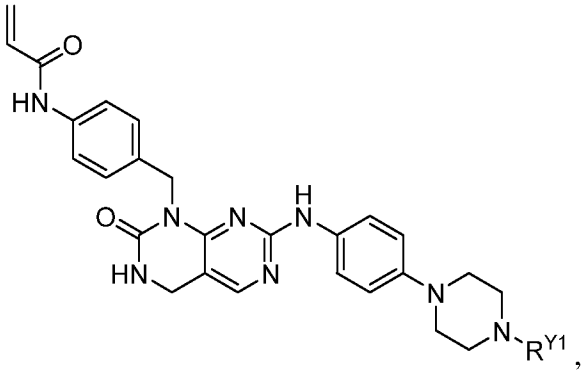
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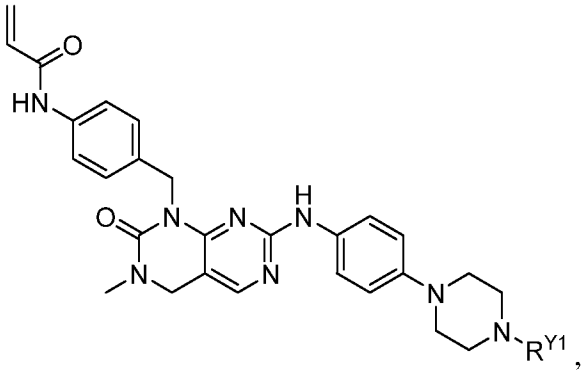
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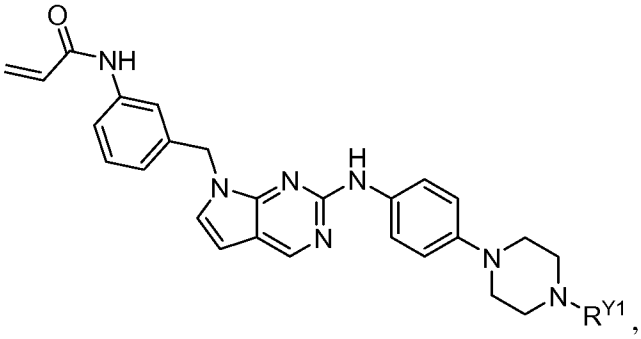
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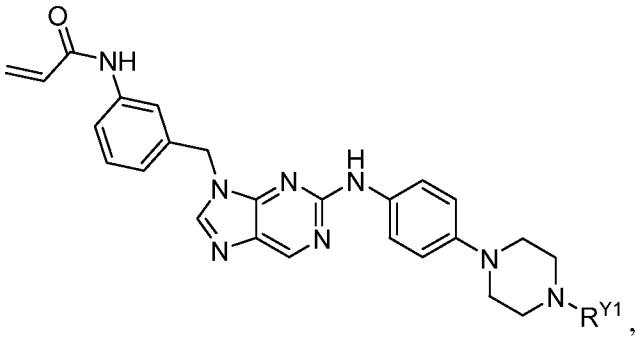
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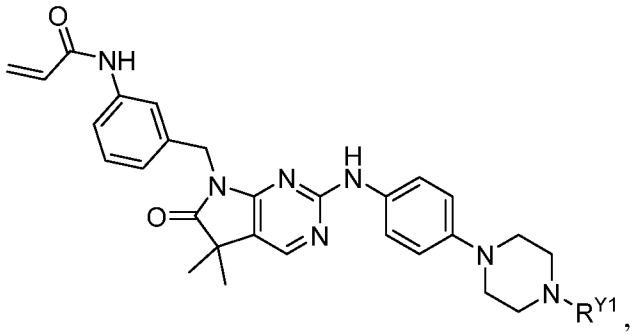


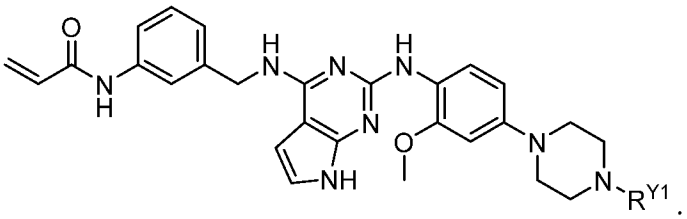
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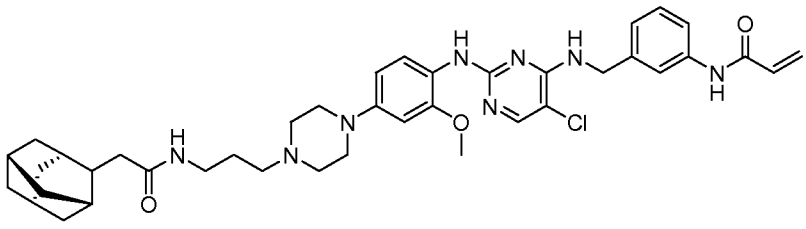




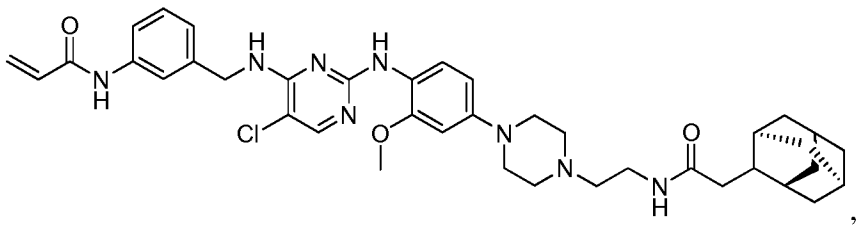


and pharmaceutically acceptable salts thereof. In certain embodiments, the group R^{Y1} is $-L^1-R^H$, as defined herein.

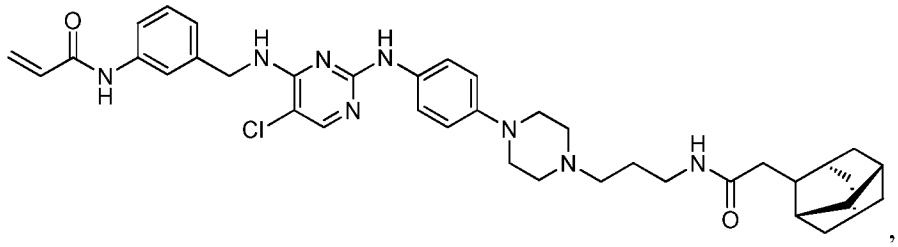
[00349] In certain embodiments, a compound described herein is a compound of the formula:



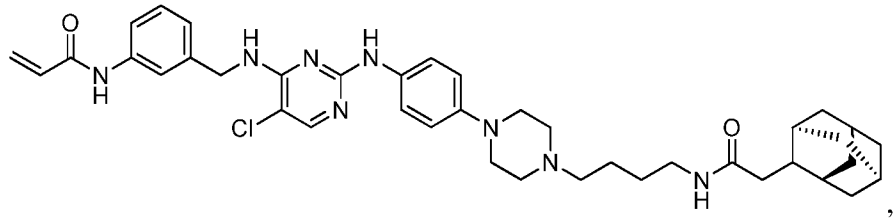
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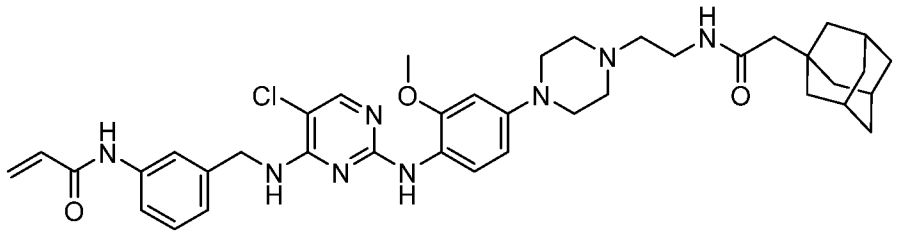
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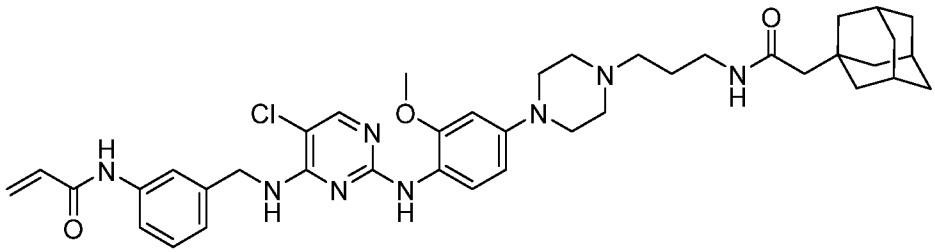
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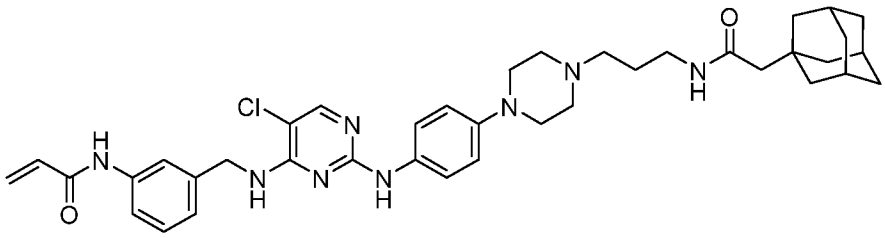
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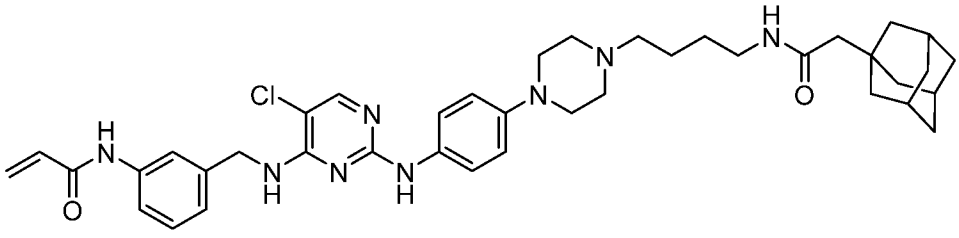
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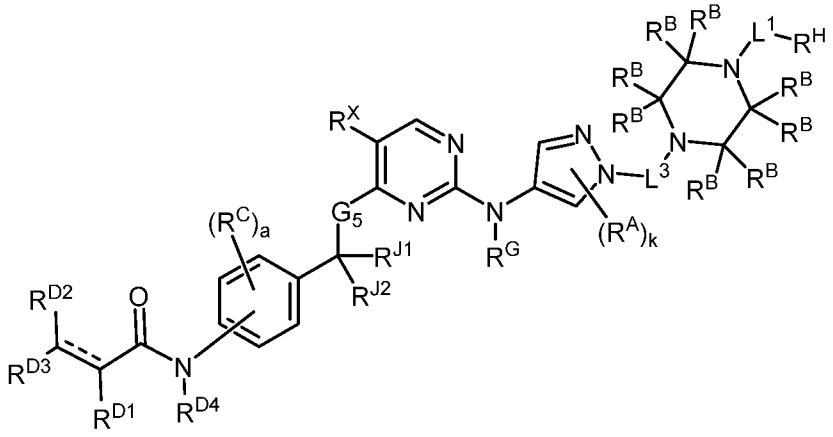
,

or a pharmaceutically acceptable salt thereof.

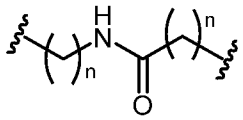
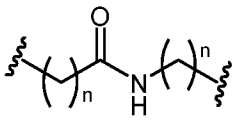
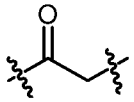
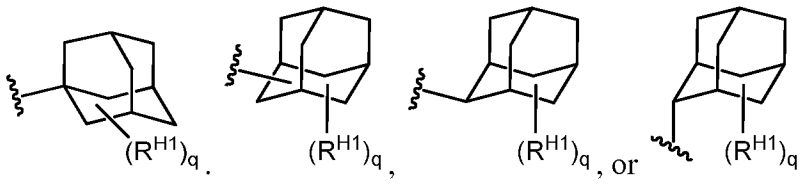
*Exemplary compounds of Formula (**II**)*

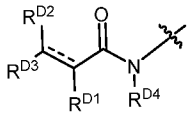
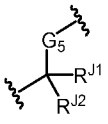
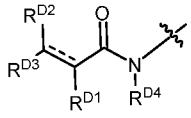
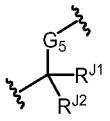
[00350] Various combinations of certain embodiments of Formula (**II**) are futher contemplated herein.

[00351] For example, in certain embodiments, a compound described herein is a compound of Formula (**IIa**):

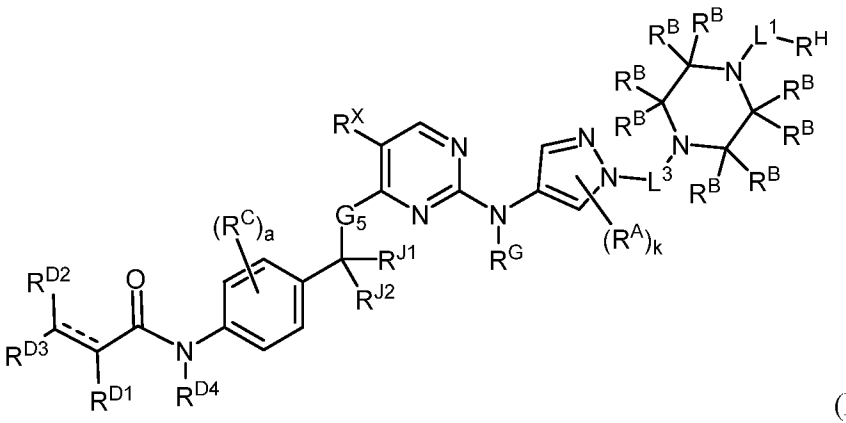


(**IIa**),

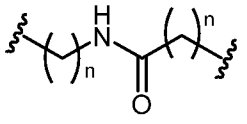
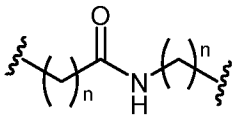
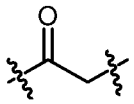
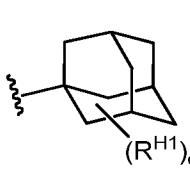
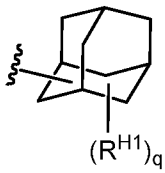
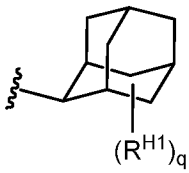
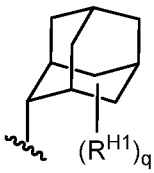
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0. In certain embodiments, all instances of R^B are hydrogen. In certain embodiments, L^3 is an unsubstituted C_{1-3}alkylene. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $-CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $-OR^{X1}$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is $-CH_3$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In

certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $-CH_3$. In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is $-CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment .

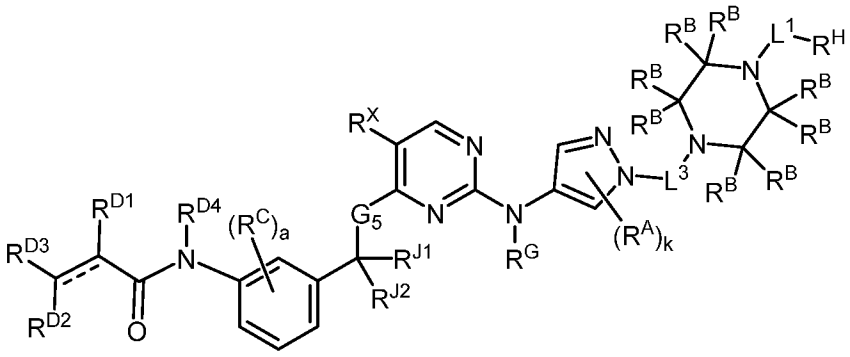
[00352] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-1**):



(**IIa-1**),

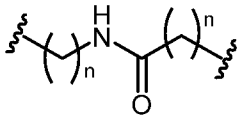
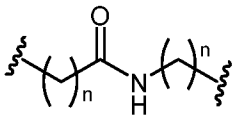
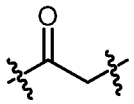
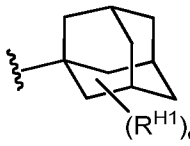
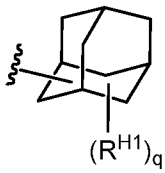
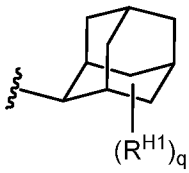
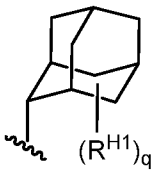
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00353] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-2**):

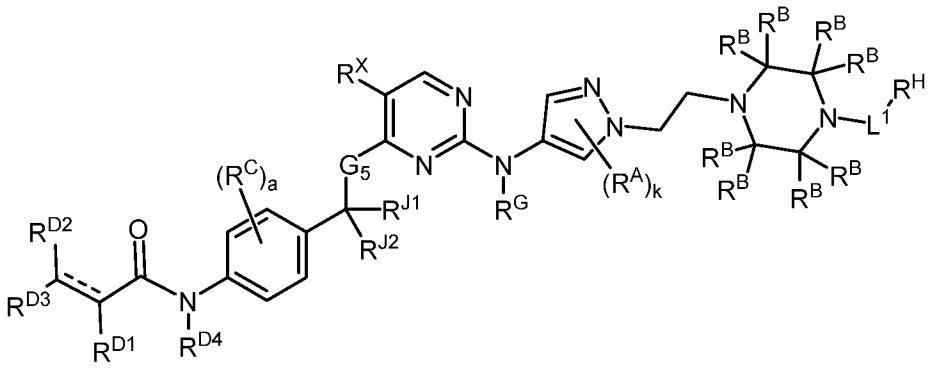


(**IIa-2**),

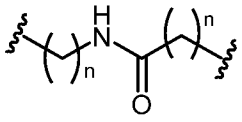
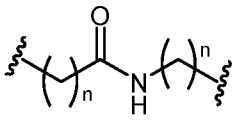
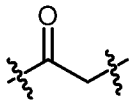
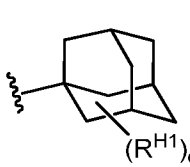
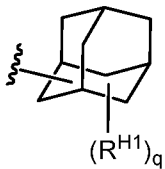
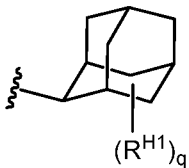
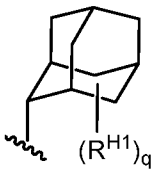
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain

embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

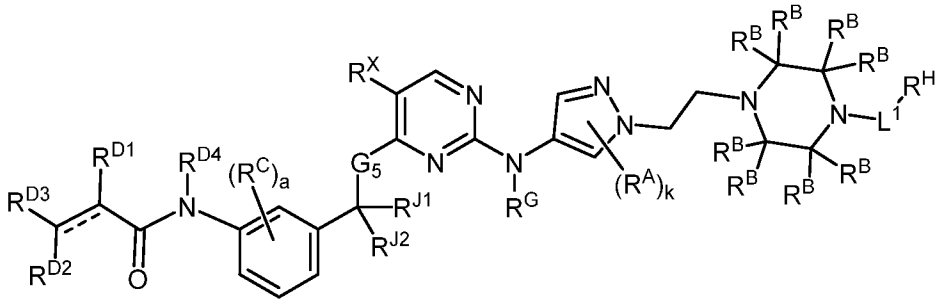
[00354] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-3**):



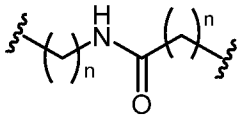
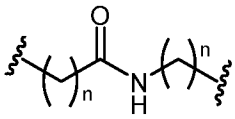
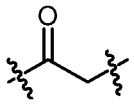
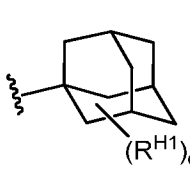
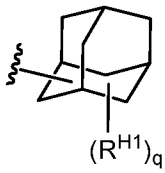
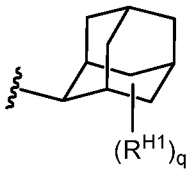
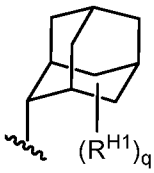
(**IIa-3**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

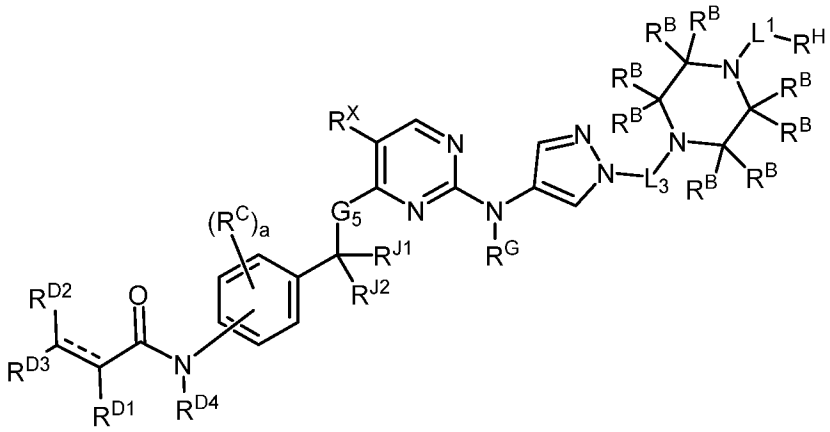
[00355] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-4**):



(**IIa-4**),

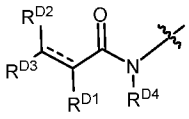
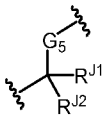
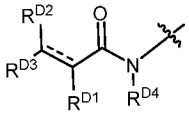
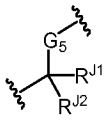
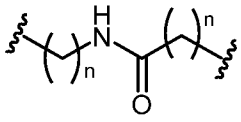
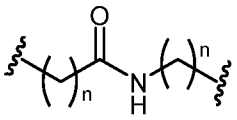
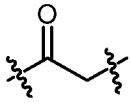
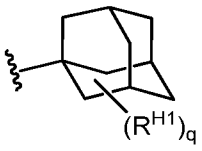
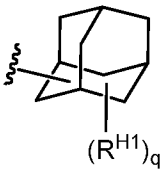
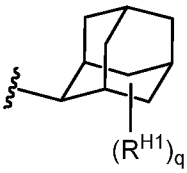
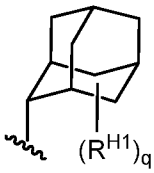
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00356] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-5**):

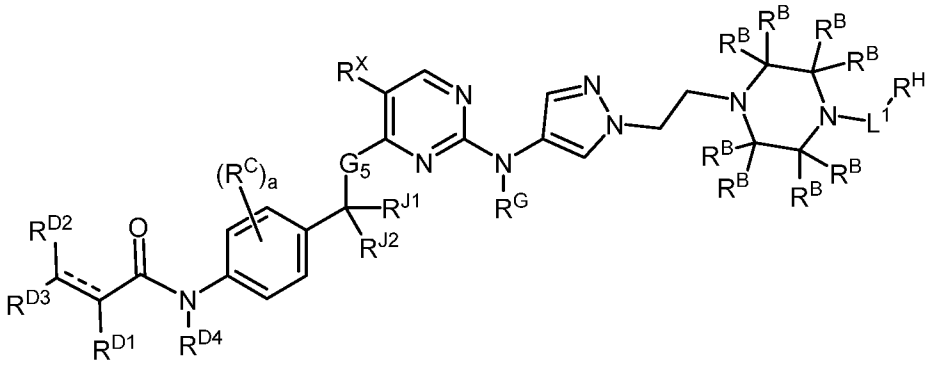


(**IIa-5**),

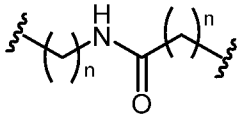
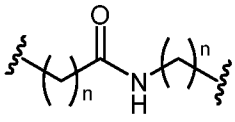
or a pharmaceutically acceptable salt thereof. In certain embodiments, the group

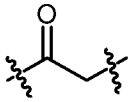
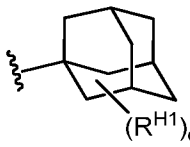
 is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is .   or . In certain embodiments, q is 0.

