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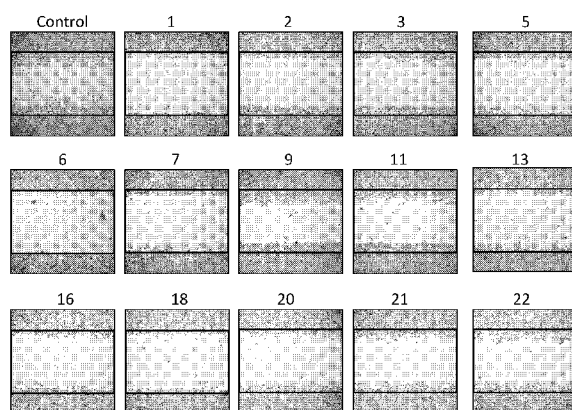
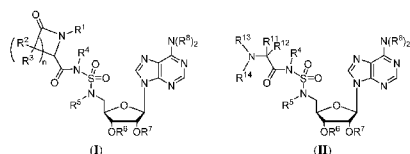
(54) **Title:** SULFANIDE ADENOSINE DERIVATIVES AND USES THEREOF

Figure 5

(57) **Abstract:** Described herein are sulfamide adenosine derivatives of Formula (I) or (II), and pharmaceutically acceptable salts, and pharmaceutical compositions thereof. Also provided are methods, uses, and kits involving the inventive compounds or pharmaceutical compositions for treating and/or preventing proliferative diseases (e.g., cancers, inflammatory diseases, and autoimmune diseases) or infectious diseases (e.g., bacterial infections, viral infections, fungal infections, and parasitic diseases) in a subject. The compounds and pharmaceutical compositions as described herein are thought to inhibit aminoacyl tRNA synthetase activity in a biological sample or subject to achieving the treatment of proliferative diseases or infectious diseases.



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SULFAMIDE ADENOSINE DERIVATIVES AND USES THEREOF

Related Applications

[0001] The present invention claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/174,362, filed June 11, 2015, which is incorporated herein by reference.

Government Support

[0002] This invention was made with government support under the grant number UL1 TR00064 from the National Institutes of Health (NIH). The government has certain rights in the invention.

Background of the Invention

[0003] The aminoacyl tRNA synthetase enzymes (aaRSs) are a large family of synthetases that play a fundamental role in protein biosynthesis processes [1]. All aaRSs use ATP to generate an activated form of the cognate amino acid—a mixed carbon-phosphorus anhydride termed aminoacyl adenylate (aaAMP), which is a key intermediate in protein biosynthesis. Because of their critical roles, the mimics of natural aaAMPs can serve as important aminoacyl tRNA synthetase inhibitors and consequently may possess significant biological activities such as anticancer or antiviral activity. One of the synthetic methods towards aaAMP derivatives involves replacement of the high-energy mixed anhydride acylphosphate bond with the more stable and non-hydrolyzable bioisosteres [2]. For example, alkylphosphate [3], ester [4,5], hydroxamate [5], N-hydroxysulfamide [6], sulfamide [6,7], β -ketophosphonate [8], sulfamate [6,9], and sulfonamide [10] linkers have been used for that purpose.

[0004] Aminoacyl sulfamides are a class of stable structural mimics of aaAMPs and generally have submicromolar K_i values for their corresponding synthetases [11,12]. Although recently several types of synthetic derivatives of aminoacyl adenylates have been reported, novel aminoacyl sulfamides with improved therapeutics properties against various diseases hold great promise in drug development.

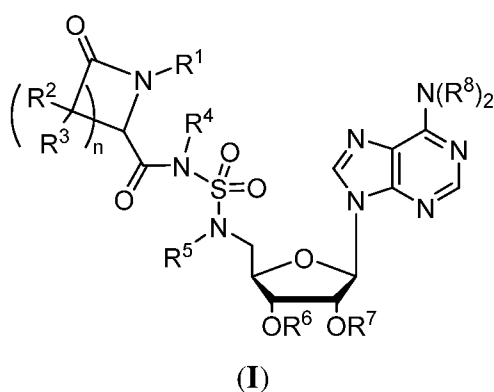
Summary of the Invention

[0005] Aminoacyl-tRNA synthetases (aaRS) are central enzymes in protein production, providing the charged tRNAs needed for appropriate construction of peptide chains. Once

these enzymes are inhibited, protein biosynthesis is halted, which in turn results in the attenuation of bacterial or cell growth (Tao *et al.*, *Proc. Natl. Acad. Sci. USA* 2000, 97:783-786). Therefore, these enzymes are appealing anticancer and antibacterial drug targets. The present disclosure relates to the development of sulfamide adenosine derivatives for the treatment and/or prevention of proliferative disorders such as cancer. This present disclosure also relates to sulfamide adenosine derivatives for the treatment and/or prevention of infectious diseases such as bacterial infections and viral infections.

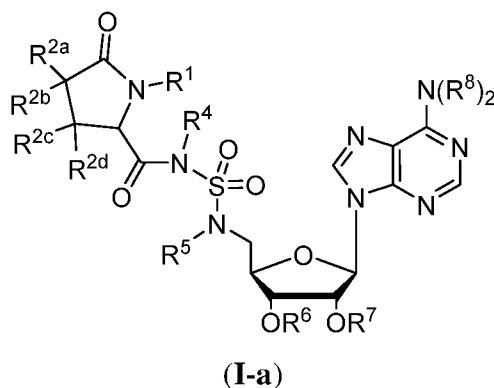
[0006] The present invention provides compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. The present invention also provides compounds of Formula (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. The present invention further provides methods of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and pharmaceutical compositions thereof, to prevent and/or treat proliferative diseases, such as cancers (*e.g.*, leukemia, breast cancer, lung cancer, colon cancer, or cervical cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases in a subject. The present invention also provides methods of using the inventive compounds, and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and pharmaceutical compositions thereof, to prevent and/or treat an infectious disease (*e.g.*, a bacterial infection, a viral infection, a fungal infection, or a parasitic disease) in a subject.

[0007] In one aspect, the present invention provides compounds of Formula (I):



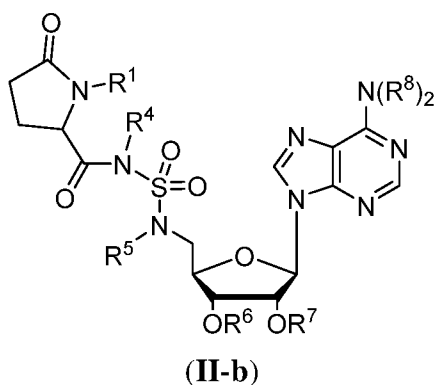
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and n are as defined herein.

[0008] In another aspect, the present invention provides compounds of Formula **(I-a)**:



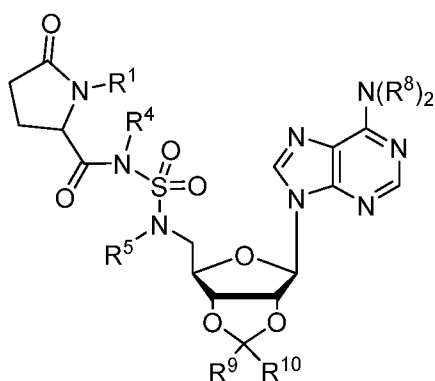
and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^1 , R^{2a} , R^{2b} , R^{2c} , R^{2d} , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein.

[0009] In one aspect, the present invention provides compounds of Formula **(II-b)**:



and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein.

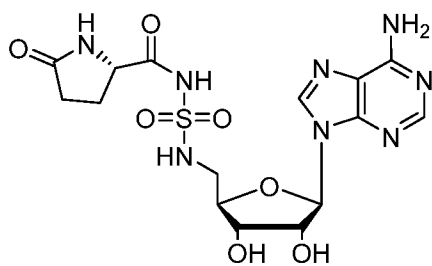
[00010] In one aspect, the present invention provides compounds of Formula (II-c):



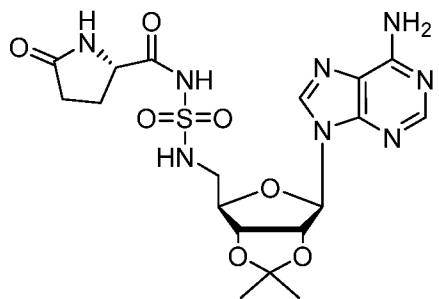
(II-c)

and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, wherein R^1 , R^4 , R^5 , R^9 , R^{10} , and R^8 are as defined herein.

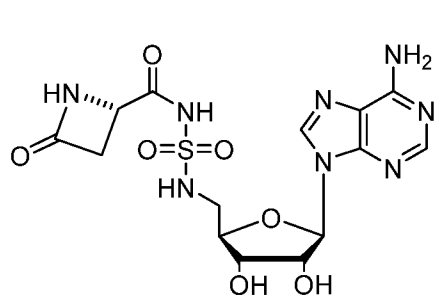
[00011] Exemplary compounds of Formula (I) include, but are not limited to:



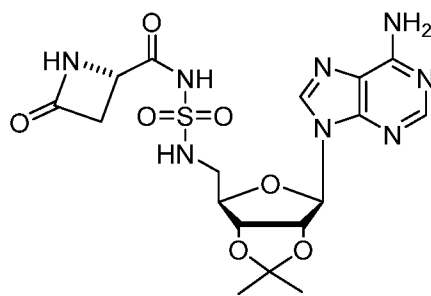
(L-Gln-lactam-SA, L-pGlu, or L-pGluSA),



,



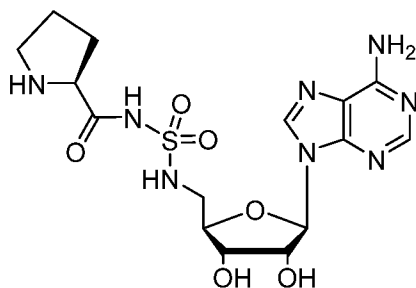
, and



.

Compound Number		R ^{II}
Arg-SA	Arg or ArgSA	-CH ₂ CH ₂ CH ₂ NHC(=NH)NH ₂
Ala-SA	Ala or AlaSA	Me
Lys-SA	Lys or LysSA	-CH ₂ CH ₂ CH ₂ CH ₂ NH ₂
Val-SA	Val or ValSA	-CH ₂ (CH ₃) ₂
Leu-SA	Leu or LeuSA	-CH ₂ CH(CH ₃) ₂
His-SA	His or HisSA	(1 <i>H</i> -imidazol-4-yl)methyl
Thr-SA	Thr or ThrSA	-CH(OH)Me
Asp-SA	Asp or AspSA	-CH ₂ COOH
Tyr-SA	Tyr or TyrSA	(<i>para</i> -hydroxyphenyl)methyl
Glu-SA	Glu or GluSA	-CH ₂ CH ₂ COOH
Gln-SA	Gln or GlnSA	-CH ₂ CH ₂ C(=O)NH ₂
Asn-SA	Asn or AsnSA	-CH ₂ C(=O)NH ₂
Arg-NO ₂ -SA	Arg-NO ₂ or ArgNo ₂	-CH ₂ CH ₂ CH ₂ NHC(=NH)-NH-NO ₂ .

[00015] Further exemplary compounds of Formula (II) include, but are not limited to:



(Pro-SA, Pro, or ProSA),

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

[00016] The present invention also provides pharmaceutical compositions comprising a compound of of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00017] The present invention also provides pharmaceutical compositions comprising a compound of of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions described herein include a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate,

polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[00018] The pharmaceutical composition may be useful for treating and/or preventing a proliferative disease, such as cancer, benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases in a subject. The pharmaceutical composition may also be useful for treating and/or preventing an infectious disease, such as a bacterial infection or a viral infection.

[00019] In another aspect, the present invention provides methods for treating and/or preventing proliferative diseases. Exemplary proliferative diseases include, but are not limited to, cancer (*e.g.*, leukemia, melanoma, multiple myeloma), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases in a subject.

[00020] In another aspect, the present invention provides methods for treating and/or preventing infectious diseases. Exemplary infectious diseases include bacterial infections, viral infections, fungal infections, and parasitic diseases.

[00021] In another aspect, the present invention provides kits comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. The kits of the invention may include a single dose or multiple doses of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In another aspect, the present invention provides kits comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. The kits of the invention may include a single dose or multiple doses of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof.

[00022] The provided kits may be useful for the treatment of proliferative diseases. The provided kits may be useful for the treatment of infectious diseases. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (I), or the pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or the

pharmaceutical composition thereof. In certain embodiments, the kits described herein further include instructions for administering the compound of Formula (II), or the pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or the pharmaceutical composition thereof.

[00023] The kits may also include packaging information describing the use or prescribing information for the subject or a health care professional. Such information may be required by a regulatory agency such as the U.S. Food and Drug Administration (FDA). The kit may also optionally include a device for administration of the compound or composition, for example, a syringe for parenteral administration.

[00024] The details of certain embodiments of the invention are set forth herein. Other features, objects, and advantages of the invention will be apparent from the Detailed Description, Figures, Examples, and Claims.

Definitions

Chemical definitions

[00025] 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.

[00026] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various stereoisomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen

et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw–Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The invention additionally encompasses compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[00027] 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, C₁, C₂, C₃, C₄, C₅, C₆, 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.

[00028] The term “aliphatic,” as used herein, refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term “heteroaliphatic” as used herein, refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

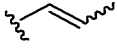
[00029] The term “aliphatic,” as used herein, refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. Likewise, the term “heteroaliphatic” as used herein, refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[00030] As used herein, “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 (“C₁ 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 (C₁), ethyl (C₂), n-propyl (C₃), isopropyl (C₃), n-butyl (C₄), tert-butyl (C₄), sec-butyl (C₄), iso-butyl (C₄), n-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and n-hexyl (C₆). Additional examples of alkyl groups include n-heptyl (C₇), n-octyl (C₈) 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.*, –CH₃). In certain embodiments, the alkyl group is a substituted C_{1–10} alkyl.

[00031] The terms “optionally substituted” and “substituted or unsubstituted” are used interchangeably.

[00032] As used herein, “heteroalkyl” refers to an alkyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₀ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₉ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₈ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₇ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₆ 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 (“heteroC₁₋₅ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₄ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₃ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ 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 (“heteroC₂₋₆ 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 heteroC₁₋₁₀ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₀ alkyl.

[00033] As used herein, “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon

atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ 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 C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), 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 C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is a substituted C₂₋₁₀ alkenyl. In an alkenyl group, a C=C double bond for which the stereochemistry is not specified (*e.g.*, -CH=CHCH₃ or ) may be an (*E*)- or (*Z*)-double bond.

[00034] As used herein, “heteroalkenyl” refers to an alkenyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ 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 (“heteroC₂₋₅ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ 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 (“heteroC₂₋₃ 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 (“heteroC₂₋₆ 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 heteroC₂₋₁₀ alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC₂₋₁₀ alkenyl.

[00035] As used herein, “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 10 carbon atoms and one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds) (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), 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 C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is a substituted C₂₋₁₀ alkynyl.

[00036] As used herein, “heteroalkynyl” refers to an alkynyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or

placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₀ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₉ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₈ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₇ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ 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 (“heteroC₂₋₅ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₄ 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 (“heteroC₂₋₃ 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 (“heteroC₂₋₆ 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 heteroC₂₋₁₀ alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC₂₋₁₀ alkynyl.

[00037] As used herein, “carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 7 ring carbon atoms (“C₃₋₇ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 4 to 6 ring carbon atoms (“C₄₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅),

cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or polycyclic (*e.g.*, containing a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) or tricyclic system (“tricyclic carbocyclyl”)) and can be saturated or can contain one or more carbon-carbon double or triple bonds. “Carbocyclyl” also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is an unsubstituted C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₀ carbocyclyl.

[00038] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 4 to 6 ring carbon atoms (“C₄₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more

substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C₃₋₁₀ cycloalkyl.

[00039] As used herein, “heterocyclyl” or “heterocyclic” refers to a radical of a 3– to 14–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3–14 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (*e.g.*, a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”) or tricyclic system (“tricyclic heterocyclyl”)), and can be saturated or can contain one or more carbon–carbon double or triple bonds. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Unless otherwise specified, each instance of heterocyclyl is independently unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is an unsubstituted 3–14 membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–14 membered heterocyclyl.

[00040] 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.

[00041] Exemplary 3–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azetidiny, 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, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6–membered heterocyclyl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholiny, dithianyl, dioxanyl. Exemplary 6–membered heterocyclyl groups containing 2 heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl, and thiepanyl. Exemplary 8–membered heterocyclyl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary bicyclic heterocyclyl groups include, without limitation, indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothienyl, tetrahydrobenzothienyl, tetrahydrobenzofuranyl, tetrahydroindolyl, tetrahydroquinoliny, tetrahydroisoquinoliny, decahydroquinoliny, decahydroisoquinoliny, octahydrochromenyl, octahydroisochromenyl, decahydronaphthyridiny, decahydro–1,8–naphthyridiny, octahydropyrrolo[3,2–b]pyrrole, indoliny, phthalimidyl, naphthalimidyl, chromanyl, chromenyl, 1H–benzo[e][1,4]diazepiny, 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]pyridiny, 2,3–dihydrofuro[2,3–b]pyridiny, 4,5,6,7–tetrahydro–1H–pyrrolo[2,3–b]pyridiny, 4,5,6,7–tetrahydrofuro[3,2–c]pyridiny, 4,5,6,7–tetrahydrothieno[3,2–b]pyridiny, 1,2,3,4–tetrahydro–1,6–naphthyridiny, and the like.