[00357] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-6**):

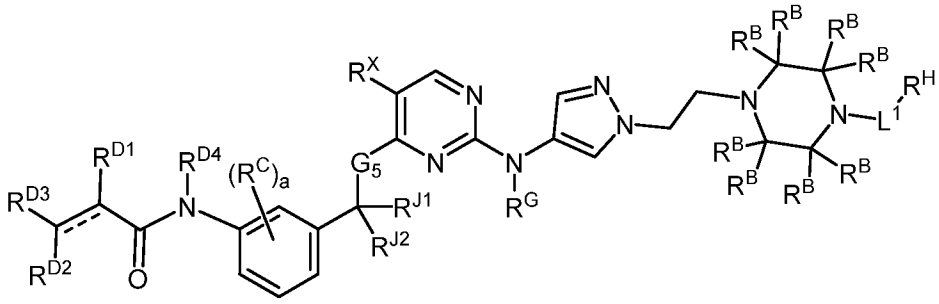


(**IIa-6**),

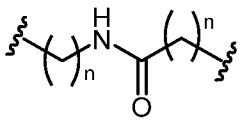
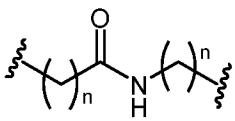
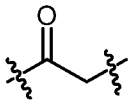
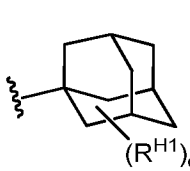
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is

. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

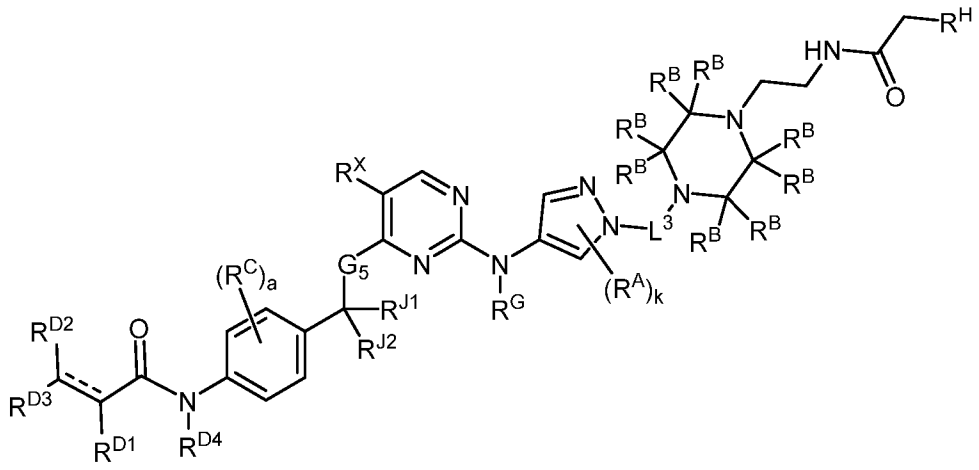
[00358] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-7**):



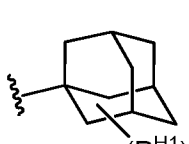
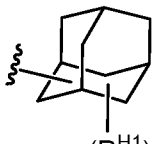
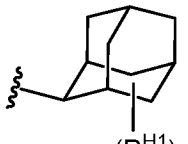
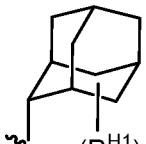
(**IIa-7**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

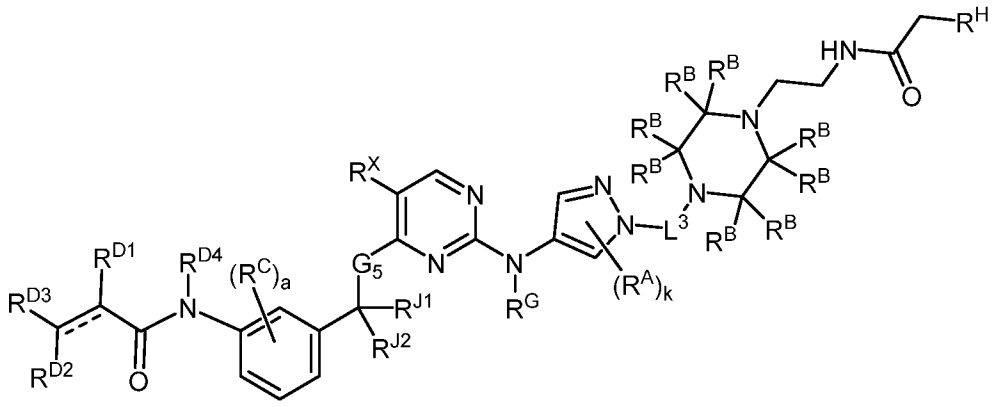
[00359] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-8**):



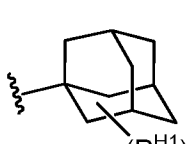
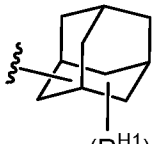
(**IIa-8**),

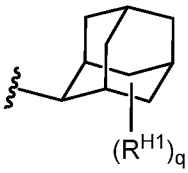
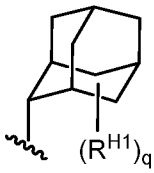
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00360] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-9**):



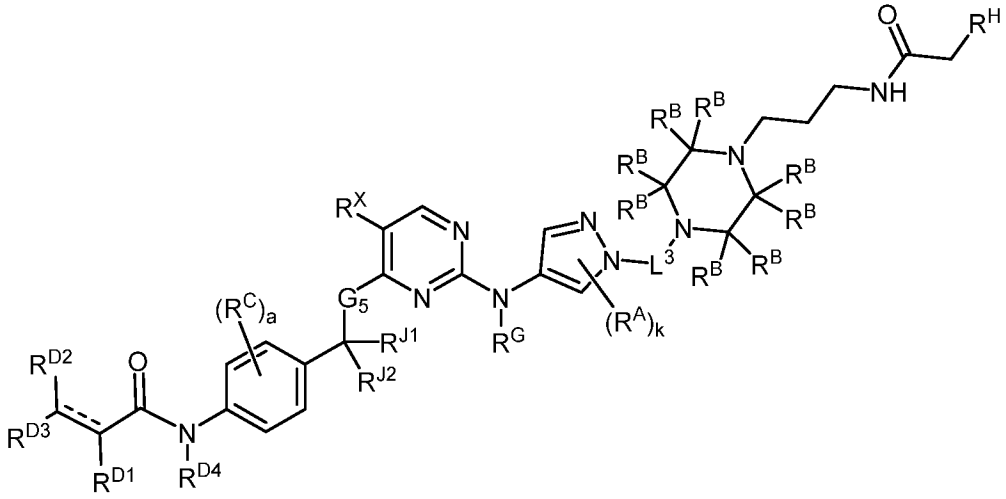
(**IIa-9**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , ,

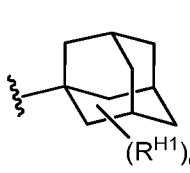
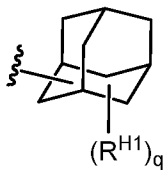
. In certain embodiments, q is 0.

[00361] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-10**):

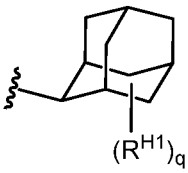
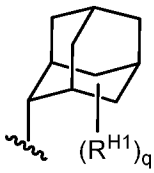


(**IIa-10**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is

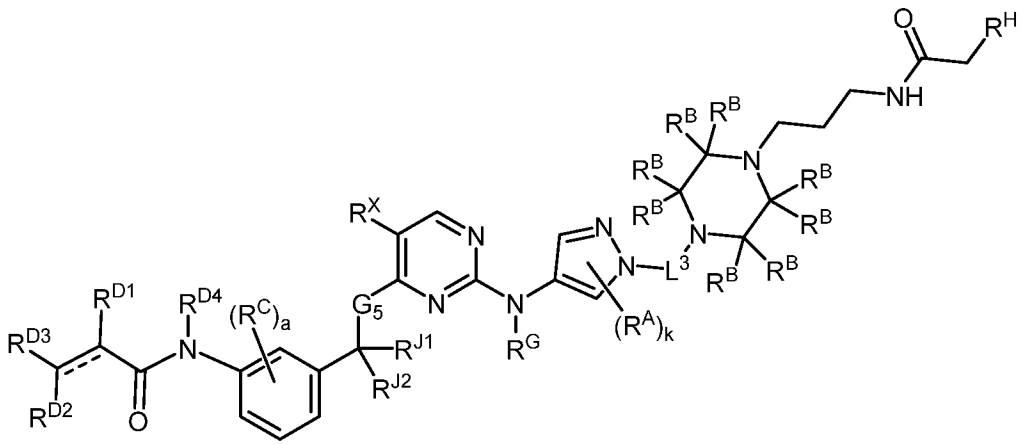



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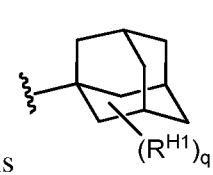
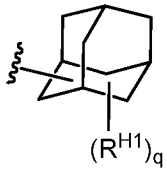
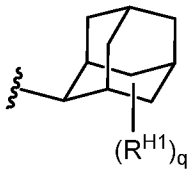
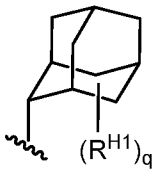



. In certain embodiments, q is 0.

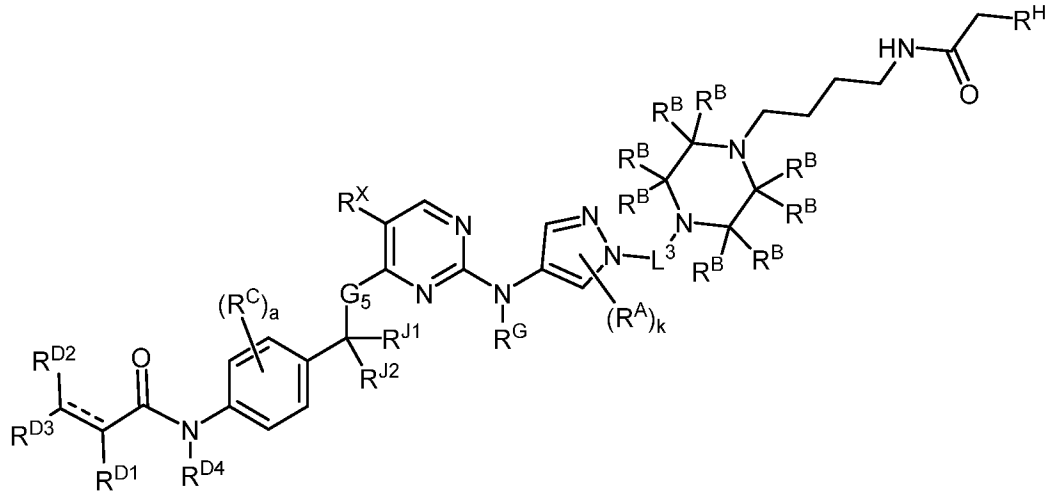
[00362] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-11**):



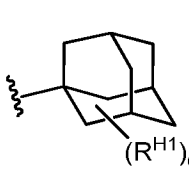
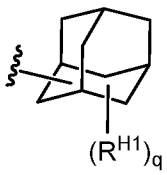
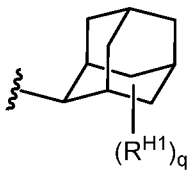
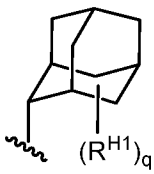
(**IIa-11**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

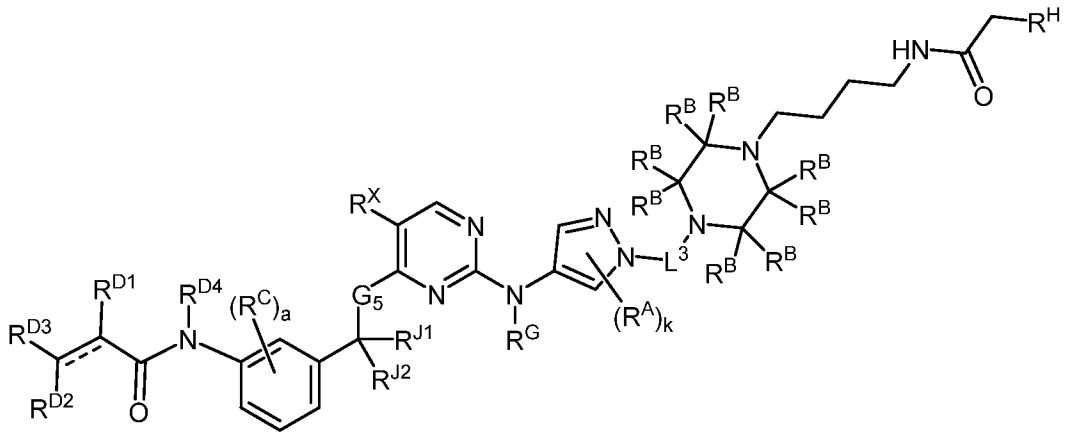
[00363] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-12**):



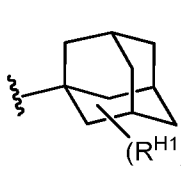
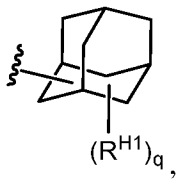
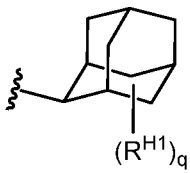
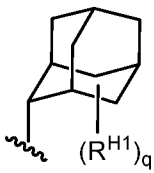
(**IIa-12**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

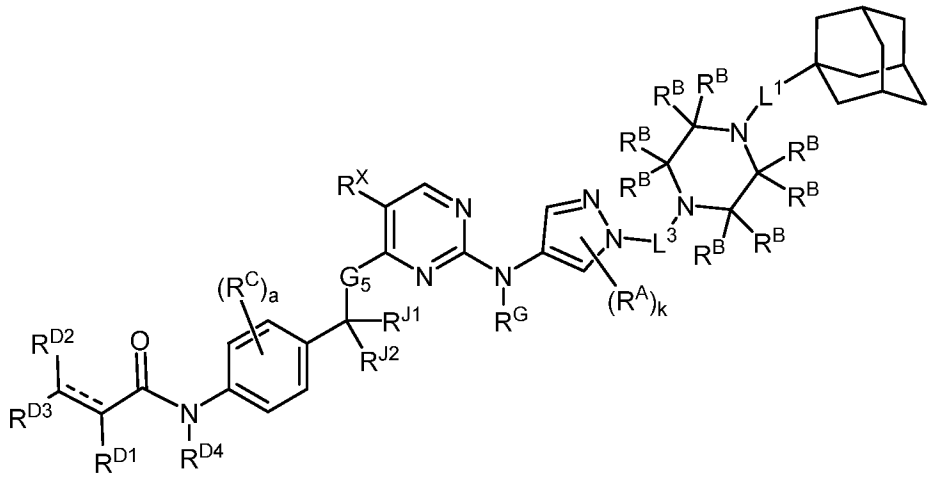
[00364] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula (**IIa-13**):



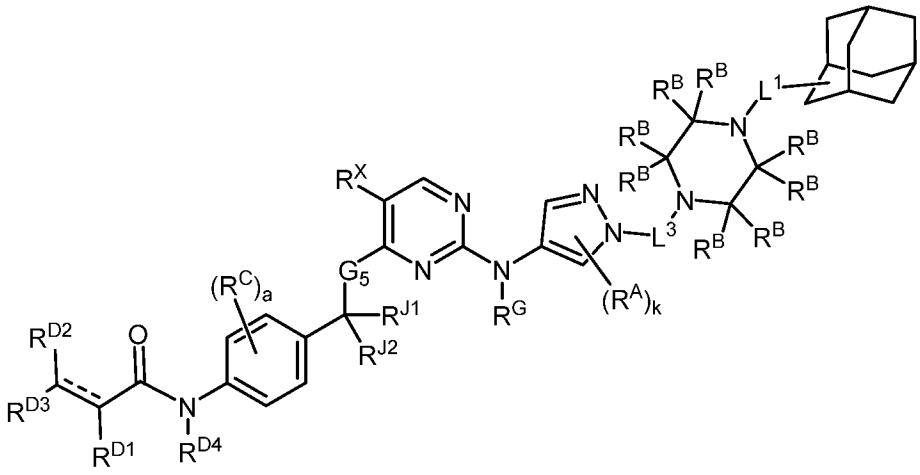
(**IIa-13**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, R^H is . , , or . In certain embodiments, q is 0.

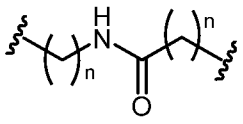
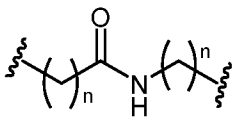
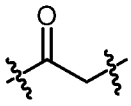
[00365] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula:



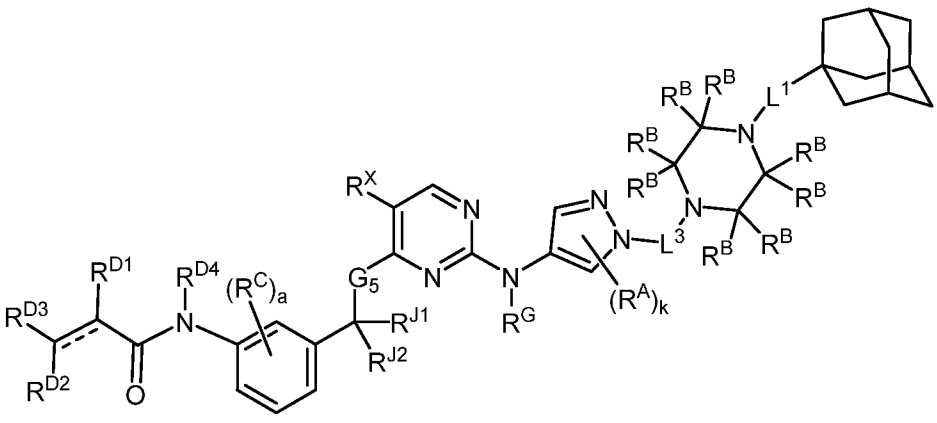
(**IIa-14**),



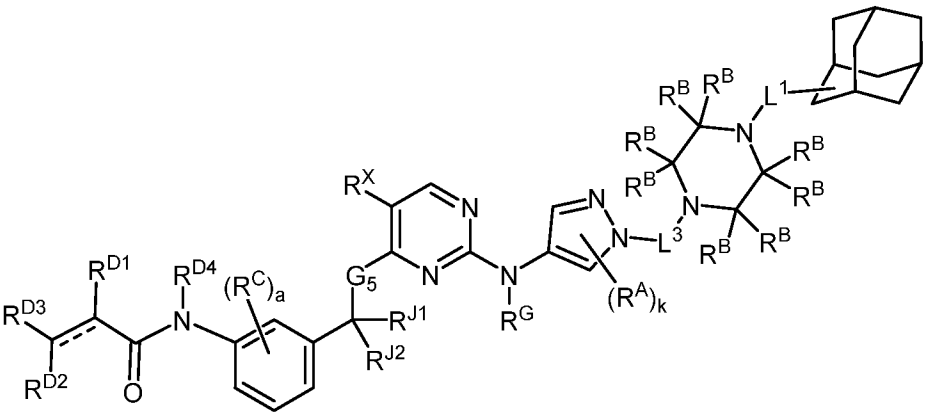
(**IIa-14a**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

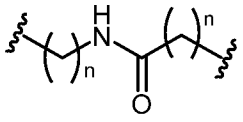
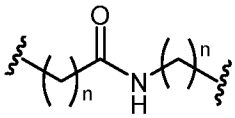
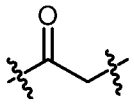
[00366] In certain embodiments, a compound of Formula (**IIa**) is a compound of Formula:



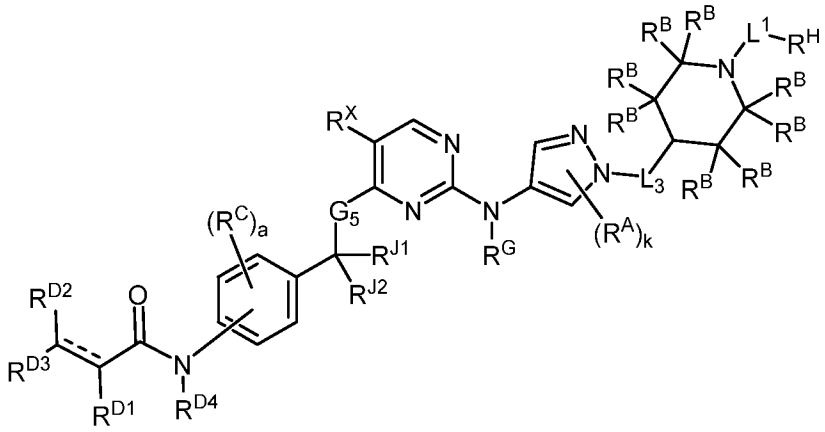
(**IIa-14**),



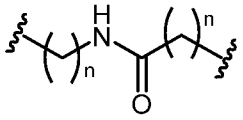
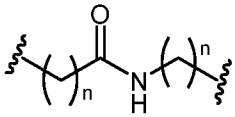
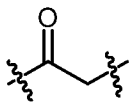
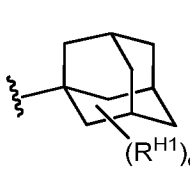
(**IIa-14a**),

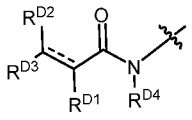
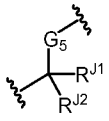
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

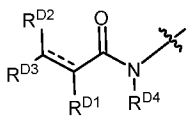
[00367] In certain embodiments, a compound described herein is a compound of Formula (**IIb**):

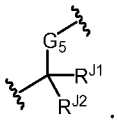


(**IIb**),

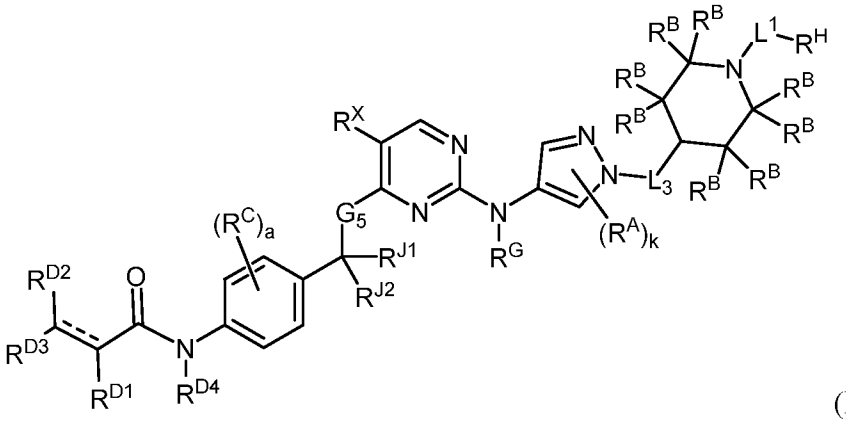
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0. In certain embodiments, all instances of R^B are hydrogen. In certain embodiments, L^3 is a bond. In certain embodiments, L^3 is an unsubstituted C_{1-3}alkylene linker. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain

embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $-CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $-OR^{X1}$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is $-CH_3$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $-CH_3$. In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is $-CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain embodiments, the group  is attached *meta* to the point of attachment .

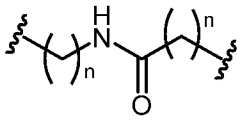
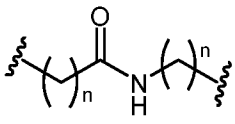
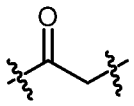
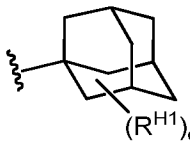
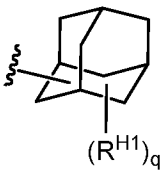
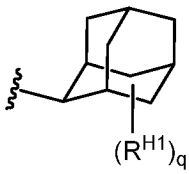
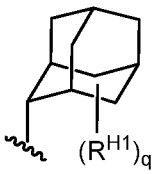
In certain embodiments, the group  is attached *para* to the point of attachment



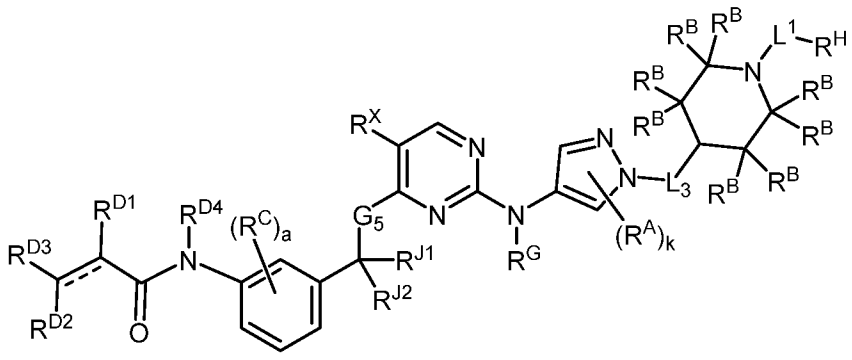
[00368] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-1**):



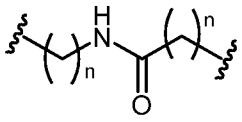
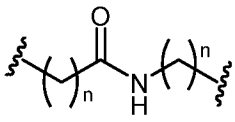
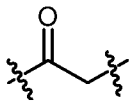
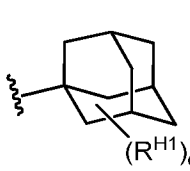
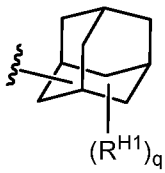
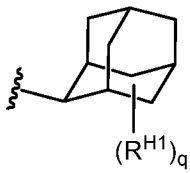
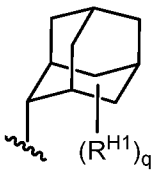
(**IIb-1**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

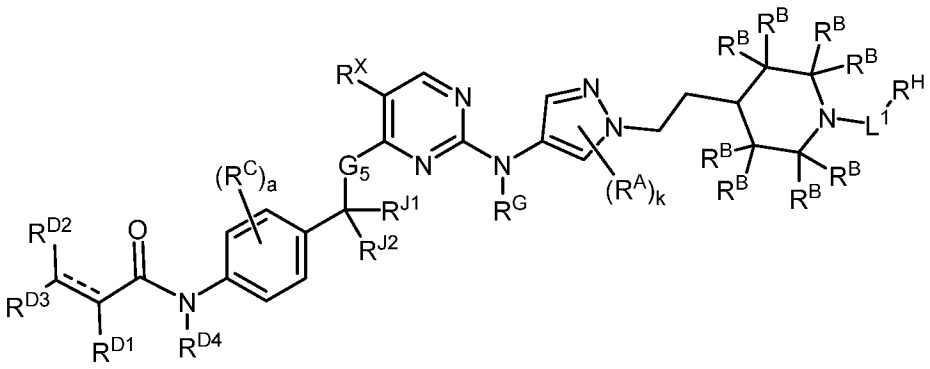
[00369] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-2**):



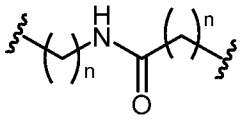
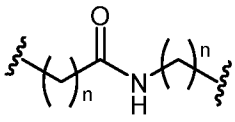
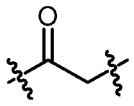
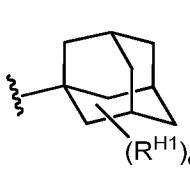
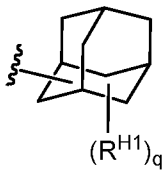
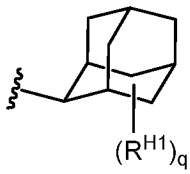
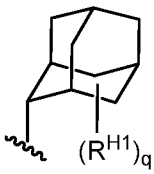
(**IIb-2**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00370] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-3**):

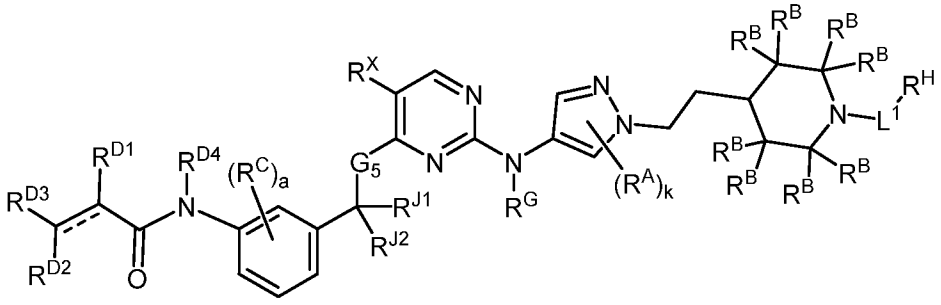


(**IIb-3**),

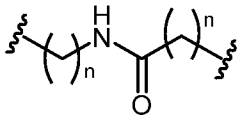
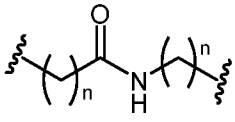
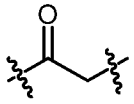
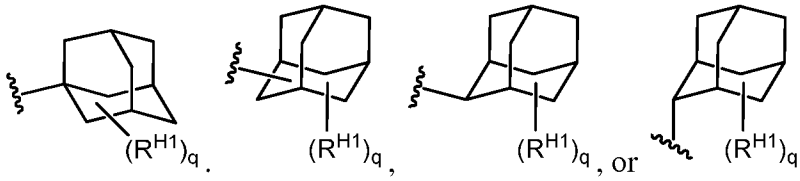
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00371] In certain embodiments, a compound of Formula (**IIb**) is a compound of

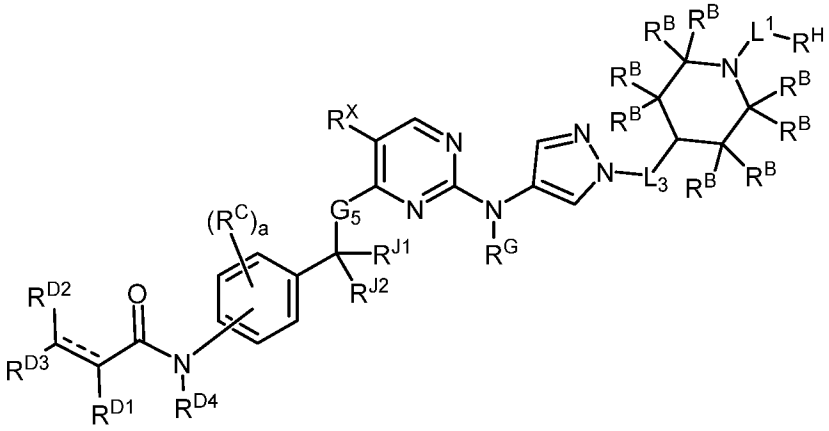
Formula (**IIb-4**):



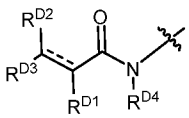
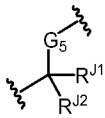
(**IIb-4**),

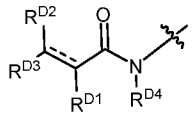
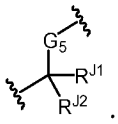
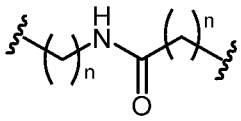
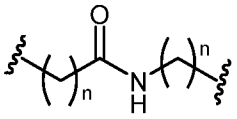
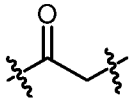
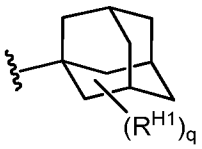
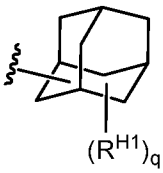
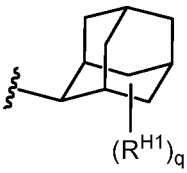
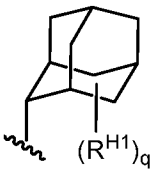
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

[00372] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-5**):

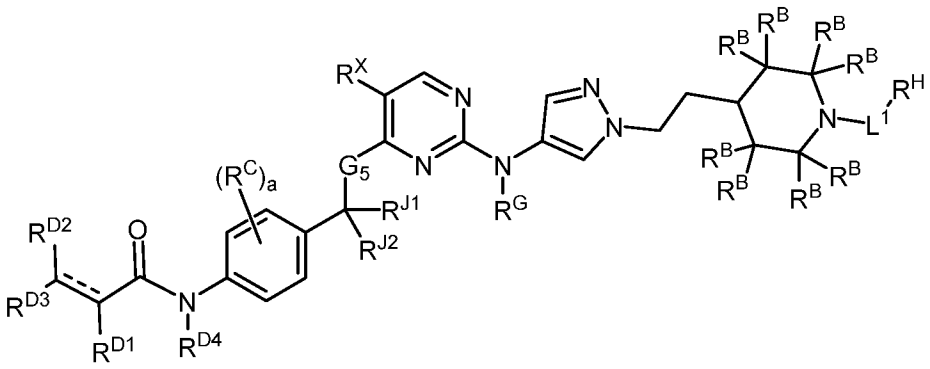


(**IIb-5**),

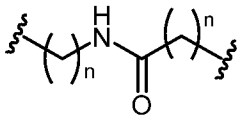
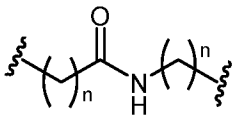
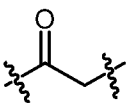
or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments,

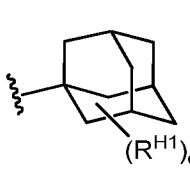
the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is .   or . In certain embodiments, q is 0.

[00373] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-6**):

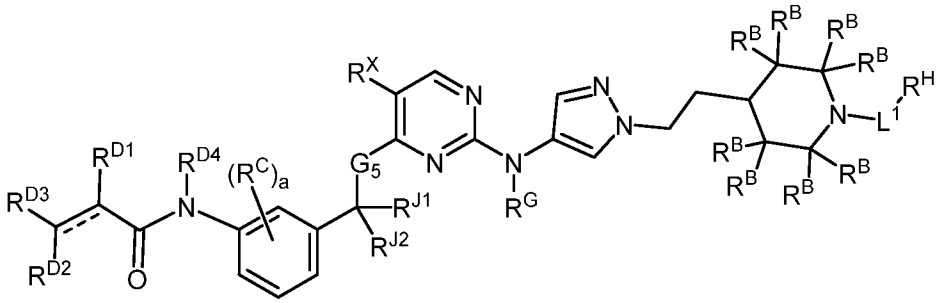


(**IIb-6**),

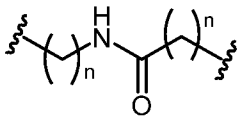
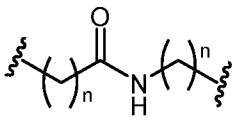
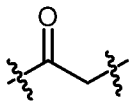
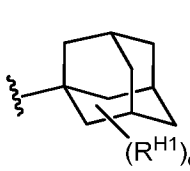
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In

certain embodiments, R^H is . In certain embodiments, q is 0.

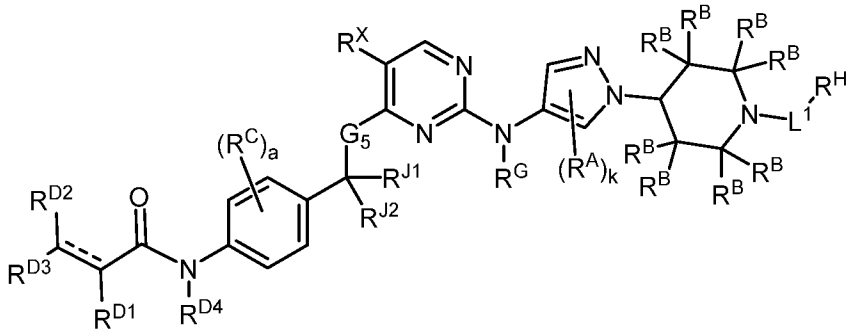
[00374] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-7**):



(**IIb-7**),

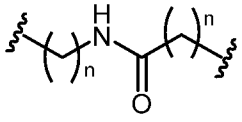
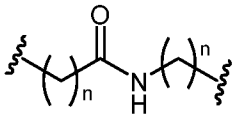
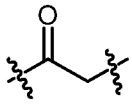
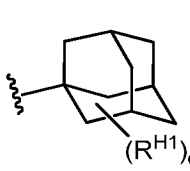
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

[00375] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-8**):

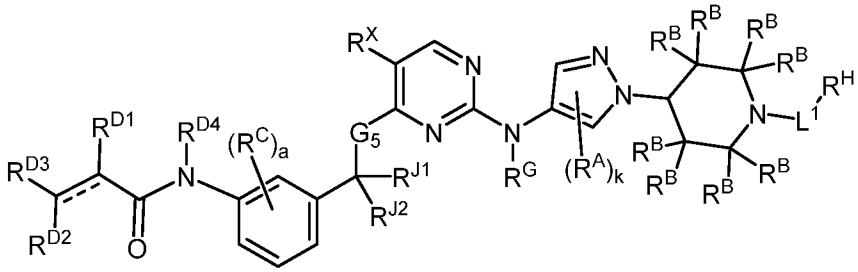


(**IIb-8**),

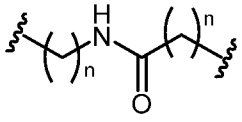
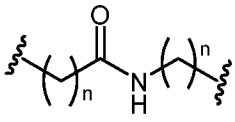
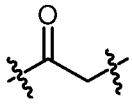
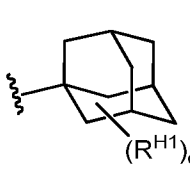
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or

unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

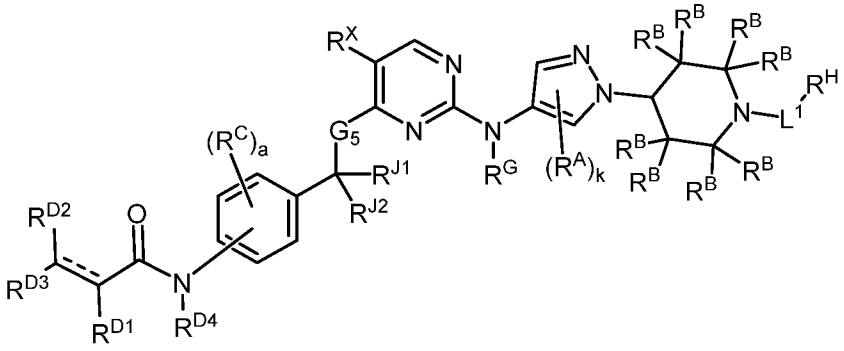
[00376] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-9**):



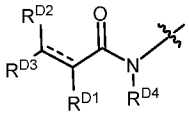
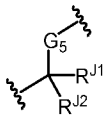
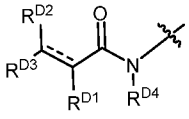
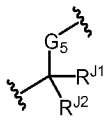
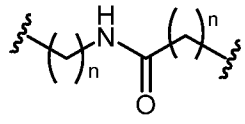
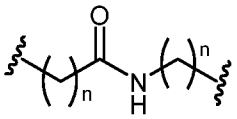
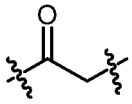
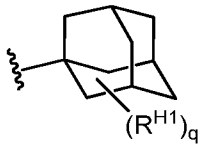
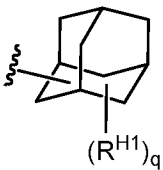
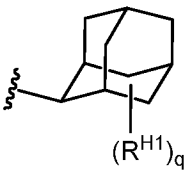
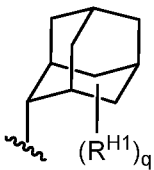
(**IIb-9**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

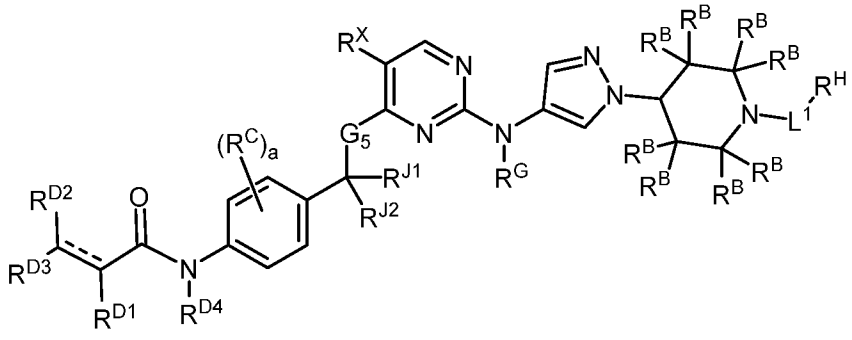
[00377] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-10**):



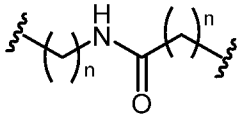
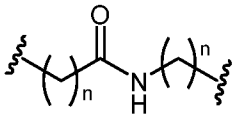
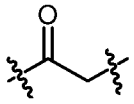
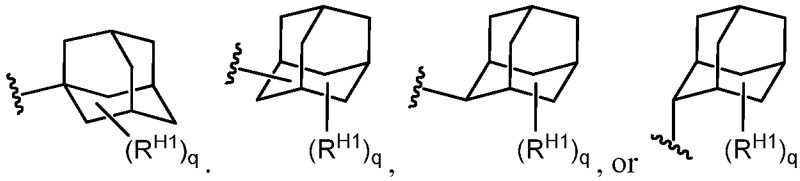
(**IIb-10**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, the group  is attached *meta* to the point of attachment . In certain embodiments, the group  is attached *para* to the point of attachment . In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . , , or . In certain embodiments, q is 0.