[00042] As used herein, “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the

aromatic ring system (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has 6 ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is an unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is a substituted C₆₋₁₄ aryl.

[00043] As used herein, “heteroaryl” refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–14 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused polycyclic (aryl/heteroaryl) ring system. Polycyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[00044] 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.

[00045] 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.

[00046] 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.

[00047] As understood from the above, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are, in certain embodiments, optionally substituted. Optionally substituted refers to a group which may be substituted or unsubstituted (*e.g.*, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” heteroalkyl, “substituted” or “unsubstituted” heteroalkenyl, “substituted” or “unsubstituted” heteroalkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted” means that at least one hydrogen present on a group is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, 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.

[00048] As used herein, the term “halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[00049] 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, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl 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 defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00050] For example, nitrogen protecting groups such as amide groups (*e.g.*, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N*'-dithiobenzylloxyacylamino)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.

[00051] Nitrogen protecting groups such as carbamate groups (*e.g.*, $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC or Boc), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate

(Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkylthio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolymethyl carbamate, 2-(trifluoromethyl)-6-chromonolymethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynlyl 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.

[00052] 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 -trimethylsilyl ethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-

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

[00053] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[00054] In certain embodiments, a nitrogen protecting group described herein is Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts.

[00055] The term “hydroxyl” or “hydroxy” refers to the group -OH. The term “substituted hydroxyl” or “substituted hydroxyl,” by extension, refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from -OR^{aa}, -ON(R^{bb})₂, -OC(=O)SR^{aa},

$-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$,
 $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$,
 $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}}))_2$,
 wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein.

[00056] 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, $-\text{R}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}}))_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[00057] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (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), dimethylhexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantate, 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 or 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-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate, *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).

[00058] In certain embodiments, an oxygen protecting group described herein is silyl, TBDPS, TBDMS, TIPS, TES, TMS, MOM, THP, *t*-Bu, Bn, allyl, acetyl, pivaloyl, or benzoyl.

[00059] Exemplary carbon atom substituents include, but are not limited to, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -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}, -CO₂H, -CHO, -C(OR^{cc})₂, -CO₂R^{aa}, -OC(=O)R^{aa},

$-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$,
 $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$,
 $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$,
 $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$,
 $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$,
 $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$,
 $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{OP}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$,
 $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{N}(\text{R}^{\text{bb}})_2)_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{OR}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3^+\text{X}^-$,
 $-\text{P}(\text{OR}^{\text{cc}})_3^+\text{X}^-$, $-\text{P}(\text{R}^{\text{cc}})_4$, $-\text{P}(\text{OR}^{\text{cc}})_4$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3^+\text{X}^-$, $-\text{OP}(\text{OR}^{\text{cc}})_2$, $-\text{OP}(\text{OR}^{\text{cc}})_3^+\text{X}^-$,
 $-\text{OP}(\text{R}^{\text{cc}})_4$, $-\text{OP}(\text{OR}^{\text{cc}})_4$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}
carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, wherein
each alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl,
heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd}
groups; wherein X^- is a counterion;

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

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

each instance of R^{bb} is, independently, selected from hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$,
 $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$,
 $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$,
 $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{N}(\text{R}^{\text{cc}})_2)_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl,
 C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10}
carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two
 R^{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; wherein X^- is a counterion;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, hetero C_{1-10} alkyl, hetero C_{2-10} alkenyl, hetero C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3-14 membered heterocyclyl, C_{6-14} aryl, and 5-14 membered heteroaryl, or two R^{cc} groups 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, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)(OR^{ee})_2$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hetero C_{1-6} alkyl, hetero C_{2-6} alkenyl, hetero C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3-10 membered heterocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, 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 $=S$; wherein X^- is a counterion;

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

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl) $_2$, $-N(C_{1-6}$ alkyl) $_2$, $-N(C_{1-6}$ alkyl) $_3^+X^-$, $-NH(C_{1-6}$ alkyl) $_2^+X^-$, $-NH_2(C_{1-6}$ alkyl) $^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl)(C_{1-6} alkyl), $-N(OH)(C_{1-6}$ alkyl), $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl), $-C(=O)(C_{1-6}$ alkyl), $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), $-OC(=O)(C_{1-6}$ alkyl), $-OCO_2(C_{1-6}$ alkyl), $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl) $_2$, $-OC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl) $C(=O)(C_{1-6}$ alkyl), $-NHCO_2(C_{1-6}$ alkyl), $-NHC(=O)N(C_{1-6}$ alkyl) $_2$, $-NHC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl), $-OC(=NH)(C_{1-6}$ alkyl), $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl) $_2$, $-C(=NH)NH(C_{1-6}$ alkyl), $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl) $_2$, $-OC(NH)NH(C_{1-6}$ alkyl), $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6}$ alkyl) $_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl) $_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ alkyl, $-SOC_{1-6}$ alkyl, $-Si(C_{1-6}$ alkyl) $_3$, $-OSi(C_{1-6}$ alkyl) $_3$, $-C(=S)N(C_{1-6}$ alkyl) $_2$, $C(=S)NH(C_{1-6}$ alkyl), $C(=S)NH_2$, $-C(=O)S(C_{1-6}$ alkyl), $-C(=S)SC_{1-6}$ alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)(OC_{1-6}$ alkyl) $_2$, $-P(=O)(C_{1-6}$ alkyl) $_2$, $-OP(=O)(C_{1-6}$ alkyl) $_2$, $-OP(=O)(OC_{1-6}$ alkyl) $_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, hetero C_{1-6} alkyl, hetero C_{2-6} alkenyl, hetero C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3-10 membered heterocyclyl, 5-10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form $=O$ or $=S$; wherein X^- is a counterion.

[00060] In certain embodiments, X^- is a counterion. A “counterion” or “anionic counterion” is a negatively charged group associated with a positively charged group in order to maintain electronic neutrality. An anionic counterion may be monovalent (i.e., including one formal negative charge). An anionic counterion may also be multivalent (i.e., including more than one formal negative charge), such as divalent or trivalent. Exemplary counterions include halide ions (e.g., F^- , Cl^- , Br^- , I^-), NO_3^- , ClO_4^- , OH^- , $H_2PO_4^-$, HCO_3^- , HSO_4^- , sulfonate ions (e.g., methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), carboxylate ions (e.g., acetate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, gluconate, and the like), BF_4^- , PF_4^- , PF_6^- , AsF_6^- , SbF_6^- , $B[3,5-(CF_3)_2C_6H_3]_4^-$, $B(C_6F_5)_4^-$, BPh_4^- , $Al(OC(CF_3)_3)_4^-$, and carborane anions (e.g., $CB_{11}H_{12}^-$ or $(HCB_{11}Me_5Br_6)^-$). Exemplary counterions which may be multivalent include CO_3^{2-} , HPO_4^{2-} , PO_4^{3-} , $B_4O_7^{2-}$, SO_4^{2-} , $S_2O_3^{2-}$, carboxylate anions (e.g., tartrate, citrate, fumarate, maleate, malate, malonate, gluconate, succinate, glutarate, adipate, pimelate, suberate, azelate, sebacate, salicylate, phthalates, aspartate, glutamate, and the like), and carboranes.

[00061] 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. In certain embodiments, the “substituted amino” is a monosubstituted amino or a disubstituted amino group.

[00062] 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 $\text{—NH(R}^{\text{bb}}\text{)}$, $\text{—NHC(=O)R}^{\text{aa}}$, $\text{—NHCO}_2\text{R}^{\text{aa}}$, $\text{—NHC(=O)N(R}^{\text{bb}}\text{)}_2$, $\text{—NHC(=NR}^{\text{bb}}\text{)N(R}^{\text{bb}}\text{)}_2$, $\text{—NHSO}_2\text{R}^{\text{aa}}$, $\text{—NHP(=O)(OR}^{\text{cc}}\text{)}_2$, and $\text{—NHP(=O)(N(R}^{\text{bb}}\text{)}_2)_2$, wherein R^{aa} , R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $\text{—NH(R}^{\text{bb}}\text{)}$ is not hydrogen.

[00063] 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 $\text{—N(R}^{\text{bb}}\text{)}_2$, $\text{—NR}^{\text{bb}}\text{C(=O)R}^{\text{aa}}$, $\text{—NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $\text{—NR}^{\text{bb}}\text{C(=O)N(R}^{\text{bb}}\text{)}_2$, $\text{—NR}^{\text{bb}}\text{C(=NR}^{\text{bb}}\text{)N(R}^{\text{bb}}\text{)}_2$, $\text{—NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $\text{—NR}^{\text{bb}}\text{P(=O)(OR}^{\text{cc}}\text{)}_2$, and $\text{—NR}^{\text{bb}}\text{P(=O)(N(R}^{\text{bb}}\text{)}_2)_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein, with the proviso that the nitrogen atom directly attached to the parent molecule is not substituted with hydrogen.

[00064] 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 $\text{—N(R}^{\text{bb}}\text{)}_3$ and $\text{—N(R}^{\text{bb}}\text{)}_3^+\text{X}^-$, wherein R^{bb} and X^- are as defined herein.

[00065] The term “acyl” refers to a group having the general formula $\text{—C(=O)R}^{\text{X1}}$, $\text{—C(=O)OR}^{\text{X1}}$, $\text{—C(=O)—O—C(=O)R}^{\text{X1}}$, $\text{—C(=O)SR}^{\text{X1}}$, $\text{—C(=O)N(R}^{\text{X1}}\text{)}_2$, $\text{—C(=S)R}^{\text{X1}}$, $\text{—C(=S)N(R}^{\text{X1}}\text{)}_2$, and $\text{—C(=S)S(R}^{\text{X1}}\text{)}$, $\text{—C(=NR}^{\text{X1}}\text{)R}^{\text{X1}}$, $\text{—C(=NR}^{\text{X1}}\text{)OR}^{\text{X1}}$, $\text{—C(=NR}^{\text{X1}}\text{)SR}^{\text{X1}}$, and $\text{—C(=NR}^{\text{X1}}\text{)N(R}^{\text{X1}}\text{)}_2$, wherein R^{X1} is hydrogen; halogen; substituted or unsubstituted hydroxyl; substituted or unsubstituted thiol; substituted or unsubstituted amino; substituted or unsubstituted acyl, cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkyl; cyclic or acyclic, substituted or unsubstituted, branched or unbranched alkenyl; substituted or unsubstituted alkynyl; substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, mono- or di- aliphaticamino, mono- or di- heteroaliphaticamino, mono- or di- alkylamino, mono- or di- heteroalkylamino, mono- or di-arylamino, or mono- or di-heteroarylamino; or two R^{X1} groups taken together form a 5- to 6-membered heterocyclic

ring. Exemplary acyl groups include aldehydes (–CHO), carboxylic acids (–CO₂H), ketones, acyl halides, esters, amides, imines, carbonates, carbamates, and ureas. Acyl substituents include, but are not limited to, any of the substituents described herein, that result in the formation of a stable moiety (*e.g.*, aliphatic, alkyl, alkenyl, alkynyl, heteroaliphatic, heterocyclic, aryl, heteroaryl, acyl, oxo, imino, thiooxo, cyano, isocyano, amino, azido, nitro, hydroxyl, thiol, halo, aliphaticamino, heteroaliphaticamino, alkylamino, heteroalkylamino, arylamino, heteroarylamino, alkylaryl, arylalkyl, aliphaticoxy, heteroaliphaticoxy, alkyloxy, heteroalkyloxy, aryloxy, heteroaryloxy, aliphaticthioxy, heteroaliphaticthioxy, alkylthioxy, heteroalkylthioxy, arylthioxy, heteroarylthioxy, acyloxy, and the like, each of which may or may not be further substituted).

[00066] 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.

[00067] As used herein, the term “salt” refers to any and all salts.

[00068] 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.

[00069] As used herein, the term “tautomer” refers to particular isomers of a compound in which a hydrogen and double bond have changed position with respect to the other atoms of the molecule. For a pair of tautomers to exist there must be a mechanism for interconversion. Examples of tautomers include keto-enol forms, imine-enamine forms, amide-imino alcohol forms, amidine-aminidine forms, nitroso-oxime forms, thio ketone-enethiol forms, *N*-nitroso-hydroxyazo forms, nitro-*aci*-nitro forms, and pyridone-hydroxypyridine forms.

Other Definitions

[00070] The following definitions are more general terms used throughout the present application:

[00071] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods known in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–

naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, non-toxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate, and aryl sulfonate.

[00072] The term “solvate” refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, DMSO, THF, diethyl ether, and the like. The compounds described herein (*e.g.*, compounds of Formula (I) or (II)) may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates.

Representative solvates include hydrates, ethanolates, and methanolates.

[00073] The term “hydrate” refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot x \text{ H}_2\text{O}$, wherein R is the compound, and x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5 \text{ H}_2\text{O}$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2 \text{ H}_2\text{O}$) and hexahydrates ($R \cdot 6 \text{ H}_2\text{O}$)).

[00074] As used herein, the term “tautomer” includes two or more interconvertible forms resulting from at least one formal migration of a hydrogen atom and at least one change in valency (*e.g.*, a single bond to a double bond, a triple bond to a double bond, or vice versa). The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) may be catalyzed by

acid or base. Exemplary tautomerizations include keto-to-enol; amide-to-imide; lactam-to-lactim; enamine-to-imine; and enamine-to-(a different) enamine tautomerizations.

[00075] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers”. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers”.

[00076] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers”. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.*, as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a “racemic mixture”.

[00077] The term “polymorphs” refers to a crystalline form of a compound (or a salt, hydrate, or solvate thereof) in a particular crystal packing arrangement. All polymorphs have the same elemental composition. Different crystalline forms usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and/or solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate. Various polymorphs of a compound can be prepared by crystallization under different conditions.

[00078] The term “prodrugs” refer to compounds, including derivatives of the compounds described herein (*e.g.*, compounds of Formula (I) or (II)), which have cleavable groups and become by solvolysis or under physiological conditions the compounds which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, *Design of Prodrugs*, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable

alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides, and anhydrides derived from acidic groups pendant on the compounds of this invention are particular prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, aryl, C₇-C₁₂ substituted aryl, and C₇-C₁₂ arylalkyl esters of the compounds described herein (*e.g.*, compounds of Formula (I) or (II)) may be preferred in certain instances.

[00079] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult, or senior adult)) and/or other non-human animals, for example, mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs) and birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys). In certain embodiments, the animal is a mammal. The animal may be a male or female and at any stage of development. A non-human animal may be a transgenic animal.

[00080] The terms “administer,” “administering,” or “administration,” as used herein refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof.

[00081] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a “pathological condition” (*e.g.*, a disease, disorder, or condition, or one or more signs or symptoms thereof) described herein. In some embodiments, treatment may be administered after one or more signs or symptoms have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of the disease or condition. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[00082] As used herein, the terms “condition,” “disease,” and “disorder” are used interchangeably.

[00083] An “effective amount” of a compound described herein (*e.g.*, compounds of Formula (I) or (II)) refers to an amount sufficient to elicit a desired biological response, *i.e.*,

treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein (*e.g.*, compounds of Formula (I) or (II)) may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment. For example, in treating cancer, an effective amount of an inventive compound may reduce the tumor burden or stop the growth or spread of a tumor. In treating macular degeneration, an effective amount of an inventive compound may improve sight, reduce the risk of vision loss, or prevent central vision loss from worsening.

[00084] A “therapeutically effective amount” of a compound described herein (*e.g.*, of Formula (I) or (II)) is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[00085] A “prophylactically effective amount” of a compound described herein (*e.g.*, compounds of Formula (I) or (II)) is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[00086] A “proliferative disease” refers to a disease that occurs due to abnormal growth or extension by the multiplication of cells (Walker, *Cambridge Dictionary of Biology*; Cambridge University Press: Cambridge, UK, 1990). A proliferative disease may be associated with: 1) the pathological proliferation of normally quiescent cells; 2) the pathological migration of cells from their normal location (*e.g.*, metastasis of neoplastic cells); 3) the pathological expression of proteolytic enzymes such as matrix metalloproteinases (*e.g.*, collagenases, gelatinases, and elastases); or 4) pathological angiogenesis as in proliferative retinopathy and tumor metastasis. Exemplary proliferative diseases include cancers (*i.e.*, “malignant neoplasms”), benign neoplasms, diseases associated

with angiogenesis or diseases associated with angiogenesis, inflammatory diseases, autoinflammatory diseases, and autoimmune diseases.

[00087] The terms “neoplasm” and “tumor” are used herein interchangeably and refer to an abnormal mass of tissue wherein the growth of the mass surpasses and is not coordinated with the growth of a normal tissue. A neoplasm or tumor may be “benign” or “malignant,” depending on the following characteristics: degree of cellular differentiation (including morphology and functionality), rate of growth, local invasion, and metastasis. A “benign neoplasm” is generally well differentiated, has characteristically slower growth than a malignant neoplasm, and remains localized to the site of origin. In addition, a benign neoplasm does not have the capacity to infiltrate, invade, or metastasize to distant sites. Exemplary benign neoplasms include, but are not limited to, lipoma, chondroma, adenomas, acrochordon, senile angiomas, seborrheic keratoses, lentigos, and sebaceous hyperplasias. In some cases, certain “benign” tumors may later give rise to malignant neoplasms, which may result from additional genetic changes in a subpopulation of the tumor’s neoplastic cells, and these tumors are referred to as “pre-malignant neoplasms.” An example of a pre-malignant neoplasm is a teratoma. In contrast, a “malignant neoplasm” is generally poorly differentiated (anaplasia) and has characteristically rapid growth accompanied by progressive infiltration, invasion, and destruction of the surrounding tissue. Furthermore, a malignant neoplasm generally has the capacity to metastasize to distant sites.

[00088] The term “metastasis,” “metastatic,” or “metastasize” refers to the spread or migration of cancerous cells from a primary or original tumor to another organ or tissue and is typically identifiable by the presence of a “secondary tumor” or “secondary cell mass” of the tissue type of the primary or original tumor and not of that of the organ or tissue in which the secondary (metastatic) tumor is located. For example, a prostate cancer that has migrated to bone is said to be metastasized prostate cancer and includes cancerous prostate cancer cells growing in bone tissue.

[00089] As used herein, the term “cancer” refers to a malignant neoplasm (*Stedman’s Medical Dictionary*, 25th ed.; Hensyl ed.; Williams & Wilkins: Philadelphia, 1990). Exemplary cancers include, but are not limited to, acoustic neuroma; adenocarcinoma; adrenal gland cancer; anal cancer; angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma); appendix cancer; benign monoclonal gammopathy; biliary cancer (*e.g.*, cholangiocarcinoma); bladder cancer; breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast); brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*,

astrocytoma, oligodendroglioma), medulloblastoma); bronchus cancer; carcinoid tumor; cervical cancer (*e.g.*, cervical adenocarcinoma); choriocarcinoma; chordoma; craniopharyngioma; colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma); connective tissue cancer; epithelial carcinoma; ependymoma; endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma); endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma); esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma); Ewing's sarcoma; eye cancer (*e.g.*, intraocular melanoma, retinoblastoma); familial hypereosinophilia; gall bladder cancer; gastric cancer (*e.g.*, stomach adenocarcinoma); gastrointestinal stromal tumor (GIST); germ cell cancer; head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)); hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL)); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, Waldenström's macroglobulinemia), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease); hemangioblastoma; hypopharynx cancer; inflammatory myofibroblastic tumors; immunocytic amyloidosis; kidney cancer (*e.g.*, nephroblastoma a.k.a. Wilms' tumor, renal cell carcinoma); liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma); lung cancer (*e.g.*, bronchogenic

carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung); leiomyosarcoma (LMS); mastocytosis (*e.g.*, systemic mastocytosis); muscle cancer; myelodysplastic syndrome (MDS); mesothelioma; myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocythosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)); neuroblastoma; neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis); neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor); osteosarcoma (*e.g.*, bone cancer); ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma); papillary adenocarcinoma; pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors); penile cancer (*e.g.*, Paget's disease of the penis and scrotum); pinealoma; primitive neuroectodermal tumor (PNT); plasma cell neoplasia; paraneoplastic syndromes; intraepithelial neoplasms; prostate cancer (*e.g.*, prostate adenocarcinoma); rectal cancer; rhabdomyosarcoma; salivary gland cancer; skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)); small bowel cancer (*e.g.*, appendix cancer); soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma); sebaceous gland carcinoma; small intestine cancer; sweat gland carcinoma; synovium; 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).

[00090] The term “angiogenesis” refers to the formation and growth of new blood vessels. Normal angiogenesis occurs in the body of a healthy subject during wound healing and for restoring blood flow to tissues after injury. The body controls angiogenesis through a number of means, *e.g.*, angiogenesis-stimulating growth factors and angiogenesis inhibitors. Many disease states, such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, and psoriasis, are characterized by abnormal (*i.e.*, increased or excessive) angiogenesis. Abnormal angiogenesis refers to angiogenesis greater than that in a normal body, especially angiogenesis in an adult not related to normal angiogenesis (*e.g.*, menstruation or wound healing). Abnormal angiogenesis can result in new blood vessels that feed diseased tissues and/or destroy normal tissues, and in the case of cancer, the new vessels

can allow tumor cells to escape into the circulation and lodge in other organs (tumor metastases). In certain embodiments, the disease associated with angiogenesis is tumor angiogenesis. In certain embodiments, the diseases associated with angiogenesis include, but are not limited to breast cancer, colorectal cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), kidney (renal cell) cancer, liver (adult primary) cancer, lymphoma, melanoma, lung cancer, ovarian epithelial cancer, pancreatic cancer, prostate cancer, stomach (gastric) cancer.

[00091] As used herein, an “inflammatory disease” refers to a disease caused by, resulting from, or resulting in inflammation. The term “inflammatory disease” may also refer to a dysregulated inflammatory reaction that causes an exaggerated response by macrophages, granulocytes, and/or T-lymphocytes leading to abnormal tissue damage and/or cell death. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes. Inflammatory diseases include, without limitation, atherosclerosis, arteriosclerosis, autoimmune disorders, multiple sclerosis, systemic lupus erythematosus, polymyalgia rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, psoriasis, cystic fibrosis, arthroseitis, rheumatoid arthritis, inflammatory arthritis, Sjogren’s syndrome, giant cell arteritis, progressive systemic sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis, pemphigus, pemphigoid, diabetes (*e.g.*, Type I), myasthenia gravis, Hashimoto’s thyroiditis, Graves’ disease, Goodpasture’s disease, mixed connective tissue disease, sclerosing cholangitis, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis, pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic allergic alveolitis, Wegener’s granulomatosis and related forms of angiitis (temporal arteritis and polyarteritis nodosa), inflammatory dermatoses, hepatitis, delayed-type hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis, ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis, cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis,

gingivitis, ileitis, iritis, laryngitis, myelitis, myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis, urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing fasciitis, and necrotizing enterocolitis.

[00092] As used herein, an “autoimmune disease” refers to a disease arising from an inappropriate immune response in the body of a subject against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (*e.g.*, in autoimmune thyroiditis) or involve a particular tissue in different places (*e.g.*, Goodpasture’s disease which may affect the basement membrane in both the lung and kidney). The treatment of autoimmune diseases is typically with immunosuppressants, *e.g.*, medications which decrease the immune response. Exemplary autoimmune diseases include, but are not limited to, glomerulonephritis, Goodspature’s syndrome, necrotizing vasculitis, lymphadenitis, peri-arteritis nodosa, systemic lupus erythematosus, rheumatoid, arthritis, psoriatic arthritis, systemic lupus erythematosus, psoriasis, ulcerative colitis, systemic sclerosis, dermatomyositis/polymyositis, anti-phospholipid antibody syndrome, scleroderma, perphigus vulgaris, ANCA-associated vasculitis (*e.g.*, Wegener’s granulomatosis, microscopic polyangiitis), urveitis, Sjogren’s syndrome, Crohn’s disease, Reiter’s syndrome, ankylosing spondylitis, Lyme arthritis, Guillain-Barre syndrome, Hashimoto’s thyroiditis, and cardiomyopathy.

[00093] The term “autoinflammatory disease” refers to a category of diseases that are similar but different from autoimmune diseases. Autoinflammatory and autoimmune diseases share common characteristics in that both groups of disorders result from the immune system attacking a subject’s own tissues and result in increased inflammation. In autoinflammatory diseases, a subject’s innate immune system causes inflammation for unknown reasons. The innate immune system reacts even though it has never encountered autoantibodies or antigens in the subject. Autoinflammatory disorders are characterized by intense episodes of inflammation that result in such symptoms as fever, rash, or joint swelling. These diseases also carry the risk of amyloidosis, a potentially fatal buildup of a blood protein in vital organs. Autoinflammatory diseases include, but are not limited to, familial Mediterranean fever (FMF), neonatal onset multisystem inflammatory disease (NOMID), tumor necrosis

factor (TNF) receptor-associated periodic syndrome (TRAPS), deficiency of the interleukin-1 receptor antagonist (DIRA), and Behçet's disease.

[00094] The term “biological sample” refers to any sample including tissue samples (such as tissue sections and needle biopsies of a tissue); cell samples (*e.g.*, cytological smears (such as Pap or blood smears) or samples of cells obtained by microdissection); samples of whole organisms (such as samples of yeasts or bacteria); or cell fractions, fragments or organelles (such as obtained by lysing cells and separating the components thereof by centrifugation or otherwise). Other examples of biological samples include blood, serum, urine, semen, fecal matter, cerebrospinal fluid, interstitial fluid, mucus, tears, sweat, pus, biopsied tissue (*e.g.*, obtained by a surgical biopsy or needle biopsy), nipple aspirates, milk, vaginal fluid, saliva, swabs (such as buccal swabs), or any material containing biomolecules that is derived from a first biological sample. Biological samples also include those biological samples that are transgenic, such as transgenic oocyte, sperm cell, blastocyst, embryo, fetus, donor cell, or cell nucleus.

[00095] As used herein, the term “infectious disease” refers to an illness caused by a pathogenic biological agent that results from transmission from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector or inanimate environment. Last J M. ed. A dictionary of epidemiology. 4th ed. New York: Oxford University Press, 1988. Infectious disease is also known as transmissible diseases or communicable diseases. In certain embodiments, infectious diseases may be asymptomatic for much or even all of their course in a given host. Infectious pathogens include some viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions.

[00096] As used herein, “aminoacyl tRNA synthetase (aaRS)” refers to an enzyme that catalyzes the esterification of a specific cognate amino acid or its precursor to one of all its compatible cognate tRNAs to form an aminoacyl-tRNA. The aminoacyl tRNA synthetases include Class I and Class II aaRS. Class I of aaRS has two highly conserved sequence motifs and aminoacylates at the 2'-OH of a terminal adenosine nucleotide on tRNA. Class II of aaRS has three highly conserved sequence motifs and aminoacylates at the 3'-OH of a terminal adenosine on tRNA. Although phenylalanine-tRNA synthetase is class II, it aminoacylates at the 2'-OH. In certain embodiments, the aaRS is Class I. In certain embodiments, the aaRS is Class II.

[00097] As used herein “inhibition”, “inhibiting”, “inhibit” and “inhibitor”, and the like, refer to the ability of a compound to reduce, slow, halt, or prevent the activity of a particular biological process involving Ras in a cell relative to vehicle.

Brief Description of the Drawings

[00098] Figure 1 shows examples of flow cytometric apoptosis staining analysis of PC-3 cells treated with drugs compared to no drug control. The cells were stained with annexin V and propidium iodide and analyzed: viable (lower left), early apoptotic (lower right), late apoptotic (upper right), and necrotic cells (upper left). The population of early apoptotic, late apoptotic, and necrotic cells increase with the drug treatment. Cells were exposed to 10 μ M drug for 48 h treatments.

[00099] Figure 2 shows the population of late apoptotic cells increase with aminoacyl sulfamides treatment against PC-3 cells.

[000100] Figure 3 shows the effect of aminoacyl sulfamides on cell cycle as analyzed by flow cytometry: M1: Sub G0/G1 phase; M2: G0/G1 phase; M3: S phase; M4: G2/M phase. FACS analysis revealed that treatment of PC-3 cells with aminoacyl sulfamides led to arrest at the subG0/G1 and S phase of the cell cycle. The sub-G1 population increased indicating that some cells underwent apoptosis. The drug shifted the PC3 cells to the sub G0/G1 and S phase after exposure to drugs for 48 h.

[000101] Figure 4 shows the PC3 cells shifted to the sub G0/G1 after exposure to drugs for 48 h.

[000102] Figure 5 shows that the drugs inhibited the PC3 cells migration after treatment of aminoacyl sulfamides.

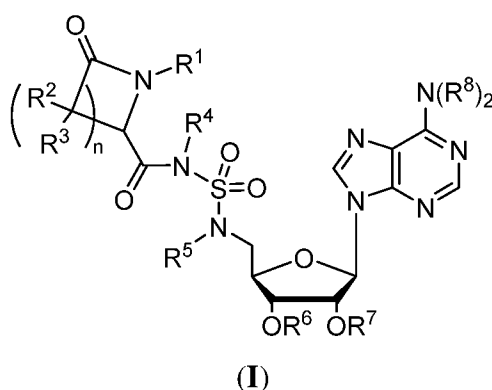
Detailed Description of Certain Embodiments of the Invention

[000103] The present invention provides compounds of Formula (I), which are derivatives of sulfamide adenosine derivatives. The present invention also provides compounds of Formula (II), which are derivatives of sulfamide adenosine derivatives. These compounds may be useful in the prevention and/or treatment of a proliferative disease. Also provided are methods of using compounds of Formula (I) to treat and/or prevent proliferative diseases. Also provided are methods of using compounds of Formula (II) to treat and/or prevent proliferative diseases. Exemplary proliferative diseases include, but are not limited to, cancers, benign neoplasms, diseases associated with angiogenesis, inflammatory diseases,

autoinflammatory diseases, and autoimmune diseases. In certain embodiments, the disease is cancer. Also provided are methods of using compounds of Formula (I) to treat and/or prevent infectious diseases. Also provided are methods of using compounds of Formula (II) to treat and/or prevent infectious diseases. In certain embodiments, the infectious disease is a bacterial infection. In certain embodiments, the infectious disease is a viral infection.

Compounds

[000104] As generally described above, provided herein are compounds of Formula (I). The compounds are aminoacyl sulfamide derivatives, belonging to a class of structural mimics of aaAMP. In certain embodiments, the present disclosure provides compounds of Formula (I):



and pharmaceutically acceptable salts thereof,
wherein:

each of R^1 , R^4 , and R^5 is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

each instance of R^8 is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or two R^8 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

each of R^6 and R^7 is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group, or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

each instance of R^2 and R^3 is independently hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl; and

n is 1, 2, 3, or 4.

[000105] As generally defined herein, R^1 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group. In certain embodiments, R^1 is hydrogen. In certain embodiments, R^1 is optionally substituted alkyl or a nitrogen protecting group. In certain embodiments, R^1 is optionally substituted alkyl. In certain embodiments, R^1 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^1 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^1 is methyl. In certain embodiments, R^1 is a nitrogen protecting group. In certain embodiments, R^1 is triphenylmethyl (Trt). In certain embodiments, R^1 is optionally substituted acyl. In certain embodiments, R^1 is acetyl. In certain embodiments, R^1 is Boc.

[000106] As generally defined herein, each instance of R^2 is independently hydrogen, halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, at least one instance of R^2 is hydrogen. In certain embodiments, at least one instance of R^2 is halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, at least one instance of R^2 is halogen. In certain embodiments, at least one instance of R^2 is F. In certain embodiments, at least one instance of R^2 is Cl. In certain embodiments, at least one instance of R^2 is Br. In certain embodiments, at least one instance of R^2 is I. In certain embodiments, at least one instance of R^2 is optionally substituted alkyl. In certain embodiments, at least one instance of R^2 is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^2 is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^2 is methyl or ethyl.

[000107] As generally defined herein, each instance of R^3 is independently hydrogen, halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, at least one instance of R^3 is hydrogen. In certain embodiments, at least one instance of R^3 is halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally

substituted heteroaryl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, at least one instance of R^3 is halogen. In certain embodiments, at least one instance of R^3 is F. In certain embodiments, at least one instance of R^3 is Cl. In certain embodiments, at least one instance of R^3 is Br. In certain embodiments, at least one instance of R^3 is I. In certain embodiments, at least one instance of R^3 is optionally substituted alkyl. In certain embodiments, at least one instance of R^3 is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^3 is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one instance of R^3 is methyl or ethyl.

[000108] As generally defined herein, R^4 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group. In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is optionally substituted alkyl or a nitrogen protecting group. In certain embodiments, R^4 is optionally substituted alkyl. In certain embodiments, R^4 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^4 is methyl. In certain embodiments, R^4 is a nitrogen protecting group. In certain embodiments, R^4 is triphenylmethyl (Trt). In certain embodiments, R^4 is optionally substituted acyl. In certain embodiments, R^4 is acetyl. In certain embodiments, R^4 is Boc.