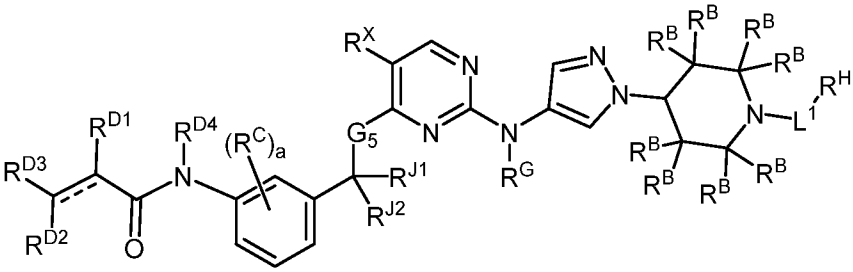
[00378] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-11**):



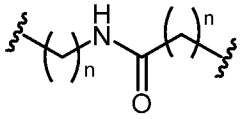
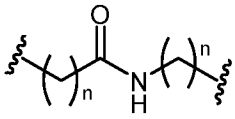
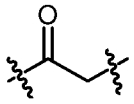
(**IIb-11**),

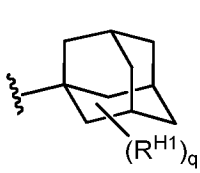
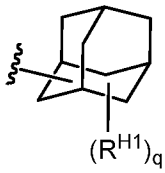
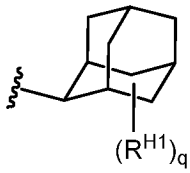
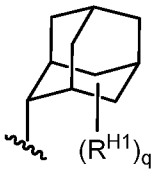
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0.

[00379] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-12**):

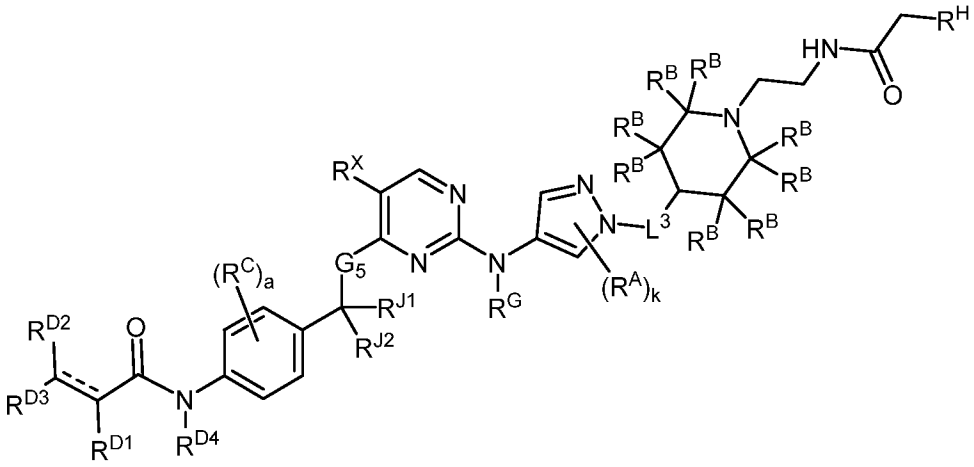


(**IIb-12**),

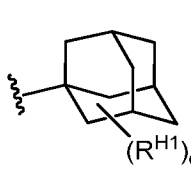
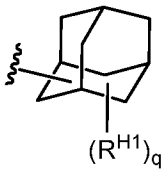
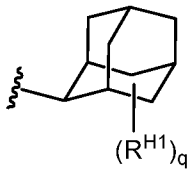
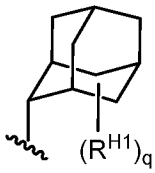
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In

certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

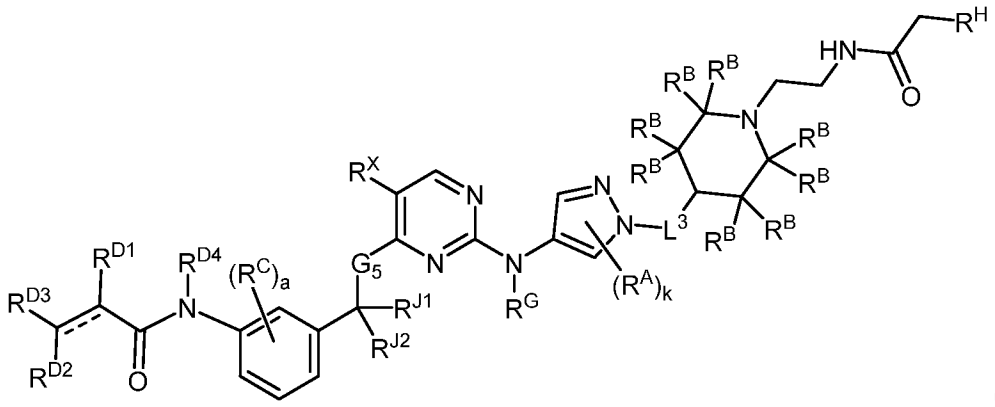
[00380] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-13**):



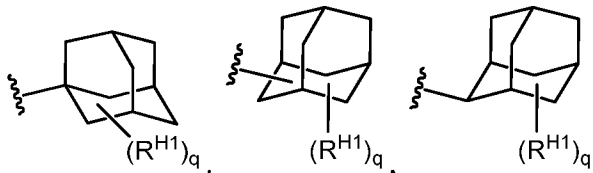
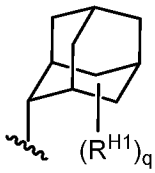
(**IIb-13**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

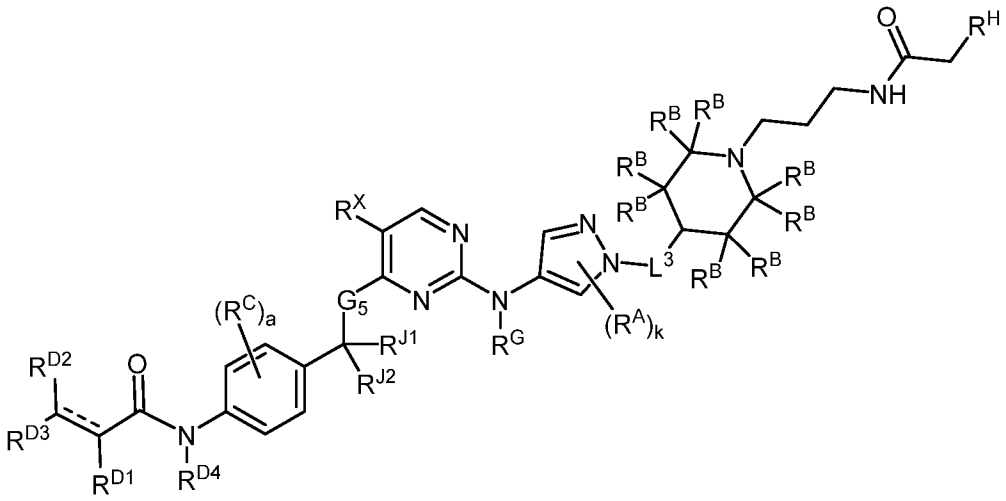
[00381] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-14**):



(**IIb-14**),

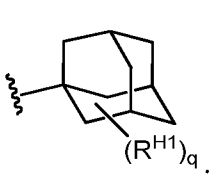
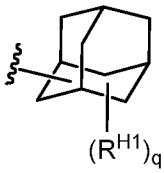
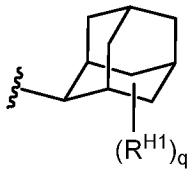
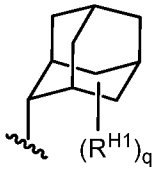
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , or . In certain embodiments, q is 0.

[00382] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-15**):

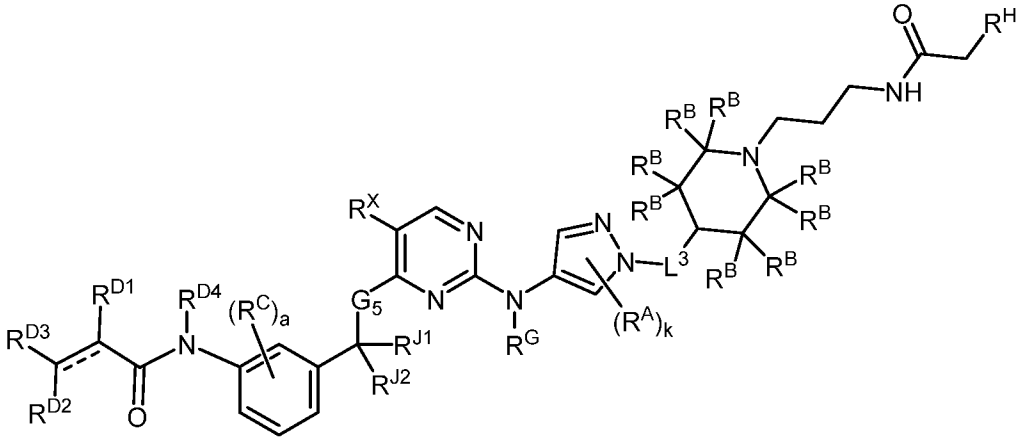


(**IIb-15**),

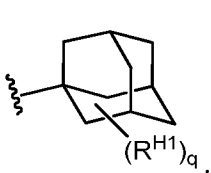
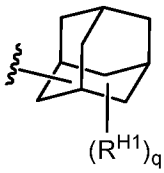
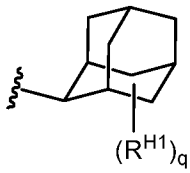
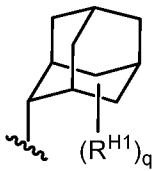
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3,

or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

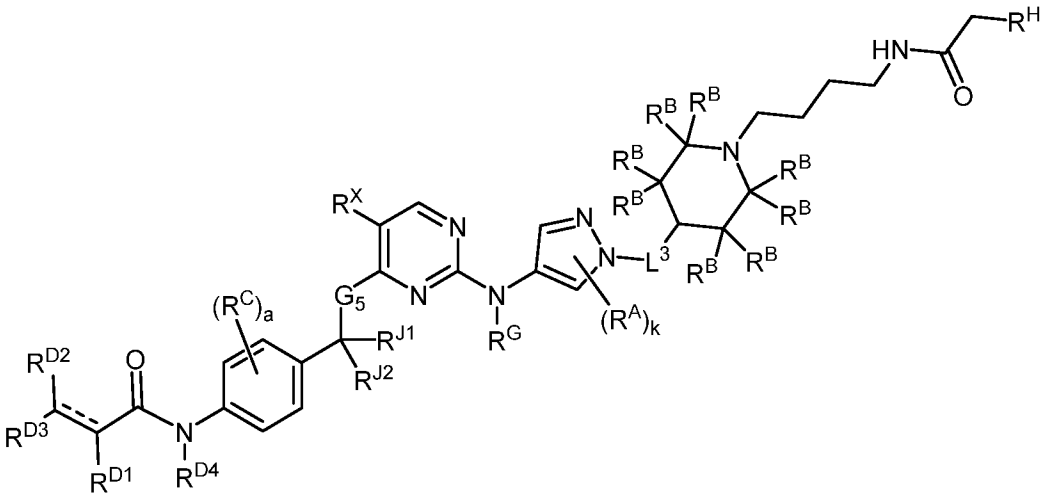
[00383] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-16**):



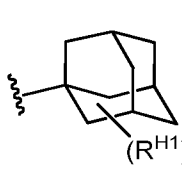
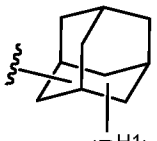
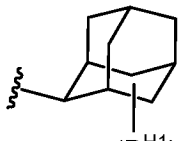
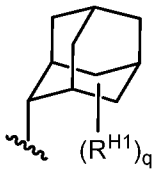
(**IIb-16**),

or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

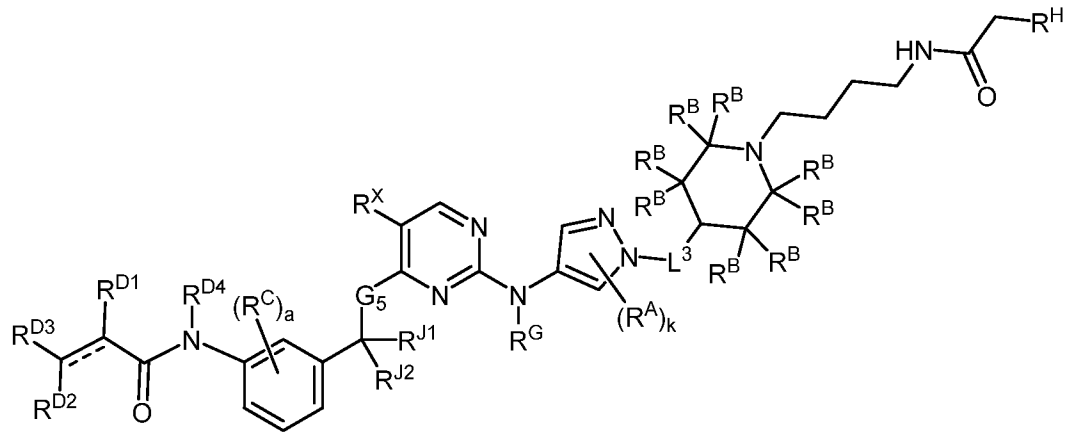
[00384] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-17**):



(**IIb-17**),

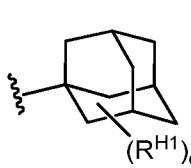
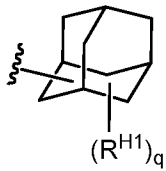
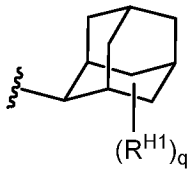
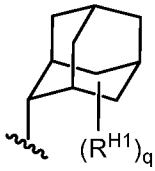
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

[00385] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula (**IIb-18**):

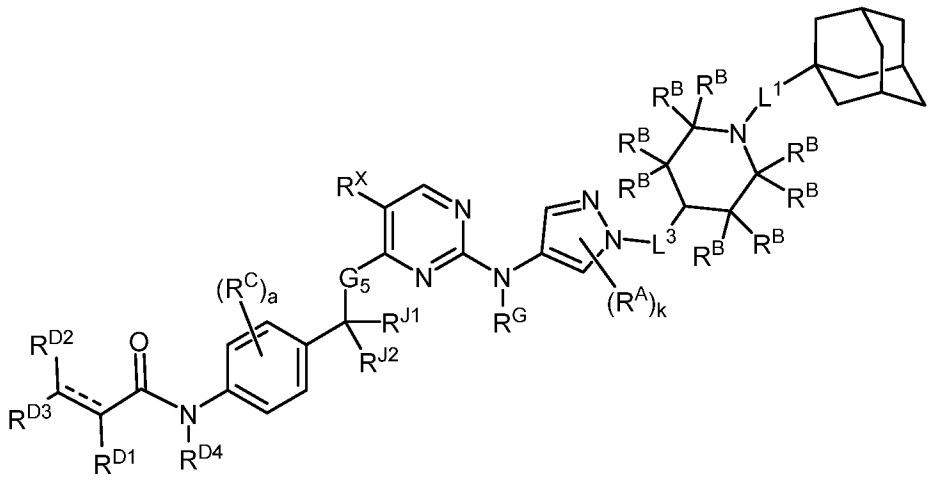


(**IIb-18**),

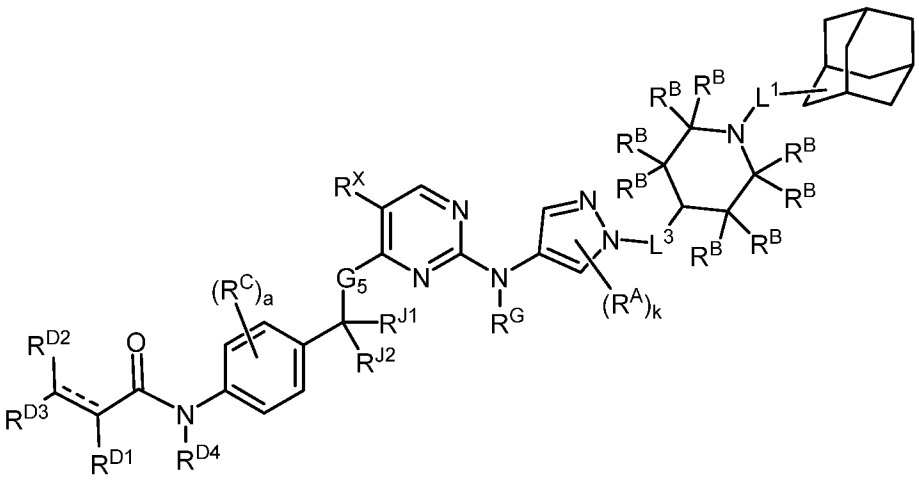
or a pharmaceutically acceptable salt thereof. In certain embodiments, R^H is substituted or unsubstituted adamantyl. In certain embodiments, each instance of n is independently 1, 2, 3,

or 4. In certain embodiments, R^H is , , , or . In certain embodiments, q is 0.

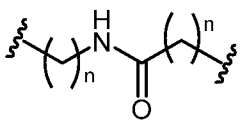
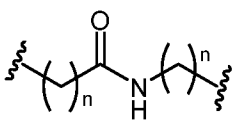
[00386] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula:

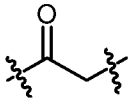


(**IIb-19**),

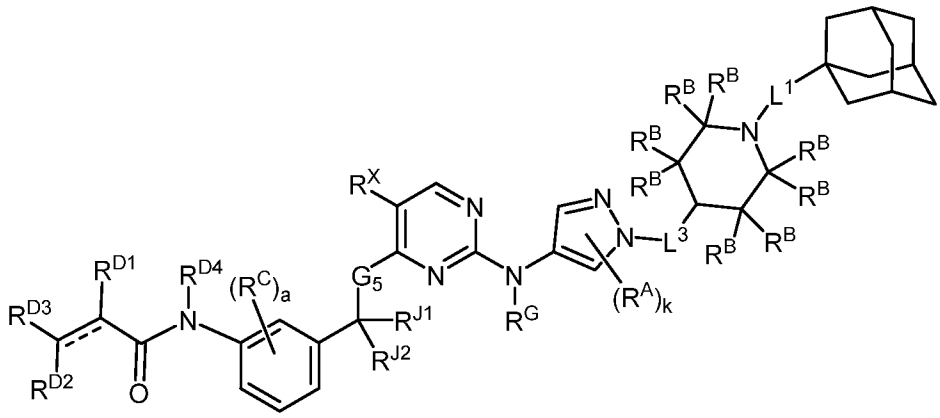


(**IIb-19a**),

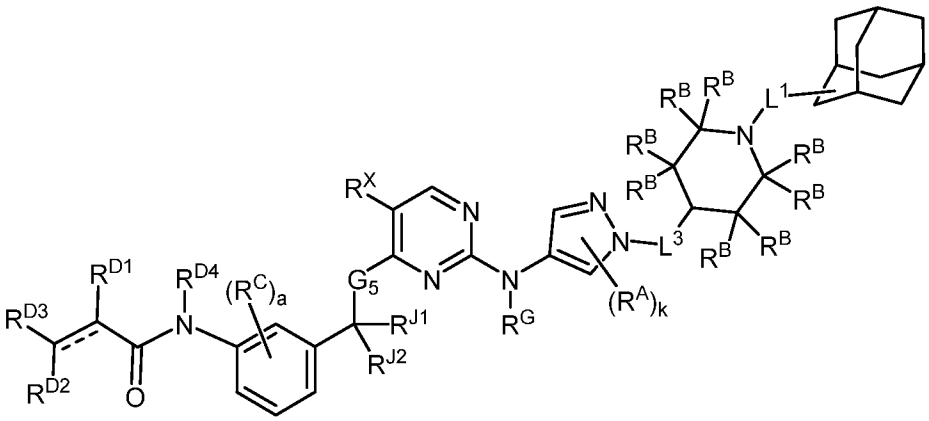
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is


. In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

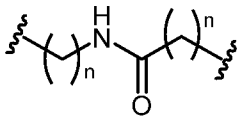
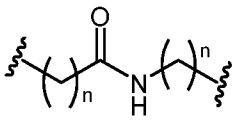
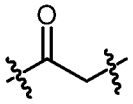
[00387] In certain embodiments, a compound of Formula (**IIb**) is a compound of Formula:



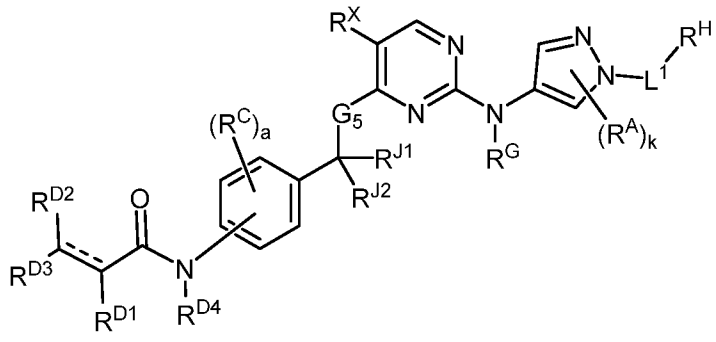
(**IIb-20**),



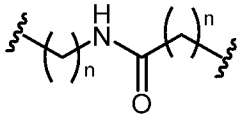
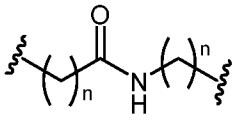
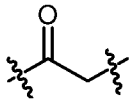
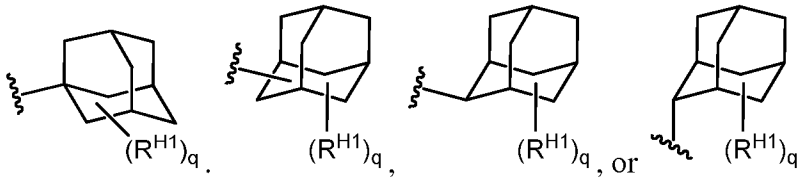
(**IIb-20a**),

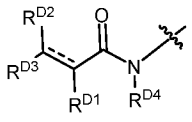
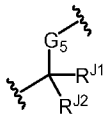
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4.