[000109] As generally defined herein, R^5 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is optionally substituted alkyl or a nitrogen protecting group. In certain embodiments, R^5 is optionally substituted alkyl. In certain embodiments, R^5 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^5 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^5 is methyl. In certain embodiments, R^5 is a nitrogen protecting group. In certain embodiments, R^5 is triphenylmethyl (Trt). In certain embodiments, R^5 is optionally substituted acyl. In certain embodiments, R^5 is acetyl. In certain embodiments, R^5 is Boc.

[000110] As generally defined herein, R^6 is hydrogen, optionally substituted alkyl, or an oxygen protecting group. In certain embodiments, R^6 is hydrogen. In certain embodiments, R^6 is optionally substituted alkyl or an oxygen protecting group. In certain embodiments, R^6 is optionally substituted alkyl. In certain embodiments, R^6 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^6 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^6 is methyl. In certain embodiments, R^6 is an oxygen protecting group. In certain embodiments, R^6 is optionally substituted acyl. In certain embodiments, R^6 is acetyl.

[000111] As generally defined herein, R^7 is hydrogen, optionally substituted alkyl, or an oxygen protecting group. In certain embodiments, R^7 is hydrogen. In certain embodiments, R^7 is optionally substituted alkyl or an oxygen protecting group. In certain embodiments, R^7

is optionally substituted alkyl. In certain embodiments, R^7 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^7 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^7 is methyl. In certain embodiments, R^7 is an oxygen protecting group. In certain embodiments, R^7 is optionally substituted acyl. In certain embodiments, R^7 is acetyl.

[000112] In certain embodiments, R^6 and R^7 are taken together the intervening atoms to form an optionally substituted heterocyclyl ring. In certain embodiments, R^6 and R^7 are taken together the intervening atoms to form an optionally substituted 5-membered heterocyclyl ring. In certain embodiments, R^6 and R^7 are taken together the intervening atoms to form an optionally substituted 6-membered heterocyclyl ring.

[000113] In certain embodiments, R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclyl ring. In certain embodiments, R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted 5-membered heterocyclyl ring. In certain embodiments, R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted 6-membered heterocyclyl ring.

[000114] As generally defined herein, each instance of R^8 is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or two R^8 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring. In certain embodiments, each instance of R^8 is different. In certain embodiments, both instances of R^8 are the same. In certain embodiments, both instances of R^8 are hydrogen. In certain embodiments, each instance of R^8 is independently optionally substituted alkyl. In certain embodiments, each instance of R^8 is independently optionally substituted C_{1-6} alkyl. In certain embodiments, each instance of R^8 is independently unsubstituted C_{1-6} alkyl (*e.g.*, methyl or ethyl). In certain embodiments, each instance of R^8 is independently substituted C_{1-6} alkyl. In certain embodiments, each instance of R^8 is independently a nitrogen protecting group. In certain embodiments, one instance of R^8 is hydrogen. In certain embodiments, one instance of R^8 is optionally substituted alkyl. In certain embodiments, one instance of R^8 is optionally substituted C_{1-6} alkyl. In certain embodiments, one instance of R^8 is unsubstituted C_{1-6} alkyl (*e.g.*, methyl or ethyl). In certain embodiments, one instance of R^8 is substituted C_{1-6} alkyl. In certain embodiments, one instance of R^8 is an oxygen protecting group. In certain embodiments, one instance of R^8 is hydrogen, and one instance of R^8 is optionally substituted alkyl. In certain embodiments, one instance of R^8 is hydrogen, and one instance of R^8 is a nitrogen protecting group. In certain embodiments, one instance of R^8 is unsubstituted alkyl (*e.g.*, methyl or ethyl), and one instance of R^8 is substituted alkyl. In certain embodiments, two R^8 are taken together the intervening atoms to form an optionally substituted heterocyclyl

ring. In certain embodiments, two R^8 are taken together the intervening atoms to form an optionally substituted 8-membered heterocyclcyl ring. In certain embodiments, two R^8 are taken together the intervening atoms to form an optionally substituted 6-membered heterocyclcyl ring.

[000115] In certain embodiments, two R^8 are taken together with their intervening atoms to form an optionally substituted heterocyclcyl ring. In certain embodiments, two R^8 are taken together with their intervening atoms to form an optionally substituted 8-membered heterocyclcyl ring. In certain embodiments, two R^8 are taken together with their intervening atoms to form an optionally substituted 6-membered heterocyclcyl ring.

[000116] As generally defined herein, n is 1, 2, 3, or 4. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3. In certain embodiments, n is 4.

[000117] In certain embodiments, n is 1; and R^1 is hydrogen. In certain embodiments, n is 1; and R^1 and R^4 are hydrogen. In certain embodiments, n is 1; and R^1 , R^4 , and R^5 are hydrogen. In certain embodiments, n is 1; and R^1 , R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 1; and R^1 is optionally substituted alkyl. In certain embodiments, n is 1; R^1 is optionally substituted alkyl; and R^4 is hydrogen. In certain embodiments, n is 1; R^1 is optionally substituted alkyl; and R^4 and R^5 are hydrogen. In certain embodiments, n is 1; R^1 is optionally substituted alkyl; and R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 1; and R^1 is a nitrogen protecting group. In certain embodiments, n is 1; and R^1 , R^4 , and R^5 are each independently a nitrogen protecting group. In certain embodiments, n is 1; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is hydrogen. In certain embodiments, n is 1; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is a nitrogen protecting group.

[000118] In certain embodiments, n is 2; and R^1 is hydrogen. In certain embodiments, n is 2; and R^1 and R^4 are hydrogen. In certain embodiments, n is 2; and R^1 , R^4 , and R^5 are hydrogen. In certain embodiments, n is 2; and R^1 , R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 2; and R^1 is optionally substituted alkyl. In certain embodiments, n is 2; R^1 is optionally substituted alkyl; and R^4 is hydrogen. In certain embodiments, n is 2; R^1 is optionally substituted alkyl; and R^4 and R^5 are hydrogen. In certain embodiments, n is 2; R^1 is optionally substituted alkyl; R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 2 and R^1 is a nitrogen protecting group. In certain embodiments, n is 2 and R^1 , R^4 , and R^5 are each independently a nitrogen protecting group. In certain embodiments, n is 2; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of

R^8 is hydrogen. In certain embodiments, n is 2; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is a nitrogen protecting group.

[000119] In certain embodiments, n is 3; and R^1 is hydrogen. In certain embodiments, n is 3; and R^1 and R^4 are hydrogen. In certain embodiments, n is 3; and R^1 , R^4 , and R^5 are hydrogen. In certain embodiments, n is 3; and R^1 , R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 3; and R^1 is optionally substituted alkyl. In certain embodiments, n is 3; R^1 is optionally substituted alkyl; and R^4 is hydrogen. In certain embodiments, n is 3; R^1 is optionally substituted alkyl; and R^4 and R^5 are hydrogen. In certain embodiments, n is 3; R^1 is optionally substituted alkyl; R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 3; and R^1 is a nitrogen protecting group. In certain embodiments, n is 3; and R^1 , R^4 , and R^5 are each independently a nitrogen protecting group. In certain embodiments, n is 3; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is hydrogen. In certain embodiments, n is 3; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is a nitrogen protecting group.

[000120] In certain embodiments, n is 4; and R^1 is hydrogen. In certain embodiments, n is 4; and R^1 and R^4 are hydrogen. In certain embodiments, n is 4; and R^1 , R^4 , and R^5 are hydrogen. In certain embodiments, n is 4; and R^1 , R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 4; and R^1 is optionally substituted alkyl. In certain embodiments, n is 4; R^1 is optionally substituted alkyl; and R^4 is hydrogen. In certain embodiments, n is 4; R^1 is optionally substituted alkyl; and R^4 and R^5 are hydrogen. In certain embodiments, n is 4; R^1 is optionally substituted alkyl; R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, n is 4; and R^1 is a nitrogen protecting group. In certain embodiments, n is 4; and R^1 , R^4 , and R^5 are each independently a nitrogen protecting group. In certain embodiments, n is 4; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is hydrogen. In certain embodiments, n is 4; R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is a nitrogen protecting group.

[000121] In certain embodiments, R^2 and R^3 are hydrogen. In certain embodiments, R^2 is hydrogen; and R^3 is optionally substituted alkyl. In certain embodiments, R^2 is hydrogen; and R^3 is halogen. In certain embodiments, R^2 and R^3 are each independently optionally substituted alkyl. In certain embodiments, R^2 and R^3 are each independently substituted alkyl. In certain embodiments, R^2 and R^3 are each independently unsubstituted alkyl. In certain

embodiments, R^2 is substituted alkyl and R^3 is unsubstituted alkyl. In certain embodiments, R^2 and R^3 are each independently halogen.

[000122] In certain embodiments, n is 1; and R^2 and R^3 are hydrogen. In certain embodiments, n is 1; R^2 is hydrogen; and R^3 is optionally substituted alkyl. In certain embodiments, n is 1; R^2 is hydrogen; and R^3 is halogen. In certain embodiments, n is 1; and R^2 and R^3 are each independently optionally substituted alkyl. In certain embodiments, n is 1; R^2 is substituted alkyl; and R^3 is unsubstituted alkyl. In certain embodiments, n is 1; and R^2 and R^3 are each independently halogen.

[000123] In certain embodiments, n is 2; and R^2 and R^3 are hydrogen. In certain embodiments, n is 2; R^2 is hydrogen; and R^3 is optionally substituted alkyl. In certain embodiments, n is 2; R^2 is hydrogen; and R^3 is halogen. In certain embodiments, n is 2; and R^2 and R^3 are each independently optionally substituted alkyl. In certain embodiments, n is 2; R^2 is substituted alkyl; and R^3 is unsubstituted alkyl. In certain embodiments, n is 2; and R^2 and R^3 are each independently halogen.

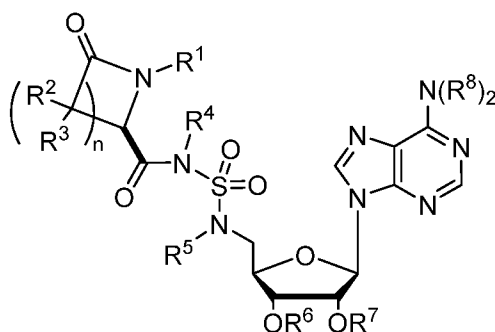
[000124] In certain embodiments, n is 3; and R^2 and R^3 are hydrogen. In certain embodiments, n is 3; R^2 is hydrogen; and R^3 is optionally substituted alkyl. In certain embodiments, n is 3; R^2 is hydrogen; and R^3 is halogen. In certain embodiments, n is 3; and R^2 and R^3 are each independently optionally substituted alkyl. In certain embodiments, n is 3; R^2 is substituted alkyl; and R^3 is unsubstituted alkyl. In certain embodiments, n is 3; and R^2 and R^3 are each independently halogen.

[000125] In certain embodiments, n is 4; and R^2 and R^3 are hydrogen. In certain embodiments, n is 4; R^2 is hydrogen; and R^3 is optionally substituted alkyl. In certain embodiments, n is 4; R^2 is hydrogen; and R^3 is halogen. In certain embodiments, n is 4; and R^2 and R^3 are each independently optionally substituted alkyl. In certain embodiments, n is 4; R^2 is substituted alkyl; and R^3 is unsubstituted alkyl. In certain embodiments, n is 4; and R^2 and R^3 are each independently halogen.

[000126] In certain embodiments, R^1 and R^4 are hydrogen. In certain embodiments, R^1 , R^4 , and R^5 are hydrogen. In certain embodiments, R^1 , R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, R^1 is optionally substituted alkyl; and R^4 is hydrogen. In certain embodiments, R^1 is optionally substituted alkyl; and R^4 and R^5 are hydrogen. In certain embodiments, R^1 is optionally substituted alkyl; and R^4 , R^5 , and each instance of R^8 are hydrogen. In certain embodiments, R^1 , R^4 , and R^5 are each independently a nitrogen protecting group. In certain embodiments, R^1 , R^4 , and R^5 are each independently a nitrogen protecting group; and each instance of R^8 is hydrogen. In certain embodiments, R^1 , R^4 , and

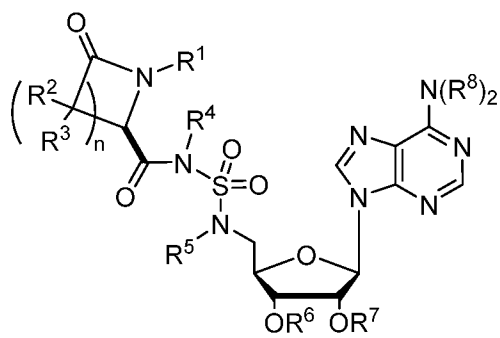
R^5 are each independently a nitrogen protecting group; and each instance of R^8 is a nitrogen protecting group.

[000127] In certain embodiments, the compound of Formula (I) is of the formula:



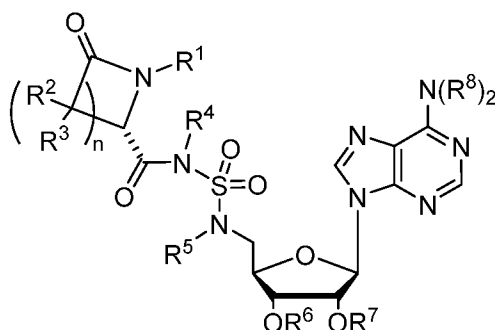
or a pharmaceutically acceptable salt thereof.

[000128] In certain embodiments, the compound of Formula (I) is of the formula:



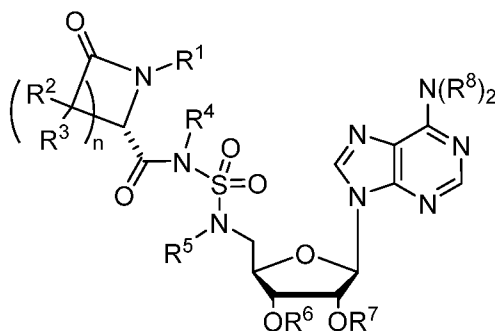
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000129] In certain embodiments, the compound of Formula (I) is of the formula:



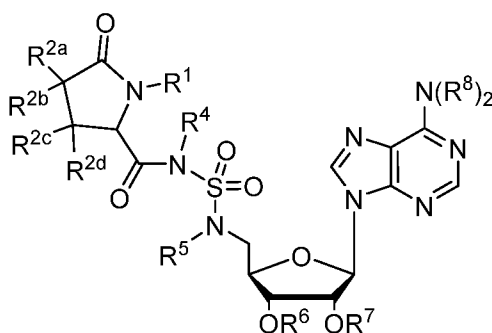
or a pharmaceutically acceptable salt thereof.

[000130] In certain embodiments, the compound of Formula (I) is of the formula:



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

[000131] In certain embodiments, the present disclosure provides compounds of Formula (I-a):



(I-a)

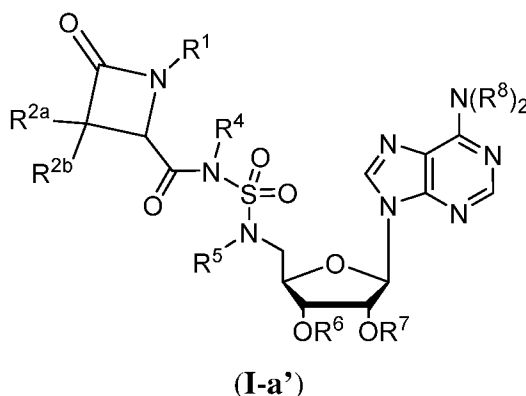
and pharmaceutically acceptable salts thereof,

wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein; and

each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl.

[000132] In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000133] In certain embodiments, the present disclosure provides compounds of Formula (I-a'):



and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein; and each of R^{2a} and R^{2b} is independently hydrogen, halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl.

[000134] In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a'), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000135] As generally defined herein, R^{2a} is independently hydrogen, halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2a} is hydrogen. In certain embodiments, R^{2a} is halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2a} is halogen. In certain embodiments, R^{2a} is F. In certain embodiments, R^{2a} is Cl. In certain embodiments, R^{2a} is Br. In certain embodiments, R^{2a} is I. In certain embodiments, R^{2a} is optionally substituted alkyl.

In certain embodiments, R^{2a} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{2a} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2a} is methyl or ethyl.

[000136] As generally defined herein, R^{2b} is independently hydrogen, halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2b} is hydrogen. In certain embodiments, R^{2b} is halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2b} is halogen. In certain embodiments, R^{2b} is F. In certain embodiments, R^{2b} is Cl. In certain embodiments, R^{2b} is Br. In certain embodiments, R^{2b} is I. In certain embodiments, R^{2b} is optionally substituted alkyl. In certain embodiments, R^{2b} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{2b} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2b} is methyl or ethyl.