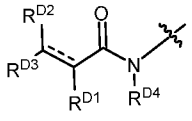
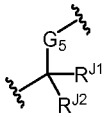
[00388] In certain embodiments, a compound described herein is a compound of Formula (**IIc**):



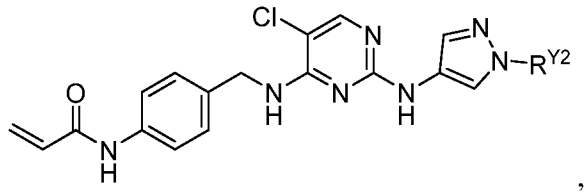
(**IIc**),

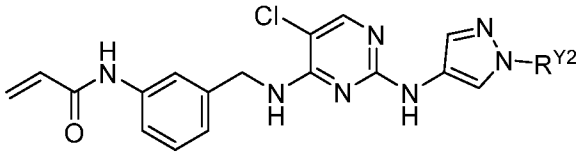
or a pharmaceutically acceptable salt thereof. In certain embodiments, L^1 is substituted or unsubstituted heteroC_{1-6}alkylene or a substituted or unsubstituted C_{1-6}alkylene. In certain embodiments, L^1 is  or . In certain embodiments, L^1 is . In certain embodiments, each instance of n is independently 1, 2, 3, or 4. In certain embodiments, R^H is . In certain embodiments, q is 0. In certain embodiments, all instances of R^B are hydrogen. In certain embodiments, at least one instance of R^A is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^A is $-CH_3$. In certain embodiments, at least one instance of R^A is $-CF_3$. In certain embodiments, R^G is hydrogen. In certain embodiments, R^G is $-CH_3$. In certain embodiments, R^X is hydrogen. In certain embodiments, R^X is –CN. In certain embodiments, R^X is $-OR^{X1}$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is $-CH_3$. In certain embodiments, R^X is $-OR^{X1}$; and R^{X1} is an oxygen protecting group. In certain embodiments, R^X is F. In certain embodiments, R^X is Cl. In certain embodiments, R^X is Br. In certain embodiments, R^X is I (iodine). In certain embodiments, R^X is unsubstituted C_{1-6} alkyl. In certain embodiments, R^X is substituted C_{1-6} alkyl. In certain embodiments, R^X is C_{1-6} alkyl substituted with at least one halogen. In certain embodiments, R^X is $-CH_3$. In certain embodiments, R^X is $-CF_3$. In certain embodiments, G_5 is S. In certain embodiments, G_5 is NR^E; and R^E is hydrogen. In certain embodiments, G_5 is NR^E; and R^E is $-CH_3$. In certain embodiments, both R^{J1} and R^{J2} are hydrogen. In certain embodiments, R^{J1} is hydrogen; and R^{J2} is substituted or unsubstituted C_{1-6}alkyl. In certain embodiments, R^{J1} is hydrogen; and R^{J2}

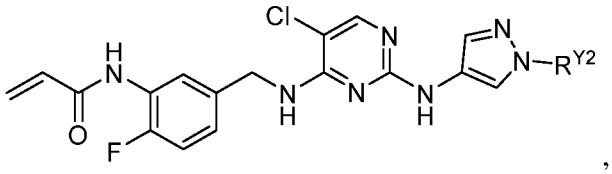
is $-CH_3$. In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, In certain embodiments, at least one instance of R^C is halogen. In certain embodiments, at least one instance of R^C is F. In certain embodiments, ==== represents a single bond. In certain embodiments, ==== represents a double bond. In certain embodiments, each of R^{D1}, R^{D2}, and R^{D3} is hydrogen. In certain embodiments, each of R^{D2} and R^{D3} is hydrogen, and R^{D1} is $-CH_3$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2N(R^{D1a})_2$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, and R^{D3} is $-CH_2OR^{D1a}$. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2N(R^{D1a})_2$, and R^{D1a} is methyl. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is hydrogen. In certain embodiments, each of R^{D1} and R^{D2} is hydrogen, R^{D3} is $-CH_2OR^{D1a}$, and R^{D1a} is methyl. In certain embodiments, R^{D4} is hydrogen. In certain embodiments, R^{D4} is substituted or unsubstituted alkyl. In certain embodiments, R^{D4} is a nitrogen protecting group. In certain embodiments, the group  is attached *meta* to the point of attachment .

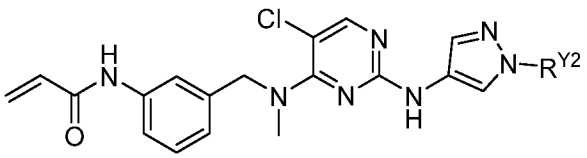
In certain embodiments, the group  is attached *para* to the point of attachment .

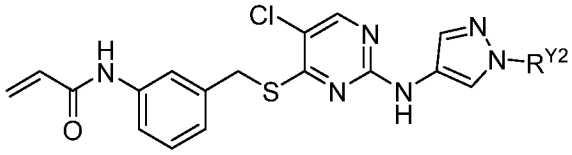
[00389] The following scaffolds are specifically contemplated for hydrophobic tagging, wherein R^{Y2} comprises a hydrophobic moiety (R^H), as defined herein:

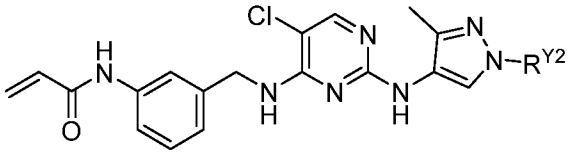
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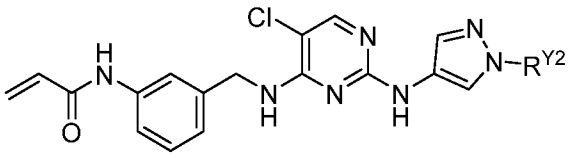
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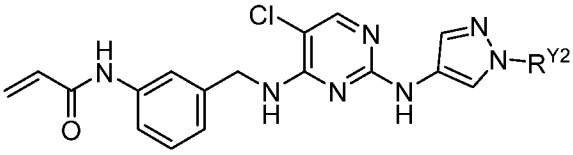

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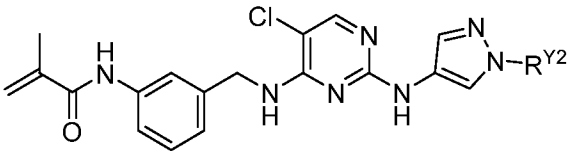

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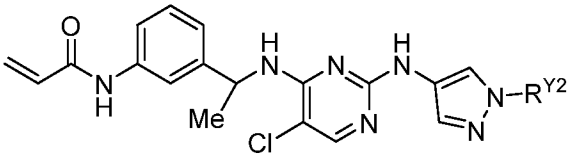

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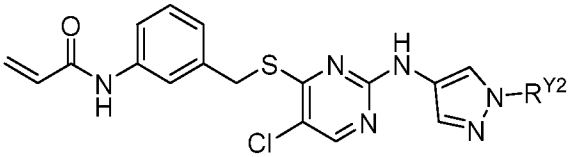

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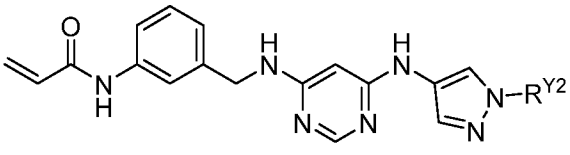

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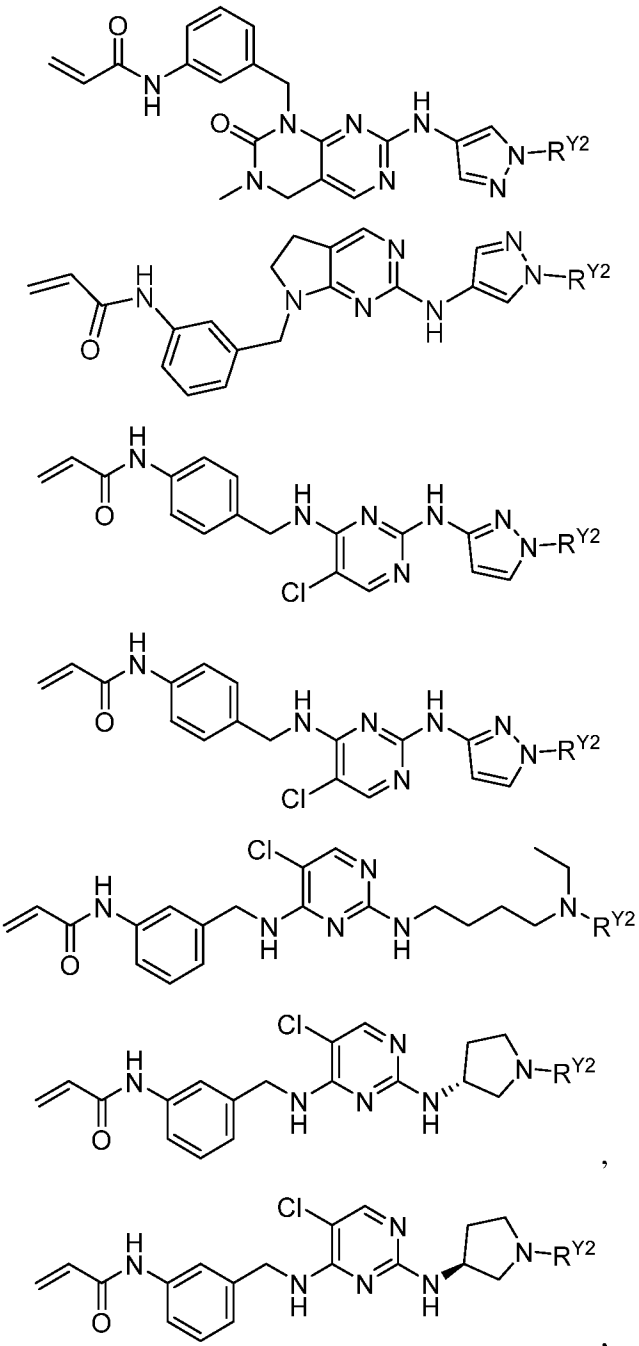

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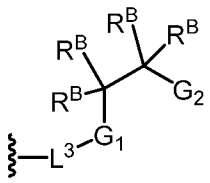

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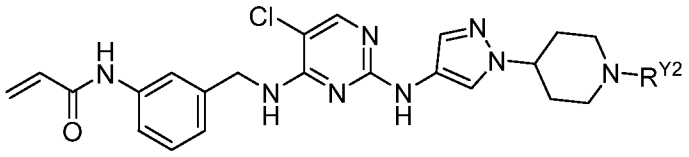

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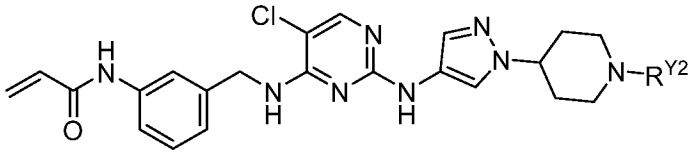


and pharmaceutically acceptable salts thereof. In certain embodiments, the group R^{Y2} is a group of formula  .

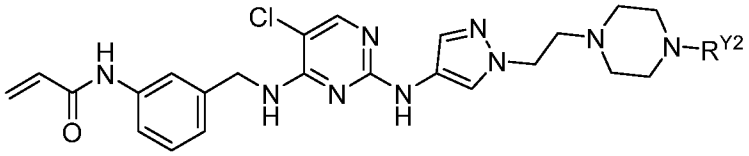
[00390] The following scaffolds are also specifically contemplated for hydrophobic tagging, wherein R^{Y2} comprises a hydrophobic moiety (R^H), as defined herein:



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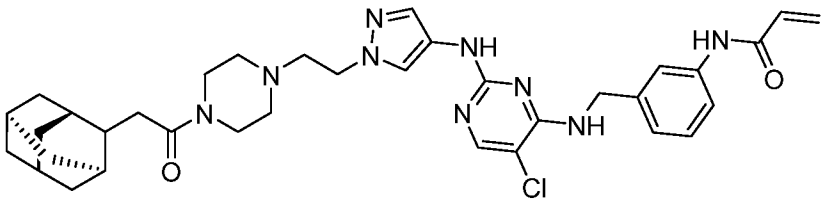
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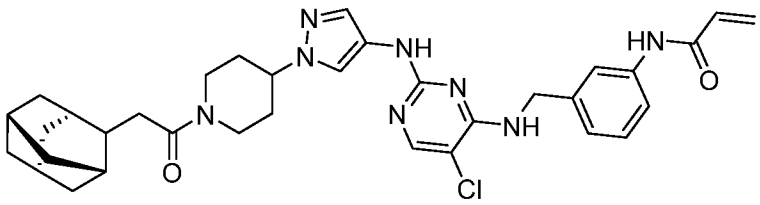
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and pharmaceutically acceptable salts thereof. In certain embodiments, the group R^{Y2} is a group of formula $-L^1-R^H$.

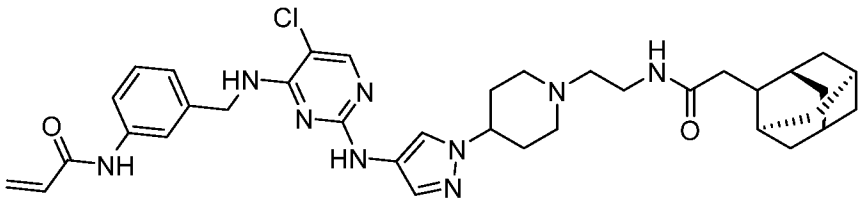
[00391] In certain embodiments, a compound described herein is a compound of the formula:



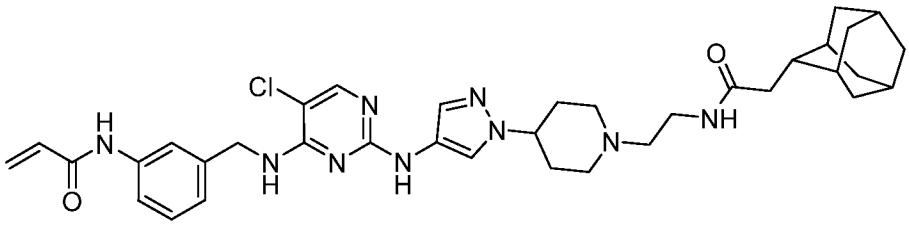
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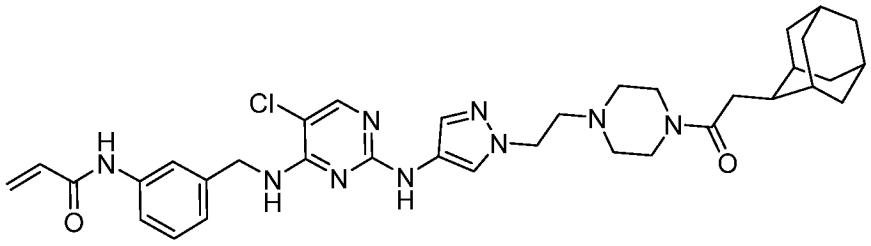
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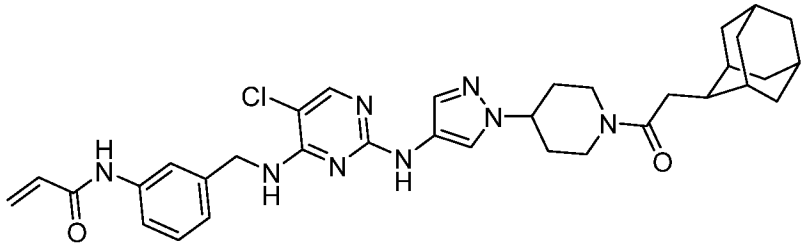
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, or



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or a pharmaceutically acceptable salt thereof.

Pharmaceutical Compositions and Kits

[00392] In certain embodiments, the present invention provides a pharmaceutical composition comprising a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient. In certain embodiments, the compound is present in an effective amount, *e.g.,* a therapeutically effective amount or a prophylactically effective amount.

[00393] Pharmaceutically acceptable excipients include any and all solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. General considerations in the formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00394] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing the compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof (the "active ingredient") into association with the 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.

[00395] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. A "unit dose" is 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.

[00396] Relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00397] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00398] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and combinations thereof.

[00399] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and combinations thereof.

[00400] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol,

oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether [Brij 30]), poly(vinyl–pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, *etc.* and/or combinations thereof.

[00401] Exemplary binding agents include starch (*e.g.* cornstarch and starch paste), gelatin, sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl–pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, *etc.*, and/or combinations thereof.

[00402] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00403] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00404] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA)

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

[00405] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00406] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00407] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta–carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00408] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti–oxidant. In other embodiments, the preservative is a chelating agent.

[00409] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D–gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid,

pyrogen–free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and combinations thereof.

[00410] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[00411] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[00412] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3–butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates are mixed with solubilizing agents such as Cremophor, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and combinations thereof.

[00413] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile

injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3–butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono– or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00414] The injectable formulations can be sterilized, for example, by filtration through a bacterial–retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00415] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00416] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates with suitable non–irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00417] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00418] Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as fillers in soft and hard–filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00419] The active ingredients can be in micro–encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00420] Dosage forms for topical and/or transdermal administration of a compound described herein may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or

additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00421] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00422] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically–administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00423] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low–boiling propellant in a sealed container. Such powders

comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00424] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid non–ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00425] Pharmaceutical compositions described herein formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00426] The formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition described herein. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered. by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00427] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w)

active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or atomized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00428] A pharmaceutical composition described herein can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other opthalmically administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[00429] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of pharmaceutical compositions can be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005.

[00430] Still further encompassed by the invention are pharmaceutical packs and/or kits. Pharmaceutical packs and/or kits provided may comprise a provided composition and a container (*e.g.,* a vial, ampoule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a suitable aqueous carrier for dilution or suspension of the provided composition for preparation of administration to a subject. In some embodiments, contents of provided formulation container and solvent container combine to form at least one unit dosage form.

[00431] Optionally, a single container may comprise one or more compartments for containing a provided composition, and/or appropriate aqueous carrier for suspension or dilution. In some embodiments, a single container can be appropriate for modification such that the container may receive a physical modification so as to allow combination of compartments and/or components of individual compartments. For example, a foil or plastic bag may comprise two or more compartments separated by a perforated seal which can be broken so as to allow combination of contents of two individual compartments once the signal to break the seal is generated. A pharmaceutical pack or kit may thus comprise such multi–compartment containers including a provided composition and appropriate solvent and/or appropriate aqueous carrier for suspension.

[00432] Optionally, instructions for use are additionally provided in such kits described herein. Such instructions may provide, generally, for example, instructions for dosage and administration. In other embodiments, instructions may further provide additional detail relating to specialized instructions for particular containers and/or systems for administration. Still further, instructions may provide specialized instructions for use in conjunction and/or in combination with additional therapy.

Methods of Treatment, Uses, and, Administration

[00433] The present invention also provides methods of using a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, *e.g.,* by treating or preventing a condition associated with aberrant activity of a kinase in a subject in need thereof, or by reducing the activity of a kinase (*e.g., in vivo* or *in vitro*), comprising administering to the subject a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to treat or prevent the condition or reduce the activity of the kinase. Reducing activity of a kinase refers to any undesired abherrant activity, and includes, but is not limited to, over–activity and/or over–expression of the kinase compared to a normal cell.

[00434] In certain embodiments, provided is an *in vitro* method of reducing the activity of a kinase in a tissue, organ, cell, or cell culture, comprising contacting the tissue, organ, cell, or cell culture with a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to reduce the activity of the kinase.

[00435] In certain embodiments, provided is an *in vivo* method of reducing the activity of a kinase in a subject in need thereof, comprising administering to the subject a compound

of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to reduce the activity of the kinase.

[00436] In certain embodiments, provided is a method of treating a condition associated with aberrant activity of a kinase in a subject in need thereof, the method comprising administering to the subject a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to treat the condition (*e.g.*, a therapeutically effective amount).

[00437] In certain embodiments, provided is a method of preventing a condition associated with aberrant activity of a kinase in a subject in need thereof, the method comprising administering to the subject a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to prevent the condition (*e.g.*, a prophylactically effective amount).

[00438] In certain embodiments, the subject described herein is an animal. In certain embodiments, the subject is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

[00439] In certain embodiments, the kinase described herein is a protein kinase. In certain embodiments, the protein kinase is tyrosine kinase. In certain embodiments, the tyrosine kinase is a non-receptor tyrosine kinase. In certain embodiments, the non-receptor tyrosine kinase is a Janus kinase (JAK). In certain embodiments, the Janus kinase is Janus kinase 1 (JAK1). In certain embodiments, the Janus kinase is Janus kinase 2 (JAK2). In certain embodiments, the Janus kinase is Janus kinase 3 (JAK3). In certain embodiments, the activity of a kinase (*e.g.*, JAK3) is selectively reduced by a compound described herein, compared to a different kinase (*e.g.*, a kinase other than JAK3, *e.g.*, JAK1, JAK2, or TYK2). In certain embodiments, the activity of a kinase (*e.g.*, JAK3) is selectively reduced by at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 60-fold, at least 70-fold, at least 80-fold, at least 90-fold, or at least 100-fold over the activity of JAK1 and/or JAK2 by a compound of Formula (**I**) or (**II**) as

described herein. In certain embodiments, the compound of Formula (**I**) or (**II**) inhibits JAK3 up to about 100-fold selectively over JAK1 and/or JAK2, which do not possess an equivalently placed cysteine residue. In certain embodiments, the tyrosine kinase is a receptor tyrosine kinase (RTK). In certain embodiments, the receptor tyrosine kinase is an epidermal growth factor receptor (EGFR) tyrosine kinase.

[00440] In certain embodiments, the compound reduces kinase activity by targeted degradation of the kinase. In certain embodiments, the compound reduces kinase activity by inducing unfolding of the kinase. In certain embodiments, the compound reduces kinase activity by inducing degradation of the kinase. In certain embodiments, the compound reduces kinase activity by covalently binding to a kinase (*e.g.*, JAK3). In certain embodiments, a compound described herein covalently binds to Cys909 of JAK3. The compounds described herein may alternatively reduce kinase activity by binding to a kinase (*e.g.,* JAK3) non-covalently (*e.g.*, through electrostatic interactions, Van der Waals interactions, π-interactions, and/or hydrophobic interactions)..