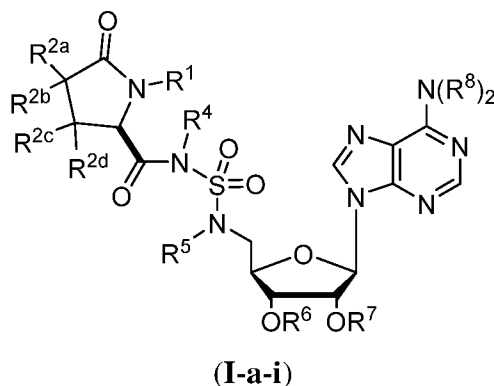
[000137] As generally defined herein, R^{2c} is independently hydrogen, halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2c} is hydrogen. In certain embodiments, R^{2c} is halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2c} is halogen. In certain embodiments, R^{2c} is F. In certain embodiments, R^{2c} is Cl. In certain embodiments, R^{2c} is Br. In certain embodiments, R^{2c} is I. In certain embodiments, R^{2c} is optionally substituted alkyl. In certain embodiments, R^{2c} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{2c} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{2c} is methyl or ethyl.

[000138] As generally defined herein, R^{2d} is independently hydrogen, halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,

optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2d} is hydrogen. In certain embodiments, R^{2d} is halogen, -CN, -NO₃, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl. In certain embodiments, R^{2d} is halogen. In certain embodiments, R^{2d} is F. In certain embodiments, R^{2d} is Cl. In certain embodiments, R^{2d} is Br. In certain embodiments, R^{2d} is I. In certain embodiments, R^{2d} is optionally substituted alkyl. In certain embodiments, R^{2d} is optionally substituted C₁₋₆ alkyl. In certain embodiments, R^{2d} is unsubstituted C₁₋₆ alkyl. In certain embodiments, R^{2d} is methyl or ethyl.

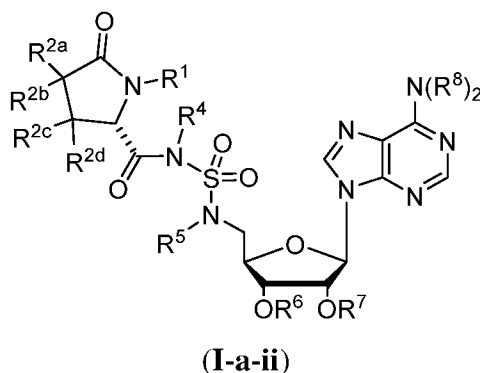
[000139] In certain embodiments, at least one of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is hydrogen. In certain embodiments, one of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is hydrogen. In certain embodiments, two of R^{2a} , R^{2b} , R^{2c} , and R^{2d} are hydrogen. In certain embodiments, three of R^{2a} , R^{2b} , R^{2c} , and R^{2d} are hydrogen. In certain embodiments, all of R^{2a} , R^{2b} , R^{2c} , and R^{2d} are hydrogen.

[000140] In certain embodiments of Formula (I-a), the present disclosure provides compounds of Formula (I-a-i):



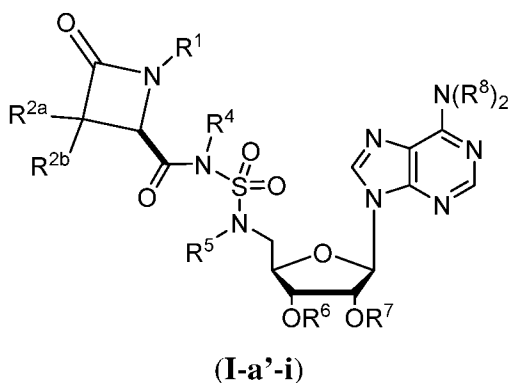
[000141] and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{2a} , R^{2b} , R^{2c} , and R^{2d} are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a-i), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000142] In certain embodiments of Formula (I-a), the present disclosure provides compounds of Formula (I-a-ii):



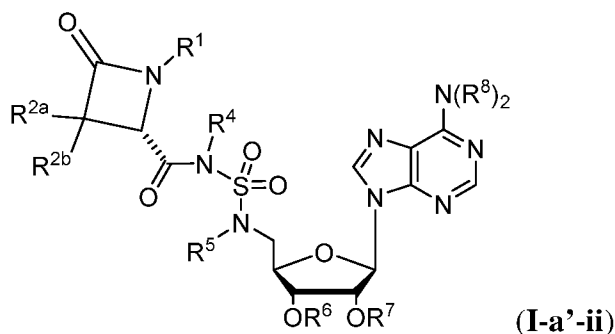
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{2a} , R^{2b} , R^{2c} , and R^{2d} are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a-ii), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000143] In certain embodiments of Formula (I-a'), the present disclosure provides compounds of Formula (I-a'-i):



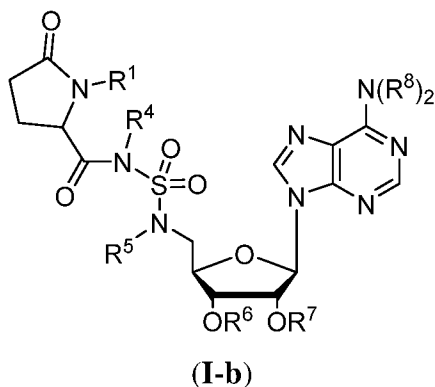
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{2a} , R^{2b} , R^{2c} , and R^{2d} are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a'-i), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000144] In certain embodiments of Formula (I-a'), the present disclosure provides compounds of Formula (I-a'-ii):



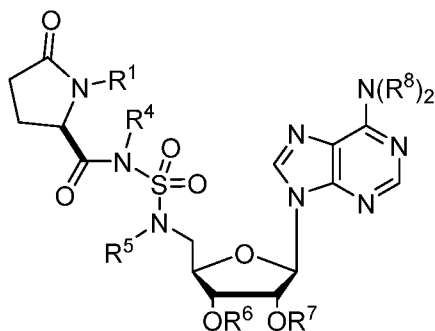
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{2a} , R^{2b} , R^{2c} , and R^{2d} are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-a'-ii), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000145] In certain embodiments of Formula (I), the present disclosure provides compounds of Formula (I-b):



and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

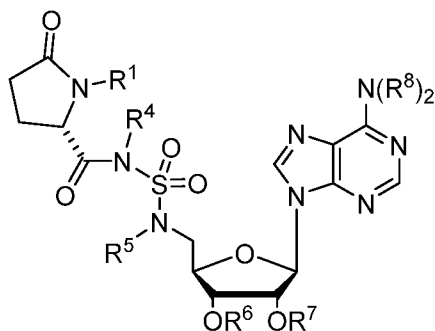
[000146] In certain embodiments of Formula (I-b), the present disclosure provides compounds of Formula (I-b-i):



(I-b-i)

and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b-i), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

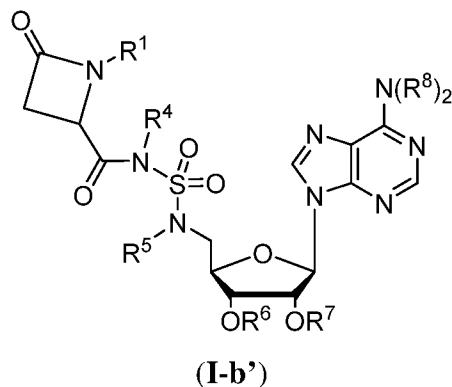
[000147] In certain embodiments of Formula (I-b), the present disclosure provides compounds of Formula (I-b-ii):



(I-b-ii)

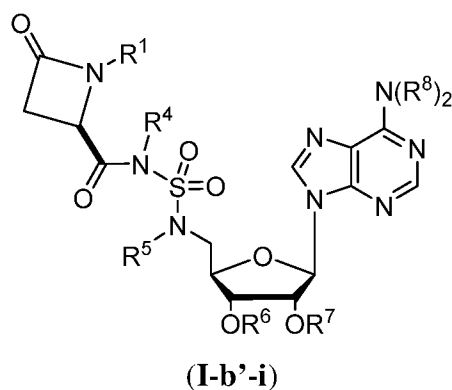
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b-ii), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000148] In certain embodiments of Formula (I), the present disclosure provides compounds of Formula (I-b'):



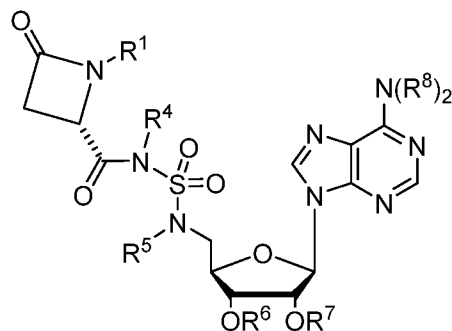
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b'), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000149] In certain embodiments of Formula (I-b'), the present disclosure provides compounds of Formula (I-b'-i):



and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b'-i), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

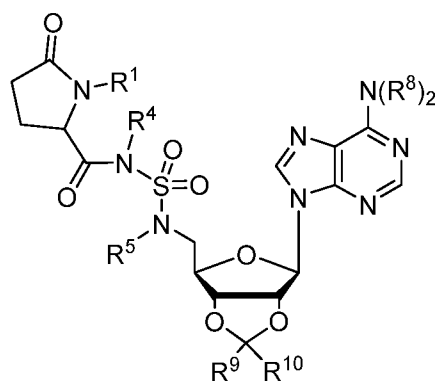
[000150] In certain embodiments of Formula (I-b'), the present disclosure provides compounds of Formula (I-b'-ii):



(I-b'-ii)

and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , R^6 , R^7 , and R^8 are as defined herein. In certain embodiments, the compound of Formula (I) is a compound of Formula (I-b'-ii), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

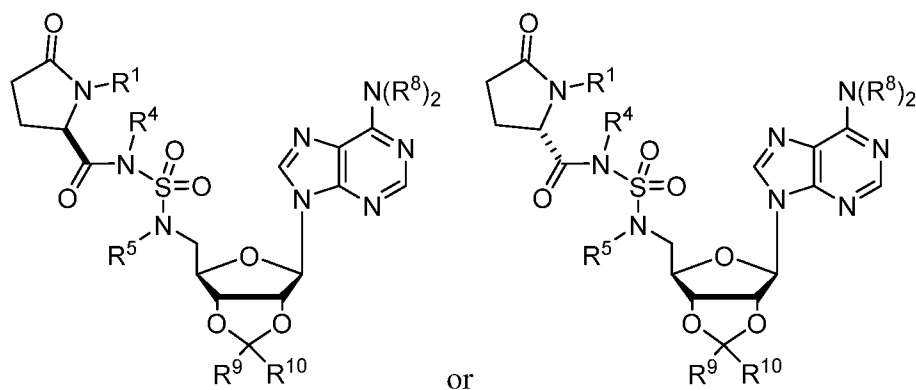
[000151] In certain embodiments of Formula (I), the present disclosure provides compounds of Formula (I-c):



(I-c)

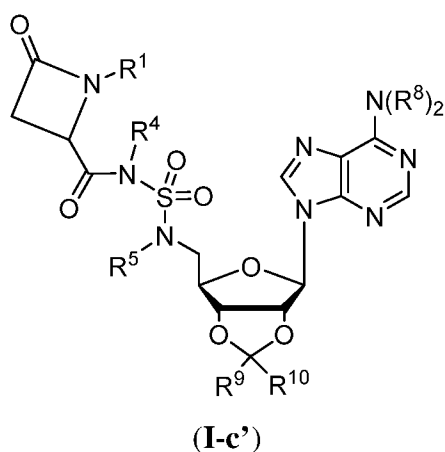
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , and R^8 are as defined herein; and each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

[000152] In certain embodiments of Formula (I-c), the present disclosure provides compounds of any one of the following formulae:



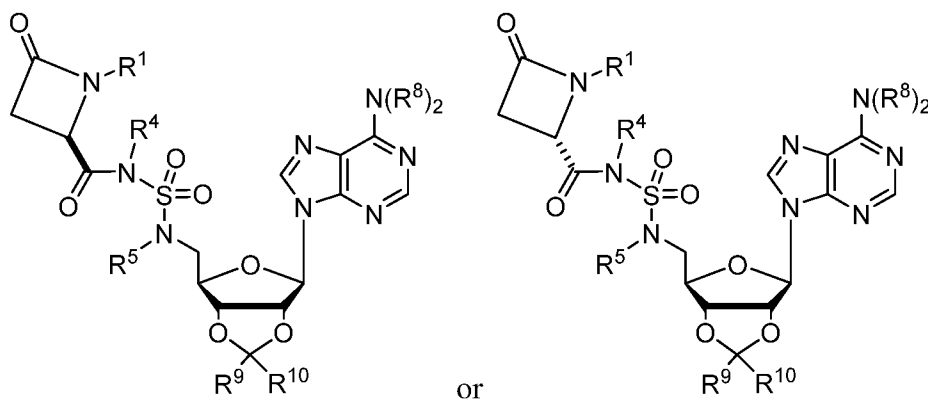
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , and R^8 are as defined herein; and each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

[000153] In certain embodiments of Formula (I), the present disclosure provides compounds of Formula (I-c'):



and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , and R^8 are as defined herein; and each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

[000154] In certain embodiments of Formula (I-c'), the present disclosure provides compounds of any one of the following formulae:



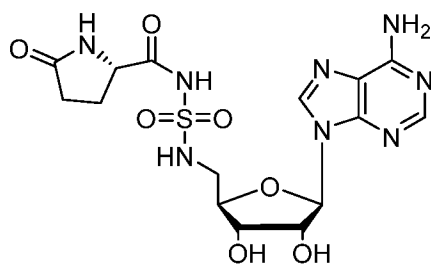
and pharmaceutically acceptable salts thereof, wherein R^1 , R^4 , R^5 , and R^8 are as defined herein; and each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

[000155] As generally defined herein, R^9 is hydrogen or optionally substituted alkyl. In certain embodiments, R^9 is hydrogen. In certain embodiments, R^9 is optionally substituted alkyl. In certain embodiments, R^9 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^9 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^9 is methyl.

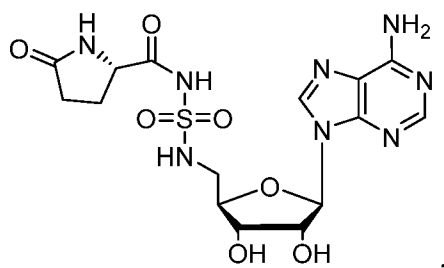
[000156] As generally defined herein, R^{10} is hydrogen or optionally substituted alkyl. In certain embodiments, R^{10} is hydrogen. In certain embodiments, R^{10} is optionally substituted alkyl. In certain embodiments, R^{10} is optionally substituted C_{1-6} alkyl. In certain embodiments, R^{10} is unsubstituted C_{1-6} alkyl. In certain embodiments, R^{10} is methyl.

[000157] In certain embodiments, R^9 and R^{10} are the same. In certain embodiments, R^9 and R^{10} are different. In certain embodiments, each of R^9 and R^{10} is independently optionally substituted alkyl. In certain embodiments, each of R^9 and R^{10} is independently optionally substituted C_{1-6} alkyl. In certain embodiments, each of R^9 and R^{10} is independently unsubstituted C_{1-6} alkyl. In certain embodiments, R^9 and R^{10} are methyl.

[000158] In certain embodiments, the compound of Formula (I) is of the formula:

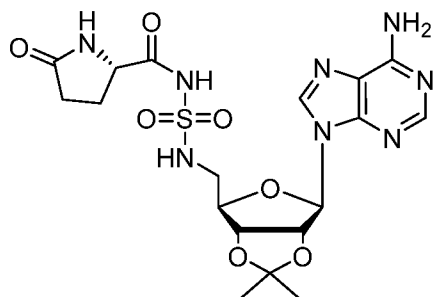


[000159] In certain embodiments, the compound of Formula (I) is of the formula:

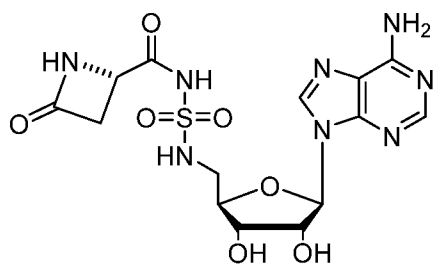


or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

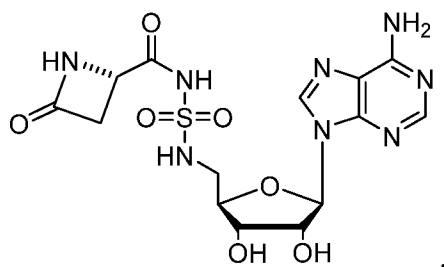
[000160] In certain embodiments, the compound of Formula (I) is of the formula:



[000161] In certain embodiments, the compound of Formula (I) is of the formula:

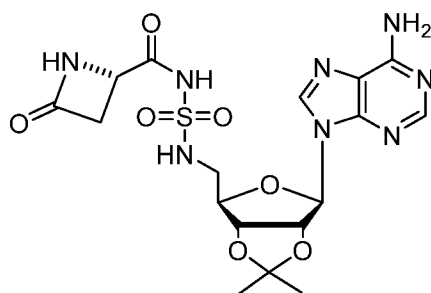


[000162] In certain embodiments, the compound of Formula (I) is of the formula:

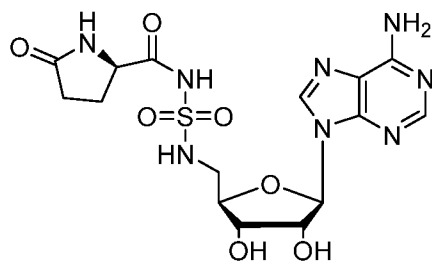


or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000163] In certain embodiments, the compound of Formula (I) is of the formula:

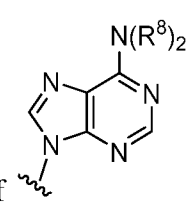


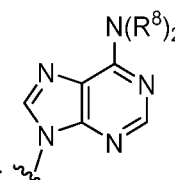
[000164] In certain embodiments, the compound of Formula (I) is of the formula:

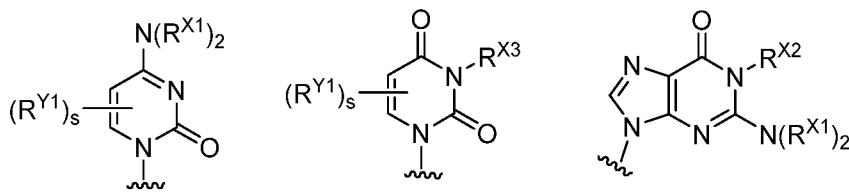


(D-Gln-lactam-SA or D-pGlu),

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

[000165] In certain embodiments of Formula (I), the base moiety of  can be replaced with another nucleobase or a derivative thereof. As used herein, a nucleobase is nitrogen-containing heteroaryl linked to a sugar within nucleosides. In certain embodiments,

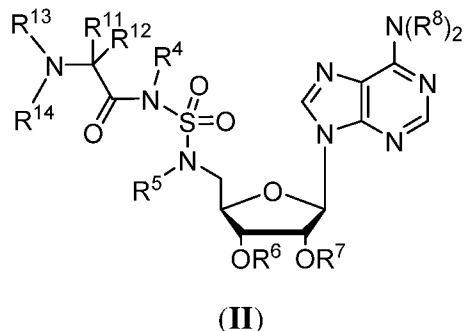
the base moiety of  in Formula (I) can be replaced with one of the following formulae:



wherein each instance of R^{X1} , R^{X2} , and R^{X3} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; each instance of R^{Y1} is independently hydrogen, halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl,

optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl; and s is 0, 1, or 2.

[000166] In another aspect, the present disclosure provides compounds of Formula (II):



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

R^{11} is hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a side chain of a natural amino acid;

R^{12} is hydrogen, halogen, or optionally substituted alkyl;

R^{13} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

R^{14} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

or R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

or R^{13} and R^{14} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

R^4 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

R^5 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

each of R^6 and R^7 is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group, or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring; and

each instance of R^8 is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or two R^8 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.

[000167] In certain embodiments, R¹¹ is hydrogen. In certain embodiments, R¹¹ is as described herein, provided that R¹¹ is not hydrogen. In certain embodiments, R¹¹ is halogen (*e.g.*, F, Cl, Br, or I).

[000168] In certain embodiments, R¹¹ is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkyl). In certain embodiments, R¹¹ is Me. In certain embodiments, R¹¹ is substituted methyl (*e.g.*, fluorinated methyl (*e.g.*, -CF₃), Bn, -CH₂SH, (1*H*-indol-3-yl)methyl, -CH₂OH, (1*H*-imidazol-4-yl)methyl, -CH₂COOH, (*para*-hydroxyphenyl)methyl, or -CH₂C(=O)NH₂). In certain embodiments, R¹¹ is Et. In certain embodiments, R¹¹ is substituted ethyl (*e.g.*, fluorinated ethyl, -CH₂CH₂SMe, -CH(OH)Me, -CH₂CH₂COOH, or -CH₂CH₂C(=O)NH₂). In certain embodiments, R¹¹ is Pr (*e.g.*, *n*-Pr or *i*-Pr). In certain embodiments, R¹¹ is substituted propyl (*e.g.*, fluorinated propyl, -CH₂CH₂CH₂NHC(=NH)NH₂ or -CH₂CH₂CH₂NHC(=NH)-NH-NO₂). In certain embodiments, R¹¹ is -CH₂CH₂CH₂NHC(=NH)-NH-NO₂. In certain embodiments, R¹¹ is Bu (*e.g.*, *n*-Bu, *s*-Bu, *t*-Bu, or *i*-Bu). In certain embodiments, R¹¹ is substituted butyl (*e.g.*, fluorinated butyl or -CH₂CH₂CH₂CH₂NH₂). In certain embodiments, R¹¹ is unsubstituted pentyl, substituted pentyl (*e.g.*, fluorinated pentyl), unsubstituted hexyl, or substituted hexyl (*e.g.*, fluorinated hexyl).

[000169] In certain embodiments, R¹¹ is substituted or unsubstituted alkenyl (*e.g.*, substituted or unsubstituted C₂₋₆ alkenyl). In certain embodiments, R¹¹ is substituted or unsubstituted alkynyl (*e.g.*, substituted or unsubstituted C₁₋₆ alkynyl). In certain embodiments, R¹¹ is substituted or unsubstituted carbocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic carbocyclyl comprising zero, one, or two double bonds in the carbocyclic ring system). In certain embodiments, R¹¹ is substituted or unsubstituted heterocyclyl (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclyl comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur). In certain embodiments, R¹¹ is substituted or unsubstituted aryl (*e.g.*, substituted or unsubstituted, 6- to 10-membered aryl). In certain embodiments, R¹¹ is substituted or unsubstituted phenyl. In certain embodiments, R¹¹ is substituted or unsubstituted heteroaryl (*e.g.*, substituted or unsubstituted, 5- to 6-membered, monocyclic heteroaryl, wherein one, two, three, or four atoms in the heteroaryl ring system are independently nitrogen, oxygen, or sulfur).

[000170] In certain embodiments, R^{11} is a side chain of a natural amino acid. In certain embodiments, R^{11} is Bn, $-\text{CH}_2\text{CH}_2\text{SMe}$, $-\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{SH}$, (1*H*-indol-3-yl)methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$, Me, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, (1*H*-imidazol-4-yl)methyl, $-\text{CH}(\text{OH})\text{Me}$, $-\text{CH}_2\text{COOH}$, (*para*-hydroxyphenyl)methyl, $-\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{NH}_2$, or $-\text{CH}_2\text{C}(=\text{O})\text{NH}_2$.

[000171] In certain embodiments, R^{12} is H. In certain embodiments, R^{12} is halogen (*e.g.*, F, Cl, Br, or I). In certain embodiments, R^{12} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{12} is Me. In certain embodiments, R^{12} is substituted methyl (*e.g.*, $-\text{CF}_3$ or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl).

[000172] In certain embodiments, R^{13} is H. In certain embodiments, R^{13} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{13} is Me. In certain embodiments, R^{13} is substituted methyl (*e.g.*, $-\text{CF}_3$ or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl). In certain embodiments, R^{13} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[000173] In certain embodiments, R^{14} is H. In certain embodiments, R^{14} is substituted or unsubstituted alkyl (*e.g.*, substituted or unsubstituted C_{1-6} alkyl). In certain embodiments, R^{14} is Me. In certain embodiments, R^{14} is substituted methyl (*e.g.*, $-\text{CF}_3$ or Bn), Et, substituted ethyl (*e.g.*, fluorinated ethyl), Pr, substituted propyl (*e.g.*, fluorinated propyl), Bu, or substituted butyl (*e.g.*, fluorinated butyl). In certain embodiments, R^{14} is a nitrogen protecting group (*e.g.*, Bn, Boc, Cbz, Fmoc, trifluoroacetyl, triphenylmethyl, acetyl, or Ts).

[000174] In certain embodiments, R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system are independently nitrogen, oxygen, or sulfur, provided that at least one atom in the heterocyclic ring system is nitrogen). In certain embodiments, R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted pyrrolidinyl ring.

[000175] In certain embodiments, R^{13} and R^{14} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring (*e.g.*, substituted or unsubstituted, 3- to 7-membered, monocyclic heterocyclic ring comprising zero, one, or two double bonds in the heterocyclic ring system, wherein one, two, or three atoms in the heterocyclic ring system

are independently nitrogen, oxygen, or sulfur, provided that at least one atom in the heterocyclic ring system is nitrogen).

[000176] In certain embodiments, R^4 of Formula (II) is as described herein for R^4 of Formula (I).

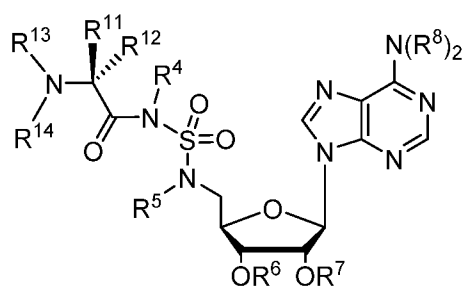
[000177] In certain embodiments, R^5 of Formula (II) is as described herein for R^5 of Formula (I).

[000178] In certain embodiments, R^6 of Formula (II) is as described herein for R^6 of Formula (I).

[000179] In certain embodiments, R^7 of Formula (II) is as described herein for R^7 of Formula (I).

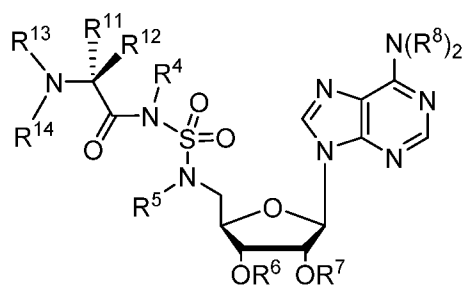
[000180] In certain embodiments, R^8 of Formula (II) is as described herein for R^8 of Formula (I).

[000181] In certain embodiments, the compound of Formula (II) is of the formula:



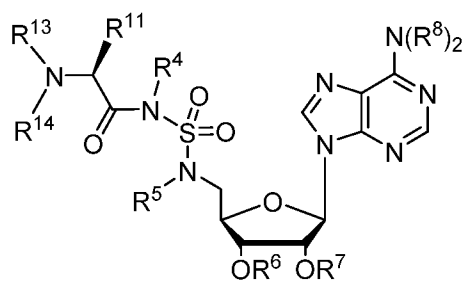
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000182] In certain embodiments, the compound of Formula (II) is of the formula:



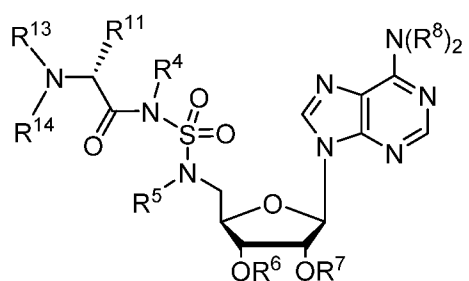
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000183] In certain embodiments, the compound of Formula (II) is of the formula:



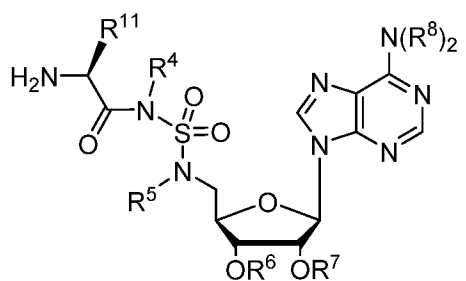
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000184] In certain embodiments, the compound of Formula (II) is of the formula:



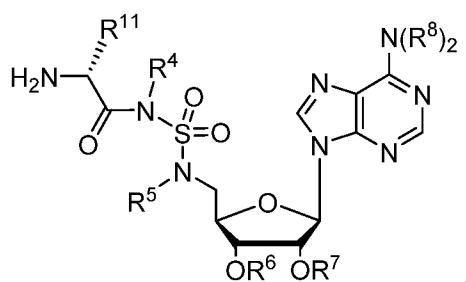
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000185] In certain embodiments, the compound of Formula (II) is of the formula:



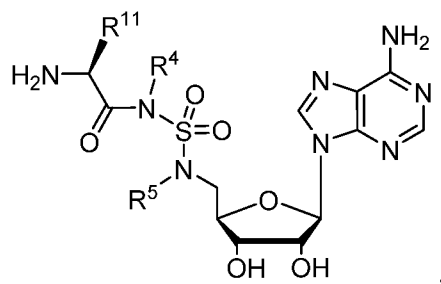
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000186] In certain embodiments, the compound of Formula (II) is of the formula:



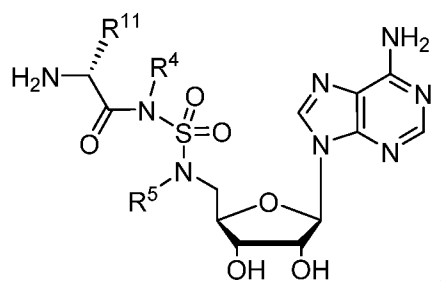
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000187] In certain embodiments, the compound of Formula (II) is of the formula:



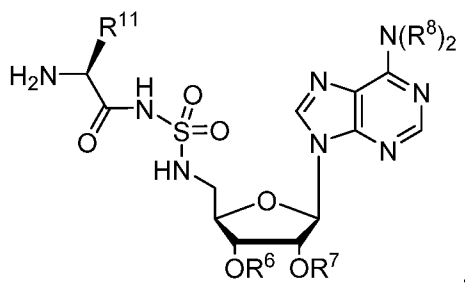
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000188] In certain embodiments, the compound of Formula (II) is of the formula:



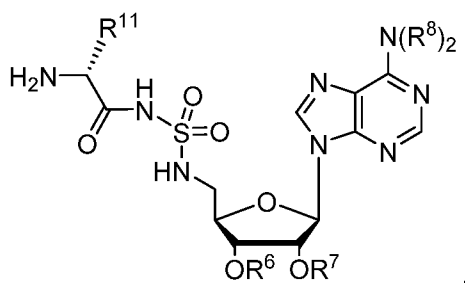
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000189] In certain embodiments, the compound of Formula (II) is of the formula:



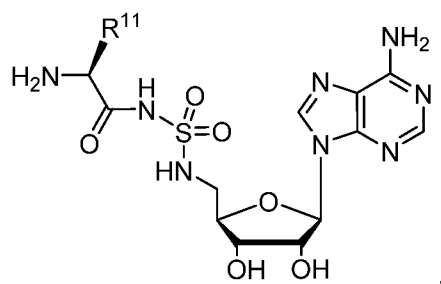
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000190] In certain embodiments, the compound of Formula (II) is of the formula:



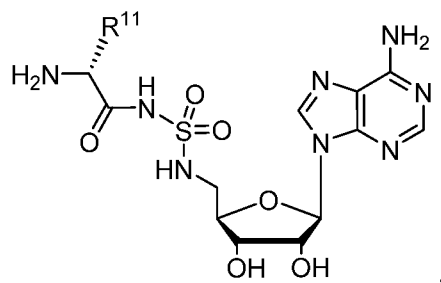
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000191] In certain embodiments, the compound of Formula (II) is of the formula:



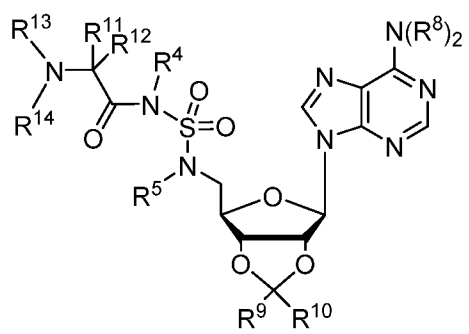
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof.

[000192] In certain embodiments, the compound of Formula (II) is of the formula:



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

[000193] In certain embodiments, the compound of Formula (II) is of the formula:

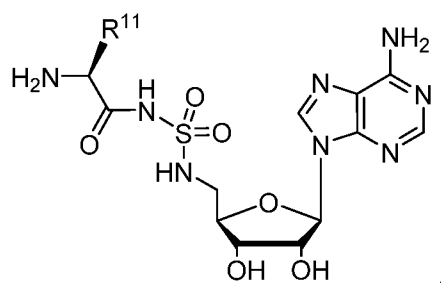


or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein each of R⁹ and R¹⁰ is independently hydrogen or optionally substituted alkyl.

[000194] In certain embodiments, R⁹ of Formula (II) is as described herein for R⁹ of Formula (I).

[000195] In certain embodiments, R¹⁰ of Formula (II) is as described herein for R¹⁰ of Formula (I).