[00441] Exemplary conditions associated with aberrant activity of a kinase includes, but are not limited to, proliferative diseases, inflammatory disorders, autoimmune disorders, painful conditions, and viral infections.

[00442] In certain embodiments, the condition associated with aberrant activity of a kinase is a proliferative disease. Exemplary proliferative diseases include, but are not limited to, tumors, begnin neoplasms, pre–malignant neoplasms (carcinoma *in situ*), and malignanat neoplasms (cancers). Exemplary cancers include, but are not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.,* lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.,* cholangiocarcinoma), bladder cancer, breast cancer (*e.g.,* adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (*e.g.,* meningioma; glioma, *e.g.,* astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.,* cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.,* colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.,* Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.,* adenocarcinoma of the esophagus, Barrett's adenocarcinoma), Ewing's sarcoma, eye cancer (*e.g.,* intraocular melanoma, retinoblastoma), familiar hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.,* stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head

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

cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.,* pancreatic andenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (*e.g.,* Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (*e.g.,* prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.,* squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.,* appendix cancer), soft tissue sarcoma (*e.g.,* malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (*e.g.,* seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.,* papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer and vulvar cancer (*e.g.*, Paget's disease of the vulva). In certain embodiments, the cancer is a hematological malignancy. In certain embodiments, the cancer is lymphoma. In certain embodiments, the cancer is leukemia.

[00443] In certain embodiments, the condition associated with aberrant activity of a kinase is an inflammatory disorder. The term "inflammatory disorder" refers to those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00444] Exemplary inflammatory disorders include, but are not limited to, inflammation associated with acne, anemia (*e.g.,* aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis,

Chagas disease, chronic obstructive pulmonary disease, cermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain–Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myeasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious aneaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, schleroderma, scierodoma, sarcoidosis, spondyloarthopathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis.

[00445] In certain embodiments, the inflammatory disorder is inflammation associated with a proliferative disease, *e.g.,* inflammation associated with cancer.

[00446] Janus kinases (JAKs) play multiple roles downstream of cytokine signaling in both immune and non-immune cells. Autoimmunity is driven by an aberrant adaptive immune response to self-antigens and JAK-STAT (signal transducer and activator of transcription) signaling is known to play a key role in this process. Thus, JAK inhibitors may have considerable potential for the development of drugs to treat autoimmunity. JAK3 is an especially attractive target as, unlike other JAKs, its expression is restricted to the immune system. Thus, in certain embodiments, the condition associated with aberrant activity of a kinase is an autoimmune disorder. Exemplary autoimmune disorders include, but are not limited to, arthritis (*e.g.,* rheumatoid arthritis, spondyloarthopathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's

syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non–ulcerative dyspepsia (NUD) and non–cardiac chest pain (NCCP, including costo–chondritis)). In certain embodiments, the autoimmune disorder is rheumatoid arthritis. In certain embodiments, the autoimmune disorder is psoriasis.

[00447] In certain embodiments, the autoimmune disorder is associated with inflammation or a painful condition.

[00448] In certain embodiments, the condition associated with aberrant activity of a kinase is a painful condition. A “painful condition” includes, but is not limited to, neuropathic pain (*e.g.,* peripheral neuropathic pain), central pain, deafferentiation pain, chronic pain (*e.g.*, chronic nociceptive pain, and other forms of chronic pain such as post–operative pain, *e.g.,* pain arising after hip, knee, or other replacement surgery), pre –operative pain, stimulus of nociceptive receptors (nociceptive pain), acute pain (*e.g.*, phantom and transient acute pain), noninflammatory pain, inflammatory pain, pain associated with cancer, wound pain, burn pain, postoperative pain, pain associated with medical procedures, pain resulting from pruritus, painful bladder syndrome, pain associated with premenstrual dysphoric disorder and/or premenstrual syndrome, pain associated with chronic fatigue syndrome, pain associated with pre–term labor, pain associated with withdrawl symptoms from drug addiction, joint pain, arthritic pain (*e.g.*, pain associated with crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis or Reiter's arthritis), lumbosacral pain, musculo–skeletal pain, headache, migraine, muscle ache,

lower back pain, neck pain, toothache, dental/maxillofacial pain, visceral pain and the like. One or more of the painful conditions contemplated herein can comprise mixtures of various types of pain provided above and herein (*e.g.* nociceptive pain, inflammatory pain, neuropathic pain, etc.). In some embodiments, a particular pain can dominate. In other embodiments, the painful condition comprises two or more types of pains without one dominating. A skilled clinician can determine the dosage to achieve a therapeutically effective amount for a particular subject based on the painful condition. In certain embodiments, the painful condition is inflammatory pain. In certain embodiments, the painful condition (*e.g.,* inflammatory pain) is associated with an inflammatory disorder and/or an autoimmune disorder.

[00449] In certain embodiments, the condition associated with aberrant activity of a kinase is a viral infection. In certain embodiments, the viral infection is Dengue fever, Dengue hemorrhagic fever (DHF), Dengue shock syndrome (DSS), hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, hepatitis F, Coxsackie A virus infection, Coxsackie B virus infection, fulminant viral hepatitis, severe acute respiratory syndrome (SARS), viral myocarditis, influenza virus infection (*e.g.*, influenza A virus infection (*e.g.*, an H1N1, H1N2, H2N1, H2N2, H2N3, H3N1, H3N2, H3N8, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H7N9, H5N2, H10N7 virus infection), influenza B virus infection, influenza C virus infection), parainfluenza virus infection, an RS virus (RSV) infection (*e.g.*, RSV bronchiolitis, RSV pneumonia, especially an infant and childhood RSV infection and RSV pneumonia in the patients with cardiopulmonary disorders), measles virus infection, vesicular stomatitis virus infection, rabies virus infection, Ebola virus infection, Japanese encephalitis, Junin virus infection, human cytomegalovirus infection, herpes virus infection (*e.g.*, iltovirus infection, mardivirus infection, simplexvirus infection (herpes simplex virus 1 infection), varicellovirus infection, cytomegalovirus infection, muromegalovirus infection, proboscivirus infection, roseolovirus infection, lymphocryptovirus infection, macavirus infection, percavirus infection, rhadinovirus infection), poliovirus infection, Marburg virus infection, Lassa fever virus infection, Venezuelan equine encephalitis, Rift Valley Fever virus infection, Korean hemorrhagic fever virus infection, Crimean-Congo hemorrhagic fever virus infection, HIV infection, acquired immunodeficiency syndrome (AIDS), encephalitis, Saint Louise encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, tick-borne encephalitis, West Nile encephalitis, yellow fever, or a viral infection in subjects with immune disorders. In certain embodiments, the viral infection is an influenza virus infection. In certain embodiments, the viral infection is an influenza A virus infection. In certain embodiments,

the viral infection is human flu (*e.g.*, H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, or H10N7 virus infection). In certain embodiments, the viral infection is bird flu (*e.g.*, H5N1 or H7N9 virus infection). In certain embodiments, the viral infection is swine influenza (*e.g.*, H1N1, H1N2, H2N1, H3N1, H3N2, or H2N3 virus infection, or influenza C virus infection). In certain embodiments, the viral infection is equine influenza (*e.g.*, H7N7 or H3N8 virus infection). In certain embodiments, the viral infection is canine influenza (*e.g.*, H3N8 virus infection). In certain embodiments, the viral infection is an influenza B virus infection. In certain embodiments, the viral infection is an influenza C virus infection. In certain embodiments, the viral infection is HIV infection or AIDS. In certain embodiments, the viral infection is hepatitis C.

[00450] In still another aspect, the present invention provides methods of reducing cytokine signaling in a subject in need thereof, the method comprising administering to the subject a compound of Formula (**I**) or (**II**) or pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof, in an amount sufficient to reduce the cytokine signaling (*e.g.*, a therapeutically effective amount). In certain embodiments, the cytokine is a tumor necrosis factor (TNF), colony stimulating factor (CSF), interferon (INF), interleukin (IL-1 , IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 , IL-12, IL-13, IL-14, or IL-15), transforming growth factor (TGF), oncostatin M (OSM), leukemia inhibiting factor (LIF), platelet activating factor (PAF), or other soluble immunoregulatory peptide that mediates host defense responses, cell regulation, or cell differentiation. In certain embodiments, the cytokine is an interleukin (*e.g.*, IL-4).

[00451] Compounds of Formula (**I**) or (**II**), or pharmaceutically acceptable salts thereof may be formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions comprising a compound described herein will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00452] 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), the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[00453] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00454] 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.

[00455] In certain embodiments, the compounds described herein may be administered orally or parenterally 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.

[00456] 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.

[00457] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. The compounds or compositions can be administered in combination with additional therapeutically active agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder (for example, a compound can be administered in combination with an anti–inflammatory agent, anti–cancer agent, *etc.*), and/or it may achieve different effects (*e.g.*, control of adverse side–effects, *e.g.*, emesis controlled by an anti–emetic).

[00458] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of the compound described herein with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually. Additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the Food and Drugs Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells. In certain embodiments, the additional therapeutically agent is a cancer agent (*e.g.,* a biotherapeutic or chemotherapeutic cancer agent). In other embodiments, the additional therapeutically active agent is an anti–inflammatory agent.

EXAMPLES

[00459] 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.

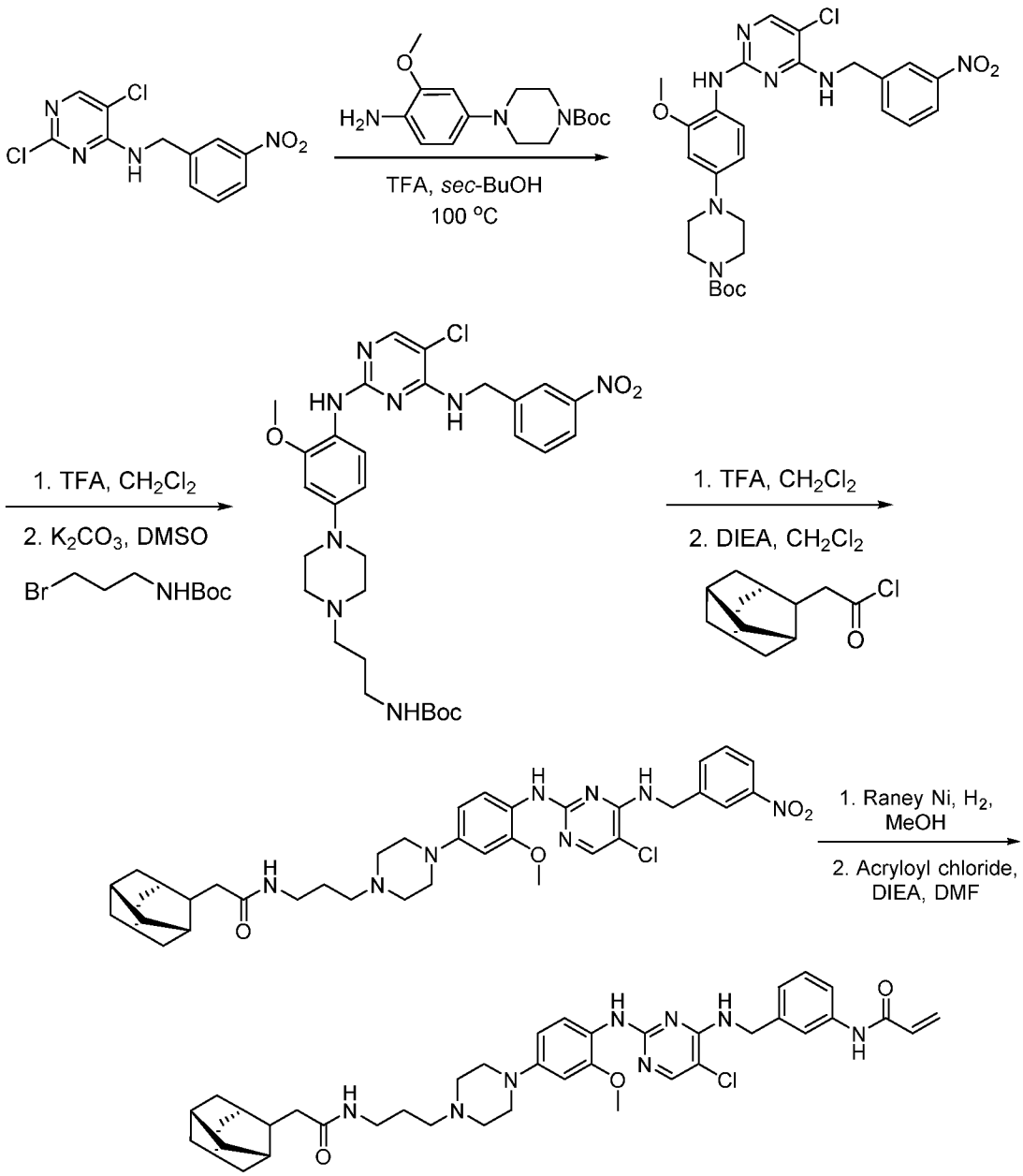
Example 1. Synthesis of the Compounds

[00460] The compounds provided herein can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures, *etc.*) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by those skilled in the art by routine optimization procedures.

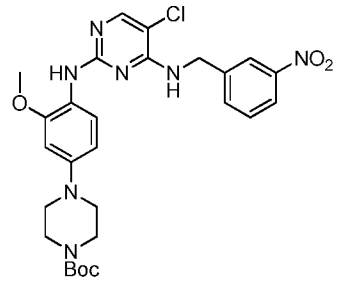
General methods and materials

[00461] All reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}) and Waters LCMS system (Waters 2489 UV/Visible Detector, Waters 3100 Mass, Waters 515 HPLC pump, Waters 2545 Binary Gradient Module, Waters Reagent Manager and Waters 2767 Sample Manager) using SunFire™ C_{18} column (4.6 × 50 mm, 5 µm particle size): solvent gradient = 100% A at 0 min, 1% A at 5 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate: 2.5 mL/min. Purification of reaction products was carried out by flash chromatography using CombiFlash®Rf with Teledyne Isco RediSep®Rf High Performance Gold or Silicycle SiliaSep™ High Performance columns (4 g, 12 g, 24 g, 40 g, or 80 g) and Waters LCMS system using SunFire™ Prep C_{18} column (19 × 50 mm, 5 µm particle size): solvent gradient = 80% A at 0 min, 10% A at 8 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate: 25 mL/min. The purity of all compounds was over 95% and was analyzed with Waters LCMS system. $^{1H\ NMR}$ and ^{13}C NMR spectra were obtained using a Varian INOVA-600 (600 MHz for ^{1}H, and 125 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform ($\delta = 7.24$) for $^{1H\ NMR}$ or dimethyl sulfoxide ($\delta = 2.50$) for $^{1H\ NMR}$ and dimethyl sulfoxide ($\delta = 39.51$) for ^{13}C NMR. Data are reported as (*br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet).

Example 1.1. Preparation of *N*-(3-(((2-((4-(4-(3-(2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)acetamido)propyl)piperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)methyl)phenyl)acrylamide

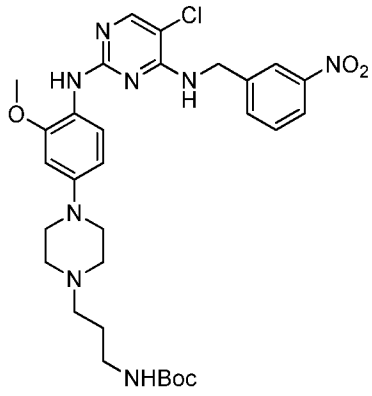


***Tert*-butyl 4-(4-((5-chloro-4-((3-nitrobenzyl)amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazine-1-carboxylate**



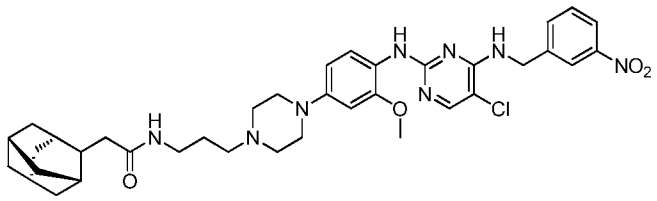
[00462] 2,5-Dichloro-*N*-(3-nitrobenzyl)pyrimidin-4-amine (150 mg, 0.5 mmol), *tert*-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (230 mg, 0.75 mmol), and trifluoroacetic acid (57 μL, 0.75 mmol) was combined in *sec*-butanol (5 mL) and stirred overnight at 100 °C. The mixture was then concentrated and purified by column chromatography (dichloromethane:methanol = 10:1) to yield 205 mg (72%) of the title product as a pale-yellow solid. MS (ESI) *m/z* 570 $(M+H)^+$.

***Tert-butyl* (3-(4-(4-((5-chloro-4-((3-nitrobenzyl)amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazin -1-yl)propyl)carbamate**



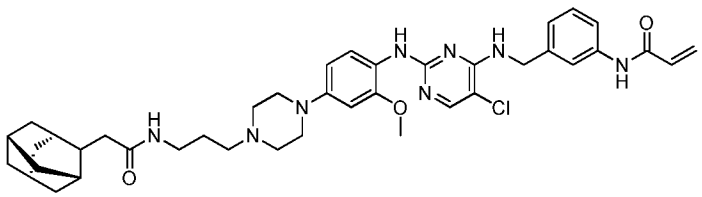
[00463] To tert-butyl 4-(4-((5-chloro-4-((3-nitrobenzyl)amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazine-1-carboxylate (170 mg, 0.3 mmol) in CH_2Cl_2 (6 mL) was added 0.6 mL trifluoroacetic acid. The mixture was stirred for 2 hr, concentrated, and dried *in vacuo*. To the obtained crude product in DMSO (3 mL) was added *tert*-butyl (3-bromopropyl)carbamate (86 mg, 0.36 mmol) and K_2CO_3 (83 mg, 0.6 mmol). The resulted mixture was stirred for 3 hr, diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (dichloromethane:methanol = 15:1) to yield 115 mg (61% for 2 steps) of the title product as a colorless oil. MS (ESI) *m/z* 627 $(M+H)^+$.

2-((1*R*,3*R*,5*R*,7*R*)-Adamantan-2-yl)-*N*-(3-(4-(4-((5-chloro-4-((3-nitrobenzyl)amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazin-1-yl)propyl)acetamide



[00464] To *tert*-butyl (3-(4-(4-((5-chloro-4-((3-nitrobenzyl) amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazin -1-yl)propyl)carbamate (95 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was added 0.3 mL trifluoroacetic acid. The mixture was stirred for 2 hr, concentrated, and dried *in vacuo*. To the obtained crude product in CH_2Cl_2 (3 mL) was added 2-((1*r*,3*r*,5*r*,7*r*)-adamantan-2-yl)acetyl chloride (40 mg, 0.18 mmol) and *N*,*N*-diisopropylethylamine (80 µL, 0.45 mmol) at 0 °C. The resulted mixture was stirred at RT for 2 hr, diluted with ethyl acetate, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (dichloromethane:methanol = 15:1) to yield 100 mg (95% for 2 steps) of the title product as a colorless oil. MS (ESI) *m/z* 703 $(M+H)^+$.

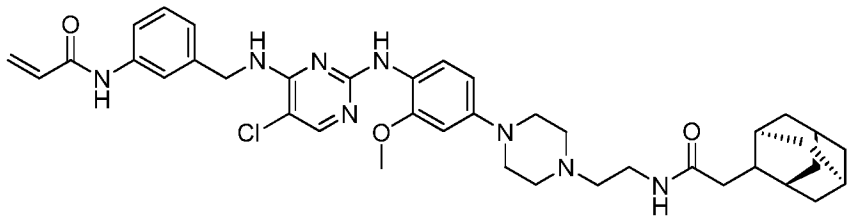
***N*-(3-(((2-((4-(4-(3-(2-((1*R*,3*R*,5*R*,7*R*)-adamantan-2-yl)acetamido)propyl)piperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)methyl)phenyl)acrylamide**



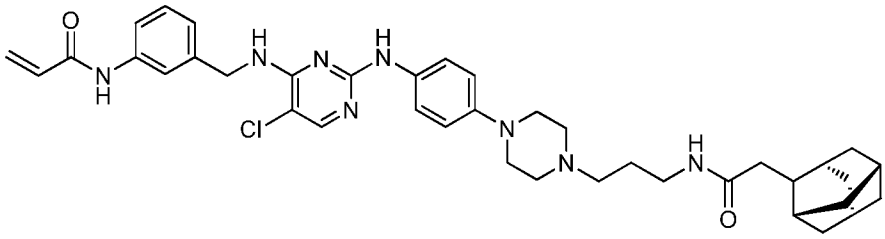
[00465] To 2-((1*R*,3*R*,5*R*,7*R*)-adamantan-2-yl)-*N*-(3-(4-(4-((5-chloro-4-((3-nitrobenzyl)amino)pyrimidin-2-yl)amino)-3-methoxyphenyl)piperazin-1-yl)propyl)acetamide (70 mg, 0.1 mmol) in MeOH (10 mL) was added 0.5 mL Raney nickel suspension in MeOH, and stirred for 3 hr under 1 atm of hydrogen. The mixture was then filtered with CELITE, and the filtrate was concentrated and dried under vacuum to give a crude product as a white solid. To the obtained white solid in DMF (2 mL) was added *N*,*N*-diisopropylethylamine (27 µL, 0.15 mmol), the stirred mixture was then cooled to -60 °C and added acryloyl chloride (8.9 µL, 0.11 mmol) dropwise. The reaction was stirred at -60 °C for 10 min, allowed to recover to RT gradually in 30 min, and purified by reverse phase HPLC to give 62 mg (TFA salt, 74% for 2 steps) of the title compound as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H), 7.90 (s, 1H), 7.89 (s, 1H), 7.81 (m, 1H), 7.69 (m, 1H), 7.67 (s, 1H), 7.59 (d, *J*

= 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.36 (s, 1H), 7.25 (dd, *J* = 8.4, 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.55 (s, 1H), 6.44 (dd, *J* = 16.8, 10.2 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 16.8 Hz, 1H), 5.74 (d, *J* = 10.2 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.01-3.09 (m, 6H), 2.47 (m, 4H), 2.33 (m, 2H), 1.91 (s, 3H), 1.67 (s, 1H), 1.65 (s, 2H), 1.59 (s, 3H), 1.56 (s, 8H). MS (ESI) *m/z* 727 $(M+H)^+$.

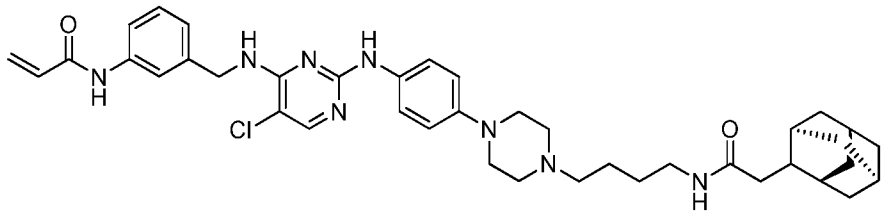
Analytical data of additional exemplary compounds



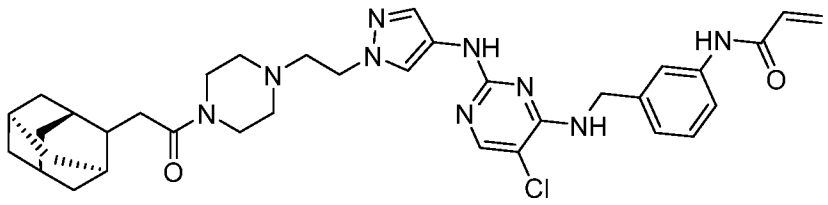
[00466] ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.90 (s, 1H), 7.80 (m, 1H), 7.65 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.58 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.25 (dd, *J* = 8.4, 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.55 (s, 1H), 6.44 (dd, *J* = 16.8, 10.2 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 6.25 (d, *J* = 16.8 Hz, 1H), 5.75 (d, *J* = 10.2 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 3.77 (s, 3H), 3.18 (m, 2H), 3.04 (m, 4H), 2.38 (m, 2H), 1.90 (s, 3H), 1.82 (s, 2H), 1.65 (s, 1H), 1.63 (s, 2H), 1.57 (s, 9H). MS (ESI) *m/z* 713 $(M+H)^+$.



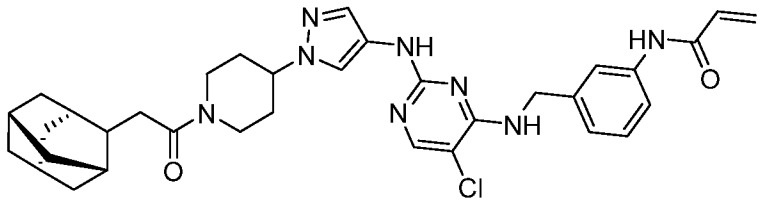
[00467] ^{1}H NMR (600 MHz, TFA salt, DMSO-d_6) δ 10.18 (s, 1H), 9.62 (br, 1H), 9.41 (br, 1H), 8.24 (br, 1H), 8.02 (s, 1H), 7.90 (m, 1H), 7.68 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.84 (s, 1H), 6.83 (s, 1H), 6.44 (dd, *J* = 16.8, 10.2 Hz, 1H), 6.26 (d, *J* = 16.8 Hz, 1H), 5.76 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.69 (m, 2H), 3.53 (m, 2H), 3.11 (m, 4H), 2.89 (m, 2H), 1.91 (s, 3H), 1.84 (s, 2H), 1.81 (m, 1H), 1.67 (s, 1H), 1.65 (s, 2H), 1.58 (s, 2H), 1.56 (s, 6H). MS (ESI) *m/z* 697 $(M+H)^+$.



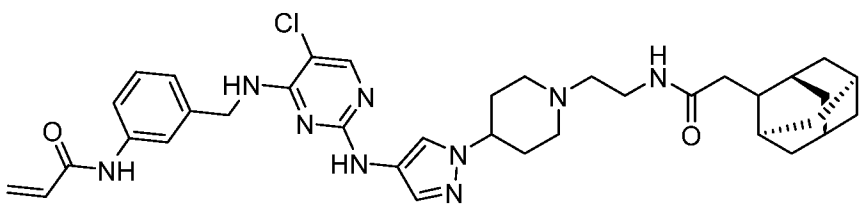
[00468] ^{1}H NMR (600 MHz, TFA salt, DMSO-d_6) δ 10.11 (s, 1H), 9.59 (br, 1H), 9.32 (br, 1H), 8.15 (br, 1H), 7.93 (s, 1H), 7.76 (m, 1H), 7.68 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 6.83 (s, 1H), 6.45 (dd, *J* = 16.8, 10.2 Hz, 1H), 6.26 (d, *J* = 16.8 Hz, 1H), 5.77 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 2H), 3.69 (m, 2H), 3.52 (m, 2H), 3.16 (m, 2H), 3.11 (m, 2H), 3.06 (m, 2H), 2.89 (m, 2H), 1.91 (s, 3H), 1.83 (s, 2H), 1.67 (s, 2H), 1.67 (s, 2H), 1.65 (s, 3H), 1.58 (s, 2H), 1.56 (s, 7H), 1.44 (s, 2H). MS (ESI) *m/z* 711 $(M+H)^+$.



[00469] MS (ESI) m/z 658 (M+H)+.



[00470] ^{1}H NMR (600 MHz, TFA salt, DMSO-d6) δ 10.15 (s, 1H), 9.61 (br, 1H), 8.39 (br, 1H), 8.04 (m, 1H), 7.59 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.35 (m, 1H), 7.28 (dd, J = 8.4, 7.8 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.42 (dd, J = 16.8, 10.8 Hz, 1H), 6.24 (d, J = 16.8 Hz, 1H), 5.73 (d, J = 10.8 Hz, 1H), 4.67 (d, J = 5.4 Hz, 1H), 4.49 (m, 2H), 4.02 (m, 2H), 3.09 (m, 1H), 2.62 (m, 1H), 2.21 (d, J = 13.2 Hz, 1H), 2.04 (d, J = 14.4 Hz, 1H), 1.92 (m, 2H), 1.43-1.88 (m, 19H). MS (ESI) m/z 629 (M+H)+.



[00471] ^{1}H NMR (600 MHz, TFA salt, DMSO-d6) δ 10.15 (s, 1H), 9.42 (br, 1H), 8.05 (m, 1H), 8.02 (m, 1H), 7.62 (s, 1H), 7.54 (m, 1H), 7.41 (m, 1H), 7.32 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.42 (dd, J = 16.8, 10.8 Hz, 1H), 6.24 (d, J = 16.8 Hz, 1H), 5.73 (d, J = 10.8 Hz, 1H), 4.66 (br, 1H), 3.65 (m, 2H), 3.42 (m, 2H), 3.14 (m, 3H), 2.08 (m, 4H), 1.93 (m, 3H), 1.88 (s, 2H), 1.52-1.70 (m, 12H). MS (ESI) m/z 672 (M+H)+.

Example 2. Biological Assays

In vitro activity assays

[00472] The *in vitro* activity of the compounds described herein in inhibiting JAK3 and other kinases were obtained using an INVITROGEN Select Screening assay as known in the art. The enzymatic IC_{50} values determined from this assay are shown in *Table 1.*

Cell proliferation analysis

CellTiter-Glo® Luminescent cell viability assay (Promega) was used to assess cell survival following treatment with the compounds described herein. 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 to 0.04 μM) for 72 hours at 37 °C. Luminescent measurement is performed using the 2104 Envision® Multilabel Reader (PerkinElmer Inc.). The cell lines employed include Ba/F3 (a murine interleukin-3 dependent pro-B cell line), NKL (a Natural Killer Cell Lymphoma (NKCL) cell line), CMK (an Acute Megakaryoblastic Leukemia (AMKL) cell line). The results are shown in *Table 1.*

Table 1. Exemplary biological assay results of exemplary compounds

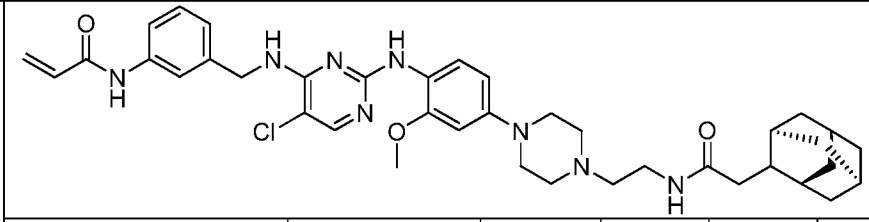
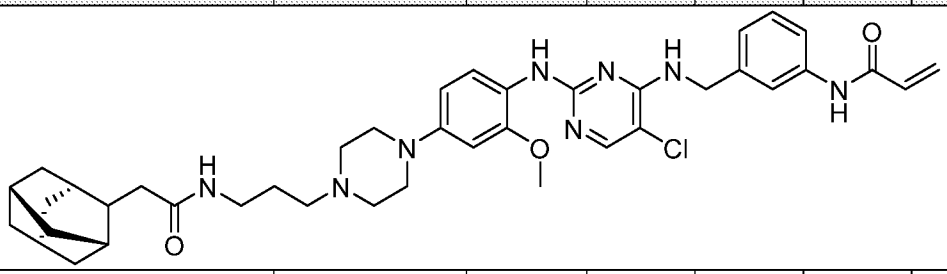
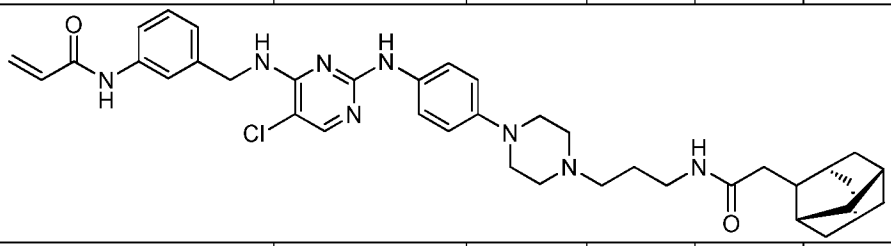
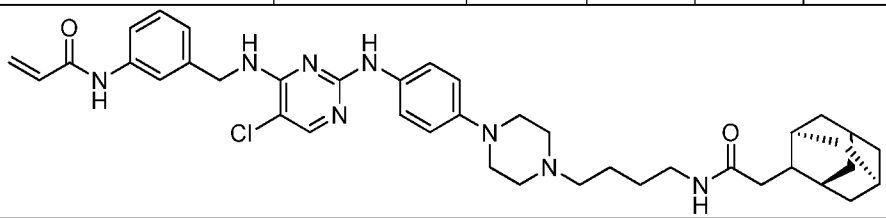
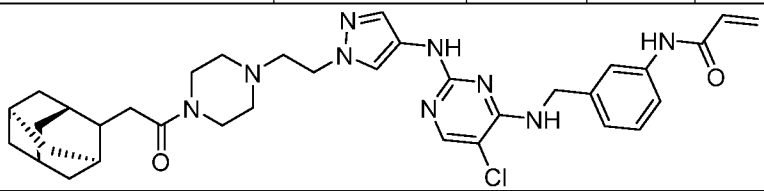
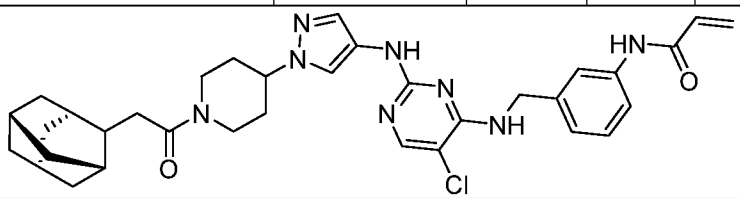
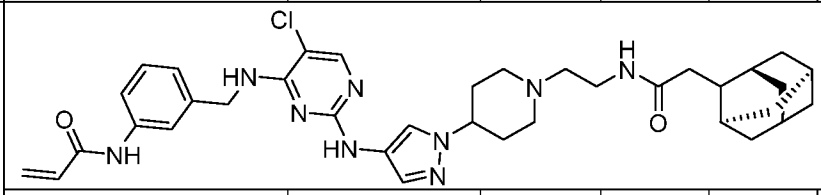
Compound	Enzy-matic IC_{50} (nM)	Ba/F3 IC_{50} (nM)					Cancer cell lines IC_{50} (nM)	
	JAK3	JAK3	JAK1	JAK2	TYK2	ABL	NKL	CMK
1								
	55.5	482	4043	8336	2992	7954	-	726

Table 1. Exemplary biological assay results of exemplary compounds

Compound	Enzy-matic IC_{50} (nM)	Ba/F3 IC_{50} (nM)					Cancer cell lines IC_{50} (nM)	
	JAK3	JAK3	JAK1	JAK2	TYK2	ABL	NKL	CMK
2								
	45	382	3353	3110	1820	3040	193	273
3								
	12.8	72.7	1120	1215	542	2263	-	490
4								
	7.95	64.8	252	415	372	623	-	38
5								
	4.9	94	1107	1371	676	1973	-	-
6								
	5.9	38	2084	3176	1.644	3.858	-	-
7								
	6.8	105	954	1443	794	2275	-	-

[00473] The results show that compounds of the present disclosure, such as compound **2**, are highly selective inhibitors of JAK3. For example, compound **2** showed a high degree of

specificity for JAK3 relative to other JAK isoforms in Ba/F3 proliferation assays (IC_{50} for JAK1 = 3353 nM, JAK2 = 3110 nM, JAK3 = 45 nM). In addition, compound **2** has shown strong anti-proliferation potency against CMK cells (IC50 = 273nM). This suggests the adamantyl group is making a strong contribution to the pharmacology of this inhibitor, likely by means of interrupting the JAK1/JAK3 heterodimer.

EQUIVALENTS AND SCOPE

[00474] 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.

[00475] 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.

[00476] This application refers to various issued patents, published patent applications,

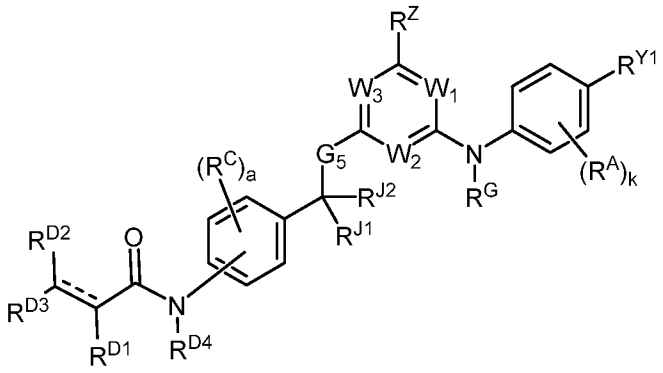
journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within 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.

[00477] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

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

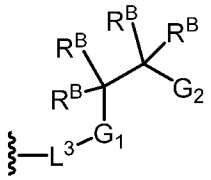


(**I**),

or a pharmaceutically acceptable salt thereof,

wherein:

W_1 is N, W_2 is N and W_3 is CR^X, or W_1 is N, W_2 is CH, and W_3 is N;

R^{Y1} is a group of formula  or $-L^1-R^H$;

L^3 is a bond or a linker selected from the group consisting of substituted and unsubstituted C_{1-6}alkylene, substituted and unsubstituted C_{2-6}alkenylene, substituted and unsubstituted C_{2-6}alkynylene, substituted and unsubstituted heteroC_{1-6}alkylene, substituted and unsubstituted heteroC_{2-6}alkenylene, and substituted and unsubstituted heteroC_{2-6}alkynylene;

G_1 is NR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H, O-L^1-R^H, or $C(R^{G2a})$-L^1-R^H; or G_1 is CHR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H or O-L^1-R^H;

each instance of R^{G1a} and R^{G2a} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or R^{G1a} and one instance of R^{G2a} are joined to form the group $-C(R^B)_2$-$C(R^B)_2$-;

L^1 is a linker selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene,

substituted and unsubstituted heteroalkynylene, substituted and unsubstituted heterocyclylene, substituted and unsubstituted carbocyclylene, substituted and unsubstituted arylene, substituted and unsubstituted heteroarylene, and combinations thereof;

R^H is a hydrophobic group selected from the group consisting of substituted and unsubstituted aryl, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heteroarylalkyl, substituted and unsubstituted carbocycylalkyl, and substituted and unsubstituted heterocyclylalkyl;

==== represents a single or double bond;

each instance of R^{D1}, R^{D2}, and R^{D3} is independently hydrogen or substituted or unsubstituted alkyl;

R^{D4} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

G^5 is O, S, or NR^E ;

each instance of R^E and R^G is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

each instance of R^{J1} and R^{J2} is independently hydrogen, halogen, or substituted or unsubstituted alkyl;

each instance of R^A and R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$;

each instance of R^B is independently hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$; or two R^B groups attached to the same carbon atom are joined to form a =O group;

each instance of R^{A1} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, a nitrogen protecting group when attached to a nitrogen atom, an oxygen protecting group when attached to an oxygen atom, or a sulfur protecting group when attached to a sulfur atom, or two R^{A1} groups are joined to

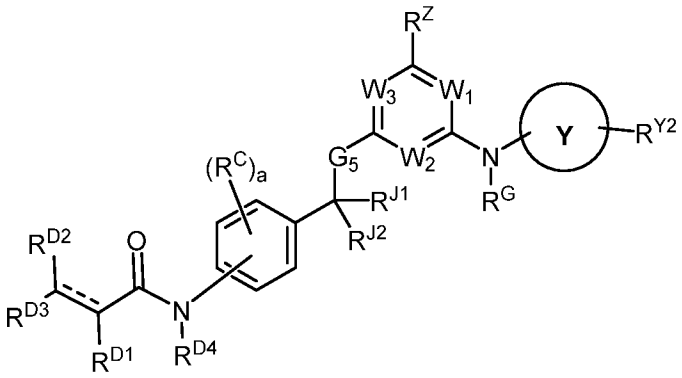
form a substituted or unsubstituted heterocyclic or substituted or unsubstituted heteroaryl ring;

a and k are each independently 0, 1, or 2, provided when k is 0, then R^A is absent, and when a is 0, then R^C is absent; and

each instance of R^X and R^Z is independently hydrogen, halogen, substituted or unsubstituted alkyl, cyclopropyl, -CN, $–OR^{X1}$, or $–NHR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to an oxygen, or a nitrogen protecting group when attached to a nitrogen, or R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring;

or R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered heterocyclic ring.

2. A compound of Formula (**II**):

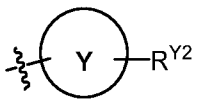


(**II**)

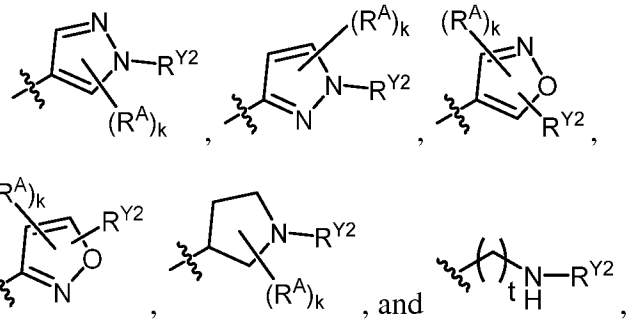
or a pharmaceutically acceptable salt thereof,

wherein:

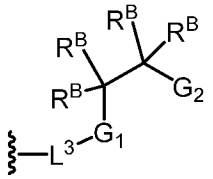
W_1 is N, W_2 is N and W_3 is CR^X, or W_1 is N, W_2 is CH, and W_3 is N;



is selected from the group consisting of:



wherein t is 2, 3, 4, 5, or 6;

R^{Y2} is a group of formula  or $-L^1-R^H$;

L^3 is a bond or a linker selected from the group consisting of substituted and unsubstituted C_{1-6}alkylene, substituted and unsubstituted C_{2-6}alkenylene, substituted and unsubstituted C_{2-6}alkynylene, substituted and unsubstituted heteroC_{1-6}alkylene, substituted and unsubstituted heteroC_{2-6}alkenylene, and substituted and unsubstituted heteroC_{2-6}alkynylene;

G_1 is NR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H, O-L^1-R^H, or $C(R^{G2a})$-L^1-R^H; or G_1 is CHR^{G1a} and G_2 is $N(R^{G2a})$-L^1-R^H or O-L^1-R^H;

each instance of R^{G1a} and R^{G2a} is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted hydroxyl, a nitrogen protecting group when attached to a nitrogen atom, or an oxygen protecting group when attached to an oxygen atom, or R^{G1a} and one instance of R^{G2a} are joined to form the group $-C(R^B)_2$-$C(R^B)_2$-;

L^1 is a linker selected from the group consisting of substituted and unsubstituted alkylene, substituted and unsubstituted alkenylene, substituted and unsubstituted alkynylene, substituted and unsubstituted heteroalkylene, substituted and unsubstituted heteroalkenylene, substituted and unsubstituted heteroalkynylene, substituted and unsubstituted heterocyclylene, substituted and unsubstituted carbocyclylene, substituted and unsubstituted arylene, substituted and unsubstituted heteroarylene, and combinations thereof;

R^H is a hydrophobic group selected from the group consisting of substituted and unsubstituted aryl, substituted and unsubstituted heteroaryl, substituted and unsubstituted carbocyclyl, substituted and unsubstituted heterocyclyl, substituted and unsubstituted aralkyl, substituted and unsubstituted heteroarylalkyl, substituted and unsubstituted carbocycylalkyl, and substituted and unsubstituted heterocyclylalkyl;

---- represents a single or double bond;

each instance of R^{D1}, R^{D2}, and R^{D3} is independently hydrogen or substituted or unsubstituted alkyl;

R^{D4} is hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

G^5 is O, S, or NR^E ;

each instance of R^E and R^G is independently hydrogen, substituted or unsubstituted alkyl, or a nitrogen protecting group;

each instance of R^{J1} and R^{J2} is independently hydrogen, halogen, or substituted or unsubstituted alkyl;

each instance of R^A and R^C is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$;

each instance of R^B is independently halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, $–OR^{A1}$, $–N(R^{A1})_2$, $–SR^{A1}$, –CN, –SCN, $–C(=NR^{A1})R^{A1}$, $–C(=NR^{A1})OR^{A1}$, $–C(=NR^{A1})N(R^{A1})_2$, $–C(=O)R^{A1}$, $–C(=O)OR^{A1}$, $–C(=O)N(R^{A1})_2$, $–NO_2$, $–NR^{A1}C(=O)R^{A1}$, $–NR^{A1}C(=O)OR^{A1}$, $–NR^{A1}C(=O)N(R^{A1})_2$, $–OC(=O)R^{A1}$, $–OC(=O)OR^{A1}$, or $–OC(=O)N(R^{A1})_2$; or two R^B groups attached to the same carbon atom are joined to form a =O group;

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

a and k are each independently 0, 1, or 2, provided when k is 0, then R^A is absent, and when a is 0, then R^C is absent; and

each instance of R^X and R^Z is independently hydrogen, halogen, substituted or unsubstituted alkyl, cyclopropyl, -CN, $–OR^{X1}$, or $–NHR^{X1}$, wherein R^{X1} is hydrogen, substituted or unsubstituted alkyl, an oxygen protecting group when attached to an oxygen, or a nitrogen protecting group when attached to a nitrogen, or R^X and R^Z are joined to form a substituted or unsubstituted 5-membered heterocyclic ring;

or R^X and R^E are joined to form a substituted or unsubstituted 5- to 6-membered heterocyclic ring.