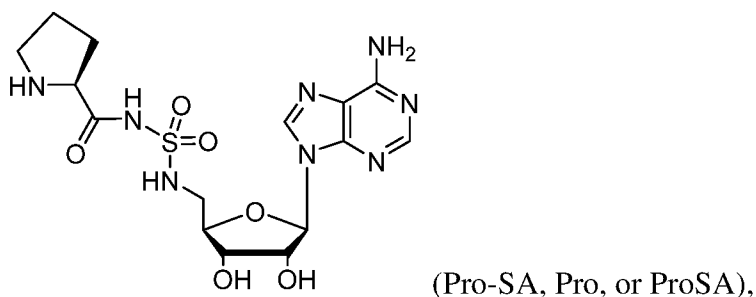
[000196] In certain embodiments, the compound of Formula (II) is of the formula:



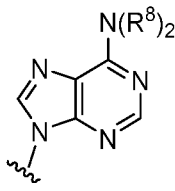
or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, wherein R¹¹ is as shown in the table below:

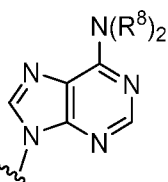
Compound Number		R ¹¹
Phe-SA	Phe or PheSA	Bn
Met-SA	Met or MetSA	-CH ₂ CH ₂ SMe
Gly-SA	Gly or GlySA	H
Ile-SA	Ile or IleSA	-CH(Me)CH ₂ CH ₃
Cys-SA	Cys or CysSA	-CH ₂ SH
Trp-SA	Trp or TrpSA	(1 <i>H</i> -indol-3-yl)methyl
Ser-SA	Ser or SerSA	-CH ₂ OH
Arg-SA	Arg or ArgSA	-CH ₂ CH ₂ CH ₂ NHC(=NH)NH ₂
Ala-SA	Ala or AlaSA	Me
Lys-SA	Lys or LysSA	-CH ₂ CH ₂ CH ₂ CH ₂ NH ₂
Val-SA	Val or ValSA	-CH ₂ (CH ₃) ₂
Leu-SA	Leu or LeuSA	-CH ₂ CH(CH ₃) ₂
His-SA	His or HisSA	(1 <i>H</i> -imidazol-4-yl)methyl
Thr-SA	Thr or ThrSA	-CH(OH)Me
Asp-SA	Asp or AspSA	-CH ₂ COOH
Tyr-SA	Tyr or TyrSA	(<i>para</i> -hydroxyphenyl)methyl
Glu-SA	Glu or GluSA	-CH ₂ CH ₂ COOH
Gln-SA	Gln or GlnSA	-CH ₂ CH ₂ C(=O)NH ₂
Asn-SA	Asn or AsnSA	-CH ₂ C(=O)NH ₂
Arg-NO ₂ -SA	Arg-NO ₂ or ArgNo2	-CH ₂ CH ₂ CH ₂ NHC(=NH)-NH-NO ₂ .

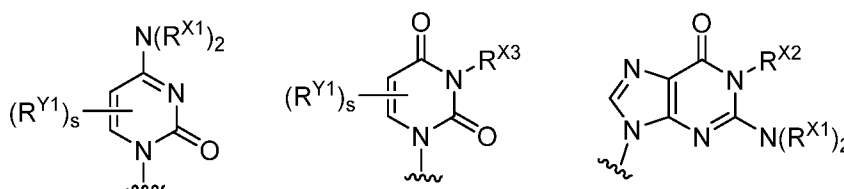
[000197] In certain embodiments, the compound of Formula (II) is of the formula:



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

[000198] In certain embodiments of Formula (II), the base moiety of  can be replaced with another nucleobase or a derivative thereof. As used herein, a nucleobase is nitrogen-containing heteroaryl linked to a sugar within nucleosides. In certain embodiments,

the base moiety of  in Formula (II) can be replaced with one of the following formulae:



wherein each instance of R^{X1} , R^{X2} , and R^{X3} is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group; each instance of R^{Y1} is independently hydrogen, halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, an optionally substituted amino group, or optionally substituted acyl; and s is 0, 1, or 2.

Pharmaceutical Compositions, Kits, and Administration

[000199] The present invention also provides pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, as described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, is provided in an effective amount in the pharmaceutical composition.

[000200] The present invention also provides pharmaceutical compositions comprising a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, as described herein, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical composition of the invention comprises a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient. In certain embodiments, the compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, is provided in an effective amount in the pharmaceutical composition.

[000201] In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount.

[000202] 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 described herein (*e.g.*, compound of Formula (I) or (II)) into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[000203] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” is a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of

the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000204] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[000205] 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.

[000206] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[000207] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose, and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[000208] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic

derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60), sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor™), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F-68, Poloxamer-188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[000209] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[000210] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives. In certain embodiments, the preservative is an antioxidant. In other embodiments, the preservative is a chelating agent.

[000211] 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.

[000212] 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.

[000213] 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.

[000214] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[000215] 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.

[000216] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (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.

[000217] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[000218] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[000219] 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 mixtures thereof.

[000220] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the conjugates of the invention are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[000221] 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.

[000222] 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.

[000223] 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.

[000224] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the conjugates of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[000225] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may include a buffering agent.

[000226] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets,

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

[000227] The active ingredient can be in a micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[000228] Dosage forms for topical and/or transdermal administration of a compound of this invention may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any needed preservatives and/or buffers as can be required. Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[000229] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin. Jet injection

devices which deliver liquid compositions to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Ballistic powder/particle delivery devices which use compressed gas to accelerate the compound in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[000230] 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.

[000231] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000232] 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).

[000233] Pharmaceutical compositions of the invention formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[000234] Formulations described herein as being useful for pulmonary delivery may be useful for intranasal delivery of a pharmaceutical composition of the invention. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[000235] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) to as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets, and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[000236] A pharmaceutical composition of the invention can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension

of the active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention.

[000237] 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.

[000238] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[000239] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the

environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[000240] 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).

[000241] 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.

[000242] In certain embodiments, the compounds described herein (*e.g.*, compounds of Formula (I) or (II)) may be at dosage levels sufficient to deliver from about 0.001 mg/kg to about 100 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, preferably from about 0.1 mg/kg to about 40 mg/kg, preferably from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, and more preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[000243] 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.

[000244] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional pharmaceutical agents. The compounds or compositions can be administered in combination with additional pharmaceutical agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. It will

also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[000245] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. Pharmaceutical agents include therapeutically active agents. Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or on a time schedule determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents 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.

[000246] Exemplary additional pharmaceutical agents include, but are not limited to, anti-proliferative agents, anti-cancer agents, anti-diabetic agents, anti-inflammatory agents, anti-bacterial agents, anti-viral agents, immunosuppressant agents, and a pain-relieving agent. Pharmaceutical agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[000247] Also encompassed by the invention are kits (*e.g.*, pharmaceutical packs). The inventive kits may be useful for preventing and/or treating a proliferative disease (*e.g.*, cancer (*e.g.*, leukemia, breast cancer, lung cancer, colon cancer, or cervical cancer), benign neoplasm, angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease). The inventive kits may also be useful for preventing and/or treating an infectious disease (*e.g.*, a bacterial infection, a viral infection, a fungal infection, or a parasitic disease). The kits provided may comprise an inventive pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable

container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of an inventive pharmaceutical composition or compound. In some embodiments, the inventive pharmaceutical composition or compound provided in the container and the second container are combined to form one unit dosage form.

[000248] Thus, in one aspect, provided are kits including a first container comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the kit of the invention includes a first container comprising a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the kits are useful in preventing and/or treating a proliferative disease in a subject. In certain embodiments, the kits are useful in preventing and/or treating an infectious disease in a subject. In certain embodiments, the kits further include instructions for administering the compound, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, and prodrug thereof, or a pharmaceutical composition thereof, to a subject to prevent and/or treat a proliferative disease.

Methods of Treatment and Uses

[000249] The present invention also provides methods of using the compounds of Formula (I), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for the treatment and/or prevention of a proliferative disease such as cancer (*e.g.*, leukemia, breast cancer, lung cancer, colon cancer, or cervical cancer), benign neoplasm, diseases related to angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease in a subject.

[000250] The present invention also provides methods of using the compounds of Formula (II), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, and prodrugs thereof, and pharmaceutical compositions thereof, for the treatment and/or prevention of a proliferative disease such as cancer (*e.g.*, leukemia, breast cancer, lung cancer, colon cancer, or cervical cancer), benign neoplasm, diseases related to angiogenesis, inflammatory disease, autoinflammatory disease, or autoimmune disease in a subject.

[000251] In some embodiments, a provided compound is useful in treating a cancer. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of cancer. In some embodiments, a provided compound is administered in combination with another pharmaceutical agent to treat cancer.

[000252] In some embodiments, compounds described herein are useful for treating a cancer including, but 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 sarcoma, eye cancer (*e.g.*, intraocular melanoma, retinoblastoma), familial 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)), hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma (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 above; 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 adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), islet cell tumors), penile cancer (*e.g.*, Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), 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).

[000253] In some embodiments, a provided compound is useful in treating a hematologic cancer. In certain embodiments, the hematologic cancer is a leukemia. In certain

embodiments, the hematologic cancer is a lymphoma. In certain embodiments, the leukemia is AML. In certain embodiments, the leukemia is CML. In certain embodiments, the leukemia is CLL. In certain embodiments, the hematologic cancer is multiple myeloma. In some embodiments, a provided compound is useful in treating a solid tumor. In certain embodiments, the solid tumor is lung cancer, pancreatic cancer, breast cancer, prostate cancer, colon cancer, or cervical cancer. In some embodiments, a provided compound is useful in treating lung cancer. In some embodiments, a provided compound is useful in treating pancreatic cancer. In some embodiments, a provided compound is useful in treating breast cancer. In some embodiments, a provided compound is useful in treating prostate cancer. In some embodiments, a provided compound is useful in treating colon cancer. In some embodiments, a provided compound is useful in treating cervical cancer.

[000254] In some embodiments, a provided compound is useful in treating advanced staged cancer. In some embodiments, a provided compound is useful in treating metastatic cancer. In some embodiments, a provided compound is useful in treating metastatic hematologic cancer (*e.g.*, leukemia, lymphoma, or myeloma). In some embodiments, a provided compound is useful in treating a metastatic solid tumor (*e.g.*, lung cancer, pancreatic cancer, breast cancer, prostate cancer, colon cancer, or cervical cancer).

[000255] In some embodiments, the proliferative disease is a benign neoplasm. All types of benign neoplasms disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is associated with angiogenesis. All types of angiogenesis disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the proliferative disease is an inflammatory disease. All types of inflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In certain embodiments, the inflammatory disease is rheumatoid arthritis. In some embodiments, the proliferative disease is an autoinflammatory disease. All types of autoinflammatory diseases disclosed herein or known in the art are contemplated as being within the scope of the invention. In some embodiments, the proliferative disease is an autoimmune disease. All types of autoimmune diseases disclosed herein or known in the art are contemplated as being within the scope of the invention.

[000256] The present invention also provides methods of inhibiting the activity of an aminoacyl tRNA synthetase in a biological sample or a subject.

[000257] The present invention also provides methods of inhibiting cell growth in a biological sample or subject.

[000258] In still another aspect, the present invention provides methods of inducing apoptosis of a cell in a biological sample or a subject.

[000259] The cell described herein may be an abnormal cell. The cell may be *in vitro* or *in vivo*. In certain embodiments, the cell is a dividing cell. In certain embodiments, the cell is a blood cell. In certain embodiments, the cell is a lymphocyte. In certain embodiments, the cell is a cancer cell. In certain embodiments, the cell is a leukemia cell. In certain embodiments, the cell is a melanoma cell. In certain embodiments, the cell is a multiple myeloma cell. In certain embodiments, the cell is a neoplastic cell. In certain embodiments, the cell is an endothelial cell. In certain embodiments, the cell is an immune cell.

[000260] In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[000261] In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, polymorph, co-crystal, tautomer, stereoisomer, isotopically labeled derivative, or prodrug thereof, or a pharmaceutical composition thereof. In certain embodiments, the methods described herein include administering to a subject or contacting a biological sample with an effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[000262] In certain embodiments, the compound is administered in combination with one or more additional pharmaceutical agents described herein. In certain embodiments, the additional pharmaceutical agent is an anti-proliferative agent. In certain embodiments, the additional pharmaceutical agent is an anti-cancer agent. Anti-cancer agents encompass biotherapeutic anti-cancer agents as well as chemotherapeutic agents. Exemplary biotherapeutic anti-cancer agents include, but are not limited to, interferons, cytokines (*e.g.*, tumor necrosis factor, interferon α , interferon γ), vaccines, hematopoietic growth factors, monoclonal serotherapy, immunostimulants and/or immunodulatory agents (*e.g.*, IL-1, 2, 4, 6, or 12), immune cell growth factors (*e.g.*, GM-CSF) and antibodies (*e.g.*, HERCEPTIN

(trastuzumab), T-DM1, AVASTIN (bevacizumab), ERBITUX (cetuximab), VECTIBIX (panitumumab), RITUXAN (rituximab), BEXXAR (tositumomab)). Exemplary chemotherapeutic agents include, but are not limited to, anti-estrogens (*e.g.*, tamoxifen, raloxifene, and megestrol), LHRH agonists (*e.g.*, goserelin and leuprolide), anti-androgens (*e.g.*, flutamide and bicalutamide), photodynamic therapies (*e.g.*, vertoporphin (BPD-MA), phthalocyanine, photosensitizer Pc4, and demethoxy-hypocrellin A (2BA-2-DMHA)), nitrogen mustards (*e.g.*, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.*, carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.*, busulfan and treosulfan), triazenes (*e.g.*, dacarbazine, temozolomide), platinum containing compounds (*e.g.*, cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.*, vincristine, vinblastine, vindesine, and vinorelbine), taxoids (*e.g.*, paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (ABRAXANE), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, *e.g.*, 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.*, etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptothecin, irinotecan, crisnatol, mytomicin C), anti-metabolites, DHFR inhibitors (*e.g.*, methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (*e.g.*, mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonucleotide reductase inhibitors (*e.g.*, hydroxyurea and deferoxamine), uracil analogs (*e.g.*, 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.*, cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (*e.g.*, mercaptopurine and Thioguanine), Vitamin D3 analogs (*e.g.*, EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.*, lovastatin), dopaminergic neurotoxins (*e.g.*, 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.*, staurosporine), actinomycin (*e.g.*, actinomycin D, dactinomycin), bleomycin (*e.g.*, bleomycin A2, bleomycin B2, peplomycin), anthracycline (*e.g.*, daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.*, verapamil), Ca²⁺ ATPase inhibitors (*e.g.*, thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (*e.g.*, axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTINTM, AZD2171), dasatinib (SPRYCEL[®], BMS-354825), erlotinib (TARCEVA[®]), gefitinib (IRESSA[®]), imatinib (Gleevec[®], CGP57148B,

STI-571), lapatinib (TYKERB[®], TYVERB[®]), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA[®]), semaxanib (semaxinib, SU5416), sunitinib (SUTENT[®], SU11248), toceranib (PALLADIA[®]), vandetanib (ZACTIMA[®], ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN[®]), bevacizumab (AVASTIN[®]), rituximab (RITUXAN[®]), cetuximab (ERBITUX[®]), panitumumab (VECTIBIX[®]), ranibizumab (Lucentis[®]), nilotinib (TASIGNA[®]), sorafenib (NEXAVAR[®]), everolimus (AFINITOR[®]), alemtuzumab (CAMPATH[®]), gemtuzumab ozogamicin (MYLOTARG[®]), temsirolimus (TORISEL[®]), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK[™]), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF[®]), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.*, bortezomib (VELCADE)), mTOR inhibitors (*e.g.*, rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Novartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genetech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine, carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbazine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin., aminopterin, and hexamethyl melamine.

[000263] In another aspect, the present invention provides methods of treating or preventing an infectious disease comprising administering to the subject a therapeutically effective amount of a compound as described herein or a pharmaceutical composition thereof. In certain embodiments, the subject is suffering from a bacterial infection. In certain embodiments, the subject is susceptible to having a bacterial infection. In certain embodiments, the subject has been exposed or is at risk of being exposed to a pathogenic microorganism. The infection may be prevented or at least the chances of infection may be reduced by the administration of a prophylactic amount of the a compound described herein.

[000264] In yet another aspect, provided is a method of treating or preventing a bacterial infection caused by bacteria that are resistant to other treatments. In certain embodiments, provided is a method of treating or preventing a bacterial infection caused by bacteria that are multi-drug tolerant. In certain embodiments, provided is a method of treating or preventing a bacterial infection caused by bacteria that are multi-drug resistant. In certain embodiments, provided is a method of treating or preventing a bacterial infection caused by bacteria that

neither grow nor die in the presence other treatments. In certain embodiments, provided is a method of treating or preventing a bacterial infection caused by bacteria that neither grow nor die as a result of other treatments. In certain embodiments, provided methods can be conducted *in vivo* (*i.e.*, by administration to a subject).