3. The compound of claim 1 or 2, wherein G_1 is NR^{G1a}.

4. The compound of claim 1 or 2, wherein G_1 is CHR^{G1a}.

5. The compound of claim 1-4, wherein G_2 is $N(R^{G2a})$-L^1-R^H.

6. The compound of claim 1-4, wherein G_2 is or O-L^1-R^H.

7. The compound of claim 1-5, wherein R^{G1a} and one instance of R^{G2a} are joined to form the group $–C(R^B)_2$-$C(R^B)_2–$.

8. The compound of claim 1 or 2, wherein ==== represents a single bond.

9. The compound of claim 1 or 2, wherein ==== represents a double bond.

10. The compound of claim 1-5, wherein R^{G2a} is hydrogen or substituted unsubstituted C_{1-6} alkyl.

11. The compound of claim 1 or 2, wherein L^3 is a bond or unsubstituted $C_{1–3}$alkylene.

12. The compound of claim 1 or 2, wherein at least one instance of R^A is substituted or unsubstituted C_{1-6} alkyl.

13. The compound of claim 1 or 2, wherein R^G is hydrogen or $–CH_3$.

14. The compound of claim 1 or 2, wherein R^X is hydrogen, -F, -Br, -Cl, –CN, or $–OR^{X1}$.

15. The compound of claim 1 or 2, wherein G^5 is NR^E; and R^E is hydrogen or $–CH_3$.

16. The compound of claim 1 or 2, wherein both R^{J1} and R^{J2} are hydrogen.

17. The compound of claim 1 or 2, wherein a is 0.

18. The compound of claim 1 or 2, wherein a is 1.

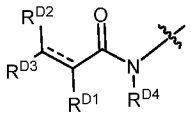
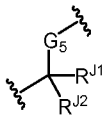
19. The compound of claim 1 or 2, wherein a is 2.

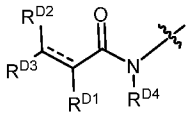
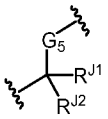
20. The compound of claim 1 or 2, wherein a is 1 or 2 and at least one instance of R^C is halogen.

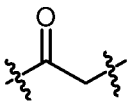
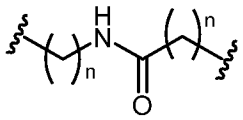
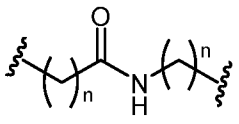
21. The compound of claim 1 or 2, wherein each of R^{D1}, R^{D2}, and R^{D3} is hydrogen.

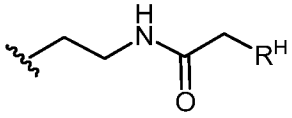
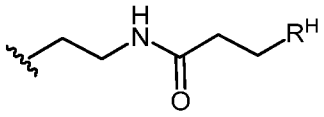
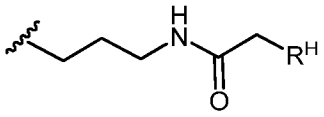
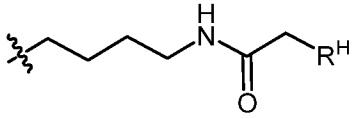
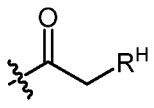
22. The compound of claim 1, 2, or 21 wherein R^{D3} is $–CH_2N(R^{D1a})_2$ or $–CH_2OR^{D1a}$.

23. The compound of claim 1, 2, 21, or 22, wherein R^{D4} is hydrogen.

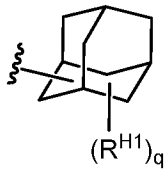
24. The compound of claim 1, 2, 21, 22, or 23, wherein the group  is attached *meta* to the point of attachment .

25. The compound of claim 1, 2, 21, 22, or 23, wherein the group  is attached *para* to the point of attachment .

26. The compound of claim 1 or 2, wherein L^1 is ,  or ; and each instance of n is independently 1, 2, 3, or 4.

27. The compound of claim 1 or 2, wherein $–L^1–R^H$ represents a group of the formula: , , , , or .

28. The compound of claim 1, 2, or 27 wherein R^H is:



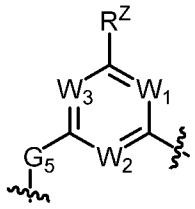
wherein:

each occurrence of R^{H1} is independently halogen, –CN, substituted or unsubstituted C_{1-6} alkyl, $–OR^{H1a}$, or $–N(R^{H1a})_2$, wherein each instance of R^{H1a} is independently substituted or unsubstituted C_{1-6} alkyl; and

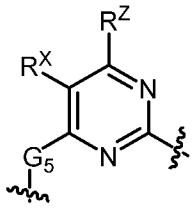
q is 0, 1, 2, or 3.

29. The compound of claim 28, wherein q is 0.

30. The compound of claim 1 or 2, wherein the ring system:

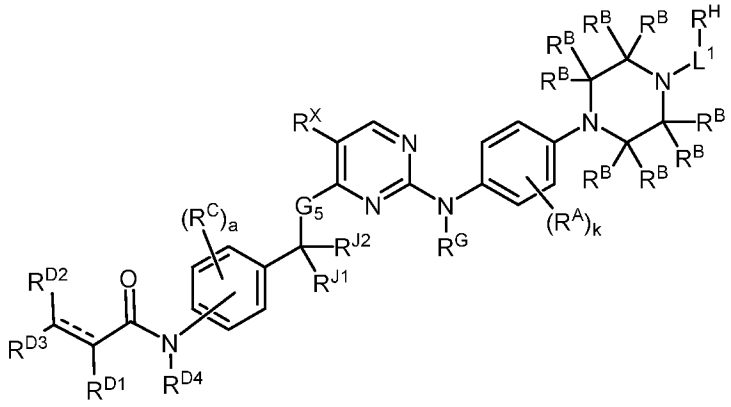


is of the formula:



.

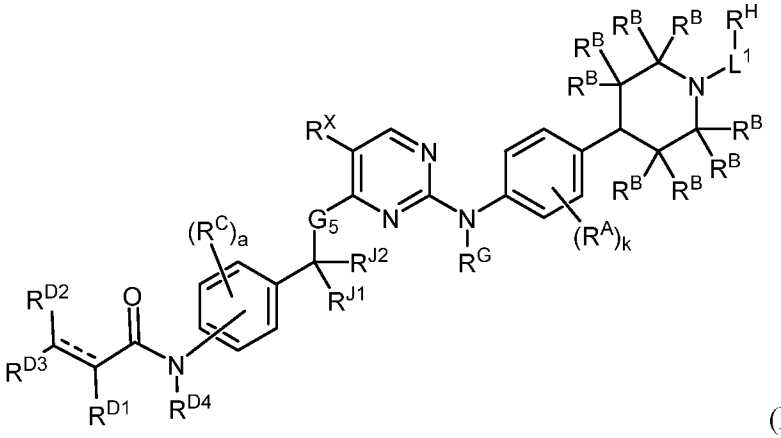
31. The compound of claim 1 of the formula:



(**Ia**),

or a pharmaceutically acceptable salt thereof.

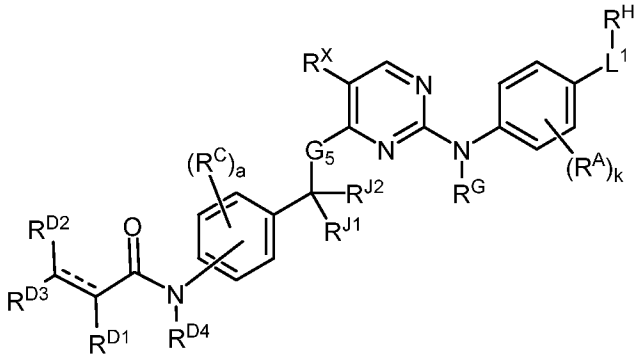
32. The compound of claim 1 of the formula:



(**Ib**),

or a pharmaceutically acceptable salt thereof.

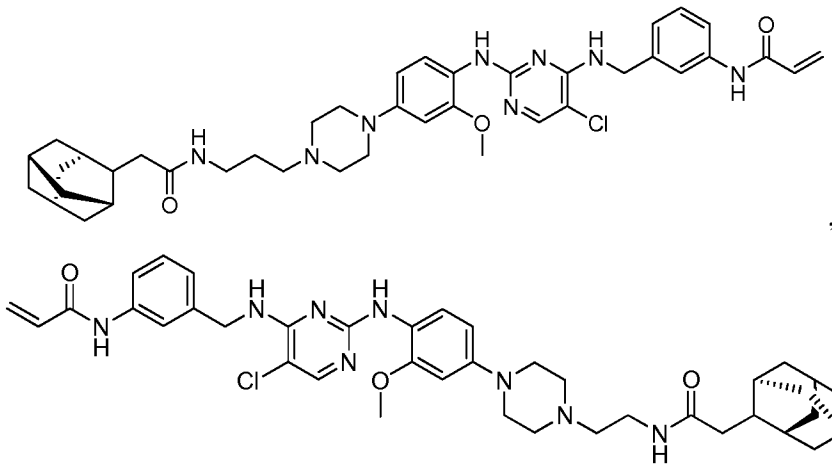
33. The compound of claim 1 of the formula:



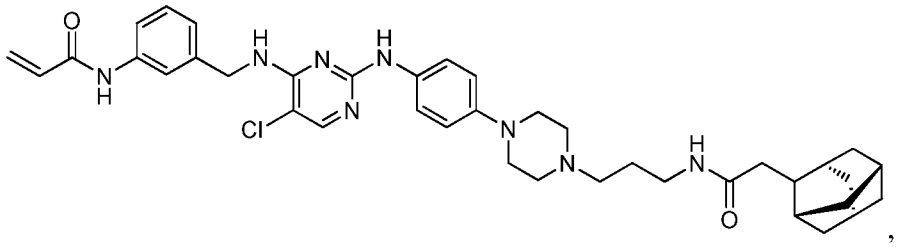
(**Ic**),

or a pharmaceutically acceptable salt thereof.

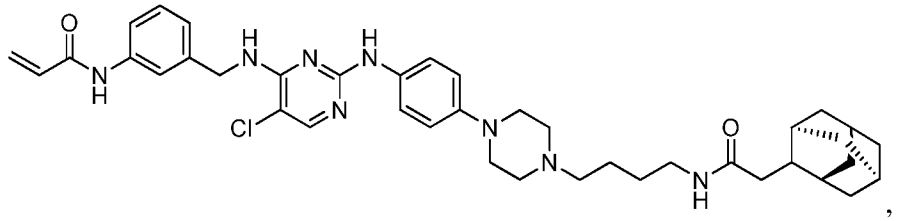
34. The compound of claim 1 selected from the group consisting of:



,



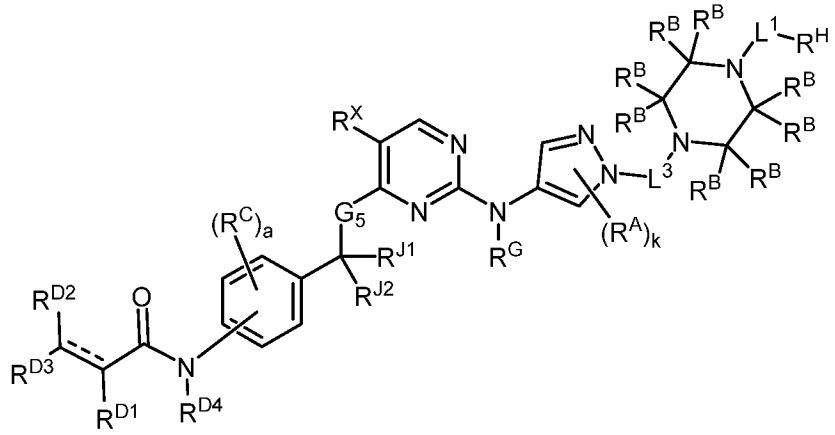
,



,

and pharmaceutically acceptable salts thereof.

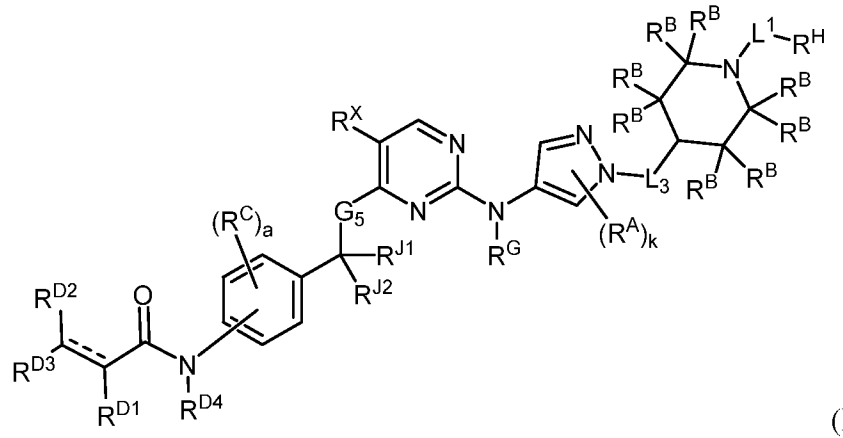
35. The compound of claim 2 of the formula:



(**IIa**),

or a pharmaceutically acceptable salt thereof.

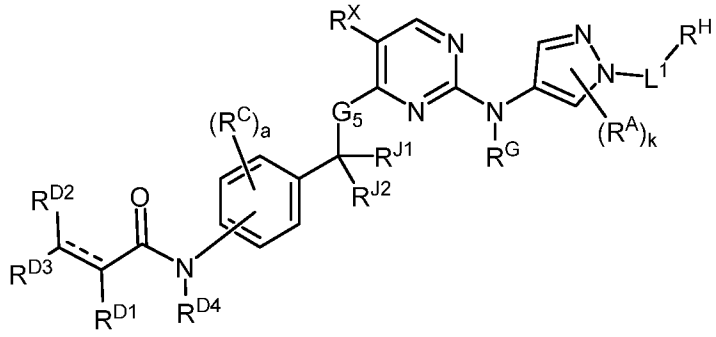
36. The compound of claim 2 of the formula:



(**IIb**),

or a pharmaceutically acceptable salt thereof.

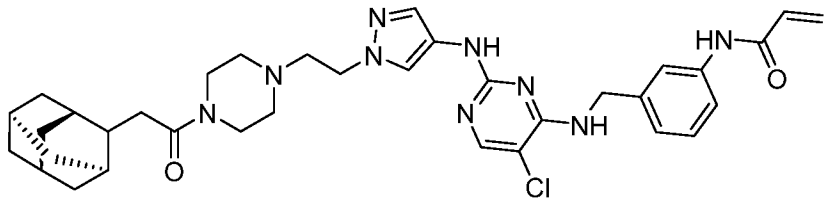
37. The compound of claim 1 of the formula:



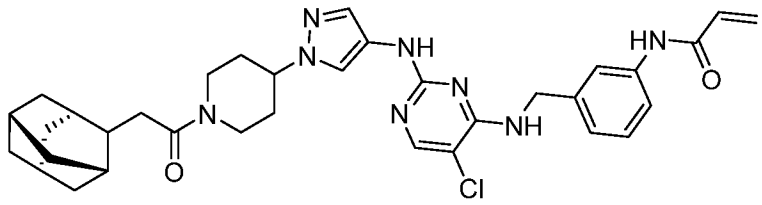
(**IIc**),

or a pharmaceutically acceptable salt thereof.

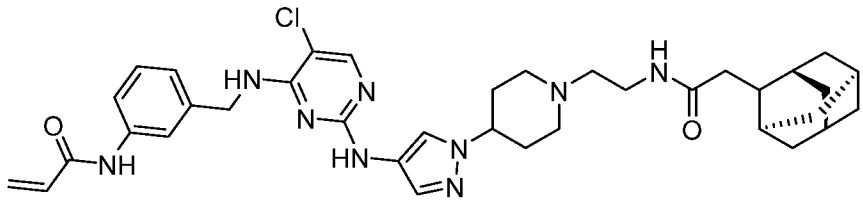
38. The compound of claim 2 selected from the group consisting of:



,



,



,

and pharmaceutically acceptable salts thereof.

39. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

40. A method of reducing the activity of a kinase in a subject in need thereof, the method comprising administering to the subject a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39, in an amount sufficient to reduce the activity of the kinase.

41. A method of treating a condition associated with aberrant activity of a kinase in a subject in need thereof, the method comprising administering to the subject a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39, in an amount sufficient to treat the condition.

42. The method of claim 40 or 41, wherein the kinase is a protein kinase.

43. The method of claim 42, wherein the protein kinase is a tyrosine kinase.

44. The method of claim 43, wherein the tyrosine kinase is a non-receptor tyrosine kinase.

45. The method of claim 44, wherein the non-receptor tyrosine kinase is a Janus kinase (JAK).

46. The method of claim 45, wherein the Janus kinase is Janus kinase 3 (JAK3).

47. The method of claim 46, wherein the activity of Janus kinase 3 (JAK3) is selectively reduced by the compound, or pharmaceutically acceptable salt thereof, compared to a kinase other than JAK3.

48. The method of claim 47, wherein the kinase other than JAK3 is Janus kinase 1 (JAK1) or Janus kinase 2 (JAK2).

49. The method of claim 43, wherein the tyrosine kinase is a receptor tyrosine kinase (RTK).

50. The method of claim 49, wherein the receptor tyrosine kinase is an epidermal growth factor receptor (EGFR) tyrosine kinase.

51. The method of any one of the preceding claims, wherein the condition is a proliferative disease, inflammatory disorder, autoimmune disorder, painful condition, or viral infection.

52. A kit comprising:

a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 39; and

instructions for using the kit.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/27294

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/505, 31/506; C07D 403/12 (2015.01)
CPC - C07D 401/14, 403/12, 403/14
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/505, 31/506; C07D 403/12 (2015.01)
CPC: C07D 401/14, 403/12, 403/14 USPC: 514/252.19, 275; 544/323

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Google Scholar; IP.com; EBSCO; SureChem; KEYWORDS: ortho substit* pyrimidin*, JAK* inhibit*, JAK1, JAK2, JAK3, EGFR, pyrimidin 2 ylamino, 5 chloro, piperidin*, piperazin*, pyrazin*, treat*, proliferative disease*, amino substit* pyrimidin*, 3 methoxyphenyl, kit*, instruct* use, 2 4 diaminopyrimidine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0329771 A1 (TREU, M et al.) 27 December 2012; page 74, see structure G1-27; page 90, see structure G1-42	1-2, 3/1-2, 4/1-2, 8/1-2, 9/1-2, 11/1-2, 12/1-2, 13/1-2, 14/1-2, 15/1-2, 16/1-2, 17/1-2, 18/1-2, 19/1-2, 20/1-2, 21/1-2, 26/1-2, 27/1-2, 30/1-2, 31-38
A	WO 2009/032694 A1 (DANA FARBER CANCER INSTITUTE) 12 March 2009; page 50, see compound No. 2-11	1, 3/1, 4/1, 8/1, 9/1, 11/1, 12/1, 13/1, 14/1, 15/1, 16/1, 17/1, 18/1, 19/1, 20/1, 21/1, 26/1, 27/1, 30/1, 31-34, 37
A	US 2011/0098280 A1 (GARCIA-ECHEVERRIA, C et al.) 28 April 2011; page 258, see compound No. 426	1, 3/1, 4/1, 8/1, 9/1, 11/1, 12/1, 13/1, 14/1, 15/1, 16/1, 17/1, 18/1, 19/1, 20/1, 21/1, 26/1, 27/1, 30/1, 31-34, 37
A	WO 2013/014162 A1 (CELLZOME) 31 January 2013; page 84, see compound 94	2, 3/2, 4/2, 8/2, 9/2, 11/2, 12/2, 13/2, 14/2, 15/2, 16/2, 17/2, 18/2, 19/2, 20/2, 21/2, 26/2, 27/2, 30/2, 35, 36, 38

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2015 (14.06.2015)	10 JUL 2015
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/27294

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-7, 10, 22-25, 28-29 and 39-52
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/27294

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2014/063061 A1 (DANA-FARBER CANCER INSTITUTE et al.) 24 April 2014; entire document	1-2, 3/1-2, 4/1-2, 8/1-2, 9/1-2, 11/1-2, 12/1-2, 13/1-2, 14/1-2, 15/1-2, 16/1-2, 17/1-2, 18/1-2, 19/1-2, 20/1-2, 21/1-2, 26/1-2, 27/1-2, 30/1-2, 31-38