[000265] Infectious diseases are typically caused by microbial pathogens (*e.g.*, viruses, viroids, prions, microorganisms such as bacteria, nematodes such as roundworms and pinworms, arthropods such as ticks, mites, fleas, and lice, fungi such as ringworm, and parasites such as protozoa, multicellular parasites, or tapeworms) into the cells (“host cells”) of a subject (“host”). In certain embodiments, the infectious disease is a bacterial infection. In certain embodiments, the infectious disease is a mycobacterial infection. In certain embodiments, the infectious disease is a viral infection. In certain embodiments, the infectious disease is a parasitic infection. In certain embodiments, the infectious disease is a multicellular-parasitic infection. In certain embodiments, the infectious disease is a fungal infection. In certain embodiments, the infectious disease is a protozoan infection.

[000266] In certain embodiments, the bacterial infection being treated or prevented is an infection caused by or involving a Gram positive bacteria. Exemplary Gram negative bacteria include, but are not limited to, *Staphylococcus*, *Streptococcus*, *Micrococcus*, *Peptococcus*, *Peptostreptococcus*, *Enterococcus*, *Bacillus*, *Clostridium*, *Lactobacillus*, *Listeria*, *Erysipelothrix*, *Propionibacterium*, *Eubacterium*, and *Corynebacterium*. In certain embodiments, the Gram positive bacteria is a bacteria of the phylum *Firmicutes*. In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Enterococcus*, *i.e.*, the bacterial infection is an *Enterococcus* infection. Exemplary *Enterococci* bacteria include, but are not limited to, *E. avium*, *E. durans*, *E. faecalis*, *E. faecium*, *E. gallinarum*, *E. solitarius*, *E. casseliflavus*, and *E. raffinosus*. In certain embodiments, the *Enterococcus* infection is an *E. faecalis* infection. In certain embodiments, the *Enterococcus* infection is an *E. faecium* infection. In certain embodiments, the bacteria is a member of the phylum *Firmicutes* and the genus *Staphylococcus*, *i.e.*, the bacterial infection is a *Staphylococcus* infection. Exemplary *Staphylococci* bacteria include, but are not limited to, *S. arlettae*, *S. aureus*, *S. auricularis*, *S. capitis*, *S. caprae*, *S. carnosus*, *S. chromogenes*, *S. cohnii*, *S. condimenti*, *S. croceolyticus*, *S. delphini*, *S. devriesei*, *S. epidermis*, *S. equorum*, *S. felis*, *S. fluroettii*, *S. gallinarum*, *S. haemolyticus*, *S. hominis*, *S. hyicus*, *S. intermedius*, *S. kloosii*, *S. leei*, *S. lenus*, *S. lugdunensis*, *S. lutrae*, *S. lyticans*, *S. massiliensis*, *S. microti*, *S. muscae*, *S. nepalensis*, *S. pasteurii*, *S. penttenkoferi*, *S. piscifermentans*, *S. pseudointermedius*, *S. pseudolugdunensis*, *S. pulvereri*, *S. rostri*, *S. saccharolyticus*, *S. saprophyticus*, *S. schleiferi*, *S.*

sciuri, *S. simiae*, *S. simulans*, *S. stepanovicii*, *S. succinus*, *S. vitulinus*, *S. warneri*, and *S. xylosus*. In certain embodiments, the *Staphylococcus* infection is an *S. aureus* infection. In certain embodiments, the *Staphylococcus* infection is an *S. epidermis* infection.

[000267] In certain embodiments, the bacterial infection being treated or prevented is an infection caused by or involving a Gram negative bacteria. Exemplary Gram negative bacteria include, but are not limited to *Escherichia coli*, *Caulobacter crescentus*, *Pseudomonas aeruginosa*, *Agrobacterium tumefaciens*, *Branhamella catarrhalis*, *Citrobacter diversus*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella typhimurium*, *Neisseria meningitidis*, *Serratia marcescens*, *Shigella sonnei*, *Neisseria gonorrhoeae*, *Acinetobacter baumannii*, *Salmonella enteritidis*, *Fusobacterium nucleatum*, *Veillonella parvula*, *Bacteroides forsythus*, *Actinobacillus actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Helicobacter pylori*, *Francisella tularensis*, *Yersinia pestis*, *Morganella morganii*, *Edwardsiella tarda*, *Acinetobacter baumannii* and *Haemophilus influenzae*. In certain embodiments, the Gram negative bacteria species is *Escherichia coli*, *Bacillus sp.*, *Salmonella sp.*, or *Mycobacterium sp.*

[000268] In certain embodiments, the bacterial infection is resistant to other antibiotic therapy. For example, in certain embodiments, the bacterial infection is vancomycin resistant (VR). In certain embodiments, the bacterial infection is a vancomycin-resistant *E. faecalis* infection. In certain embodiments, the bacterial infection is a vancomycin-resistant *E. faecium* infection. In certain embodiments, the bacterial infection is a vancomycin-resistant *Staphylococcus aureus* (VRSA) infection. In certain embodiments, the bacterial infection is a vancomycin-resistant *Enterococci* (VRE) infection. In certain embodiments, the bacterial infection is methicillin-resistant (MR). In certain embodiments, the bacterial infection is a methicillin-resistant *S. aureus* (MRSA) infection. In certain embodiments, the bacterial infection is methicillin-resistant *Staphylococcus epidermidis* (MRSE) infection. In certain embodiments, the bacterial infection is a penicillin-resistant *Streptococcus pneumonia* infection. In certain embodiments, the bacterial infection is a quinolone-resistant *Staphylococcus aureus* (QRSA) infection. In certain embodiments, the bacterial infection is multi-drug resistant *Mycobacterium tuberculosis* infection.

[000269] 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. It 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 inventive compound 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.

[000270] Exemplary additional therapeutically active agents include, but are not limited to, antibiotics, anti-viral agents, anesthetics, anti-coagulants, inhibitors of an enzyme, steroidal agents, steroidal or non-steroidal anti-inflammatory agents, antihistamine, immunosuppressant agents, antigens, vaccines, antibodies, decongestant, sedatives, opioids, pain-relieving agents, analgesics, anti-pyretics, hormones, and prostaglandins, *etc.*

Therapeutically active agents include small organic molecules such as drug compounds (*e.g.*, compounds approved by the US Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins and cells.

[000271] In certain embodiments, the additional therapeutically agent is an antibiotic. Exemplary antibiotics include, but are not limited to, penicillins (*e.g.*, penicillin, amoxicillin), cephalosporins (*e.g.*, cephalexin), macrolides (*e.g.*, erythromycin, clarithromycin, azithromycin, troleandomycin), fluoroquinolones (*e.g.*, ciprofloxacin, levofloxacin, ofloxacin), sulfonamides (*e.g.*, co-trimoxazole, trimethoprim), tetracyclines (*e.g.*, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycycline, aureomycin, terramycin, minocycline, 6-deoxytetracycline, lymecycline, meclocycline, methacycline, rolitetracycline, and glycylcycline antibiotics (*e.g.*, tigecycline)), aminoglycosides (*e.g.*, gentamicin, tobramycin, paromomycin), aminocyclitol (*e.g.*, spectinomycin), chloramphenicol, sparsomycin, and quinupristin/dalfoprisin (Syndercid™).

[000272] In certain embodiments, the antibiotic is a ribosome-targeting antibiotic. Antibiotics target ribosomes at distinct locations within functionally relevant sites. They exert their inhibitory action by diverse modes, including competing with substrate binding, interfering with ribosomal dynamics, minimizing ribosomal mobility, facilitating miscoding, hampering the progression of the mRNA chain, and blocking the nascent protein exit tunnel.

Examples of antibiotics that reveal novel ribosomal properties or enforced otherwise observed findings include the following: decoding (paromomycin); mRNA progression (spectinomycin); A-site binding to the small (tetracycline antibiotic) and the large (chloramphenicol) subunits; PTC mobility (sparsomycin); tRNA rotatory motion (quinupristin/dalfoprisin), and tunnel gating (troleandomycin); see Yonath, *Annu. Rev. Biochem.* (2005) 74:649-679.

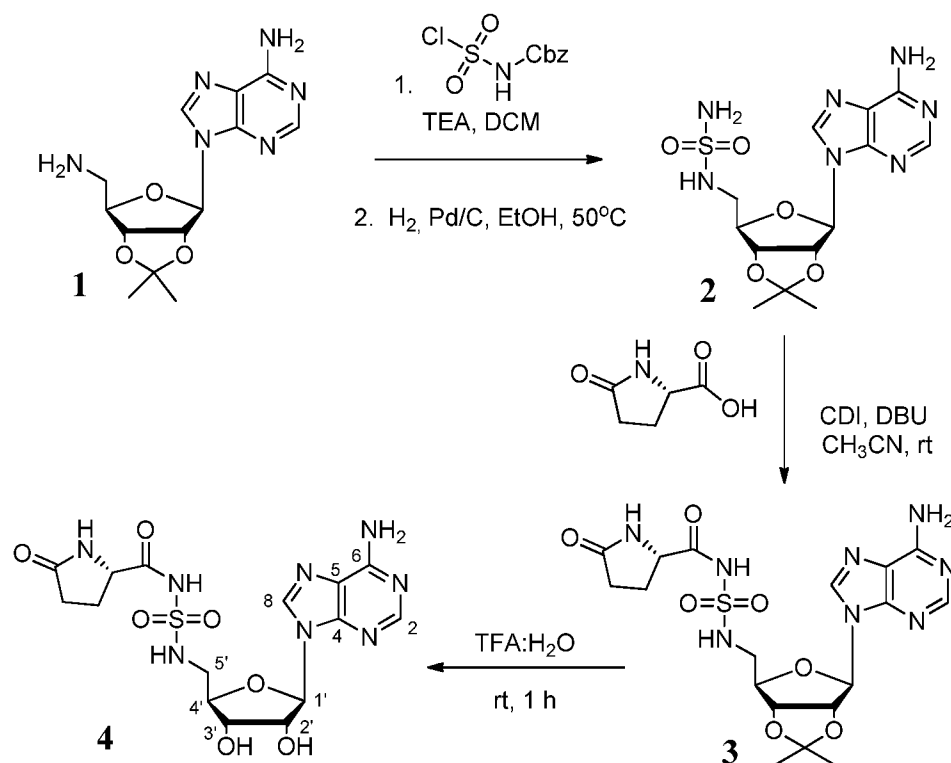
[000273] In certain embodiments, the subject being treated is a mammal. In certain embodiments, the subject is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal such as a dog or cat. In certain embodiments, the subject is a livestock animal such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent, dog, or non-human primate. In certain embodiments, the subject is a non-human transgenic animal such as a transgenic mouse or transgenic pig.

Examples

[000274] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[000275] General Procedures: ^1H and ^{13}C NMR spectra were recorded on an Oxford Activated Shield NMR instrument (Varian, Inc., Palo Alto, CA, USA) operating at 400 MHz for ^1H , and 100 MHz for ^{13}C using D_2O as the solvent. Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected. All chemicals were purchased from Sigma Aldrich (St. Louis, MO, USA) or Acros (Pittsburgh, PA, USA) and were used as received, unless stated otherwise. High resolution mass spectra was acquired on a Thermo Scientific Q Exactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer (Waltham, MA, USA) with electro spray ionization (ESI) mode. Reactions were carried out in oven-dried glassware under nitrogen atmosphere, unless otherwise noted. Analytical TLC was performed on E. Merck silica gel 60 F254 plates and visualized by UV and phosphomolybdic acid (PMA) staining. Flash column chromatography was performed on E. Merck silica gel 60 (40–63 mm). Yields refer to chromatographically and spectroscopically pure compounds.

Synthesis of Compounds



Scheme 1. Direct Synthetic Route of the pGlu-SA 4.

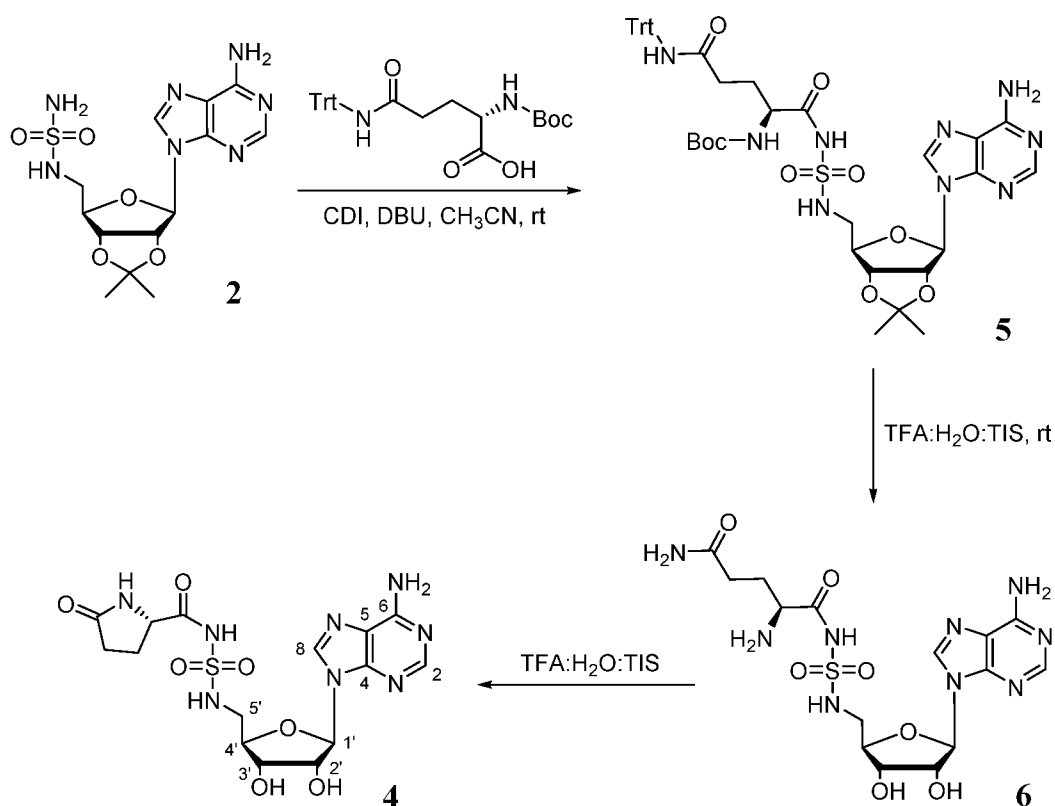
Direct Synthesis of pGlu-SA (4).

[000276] To a stirred solution of L-pyroglutamic acid (44 mg, 0.34 mmol) in dry acetonitrile/DMF mixture, the CDI (63 mg, 0.39 mmol) was added and the resulting mixture was stirred for an additional 30 min at room temperature. The above solution with activated L-pyroglutamic acid was added via syringe to a stirred suspension of sulfamide **2** (100 mg, 0.26 mmol) and DBU (55 mg, 0.36 mmol) in dry acetonitrile under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The pure compound **3** (obtained after column chromatography (silica gel, DCM/methanol 100:5; v/v)) was then treated with TFA:H₂O (5:2) mixture for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure and residue was treated with Et₂O to afford 72 mg (61%) of pure lactam **4** as a white solid. This compound is readily soluble in water. White solid. White solid. MP 170 °C (dec.). ¹H-NMR (D₂O, 400 MHz, ppm): δ 8.44 (s, 1H), 8.43 (s, 1H), 6.07 (d, *J* = 5.6 Hz, 1H), 4.83–4.75 (m, 1H), 4.49–4.40 (m, 1H), 4.39–4.22 (m, 2H), 3.44 (qd, *J* = 13.9, 4.0 Hz, 2H), 2.67–2.46 (m, 1H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.19–2.00 (m, 1H). ¹³C-NMR (D₂O, 100 MHz, ppm): δ 181.9, 173.5, 150.3,

147.8, 145.0, 143.3, 119.3, 89.3, 83.2, 73.3, 70.7, 56.9, 44.0, 28.9, 25.0. HRMS (ESI): calcd. for $C_{15}H_{21}N_8O_7S$ $[M + H]^+$ 457.1254, found 457.1236.

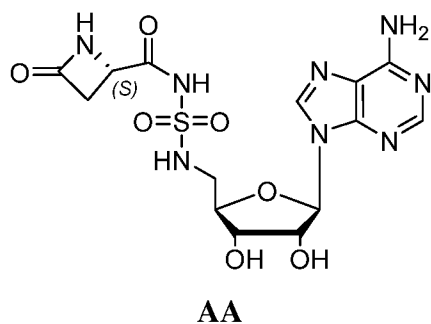
Indirect Synthesis of pGlu-SA (4).

[000277] To a stirred solution of Boc-L-Gln(Trt)-OH (166 mg, 0.34 mmol) in dry acetonitrile, the CDI (63 mg, 0.39 mmol) was added and resulting yellow mixture was stirred additional 30 min at room temperature. The above solution with activated glutamine was added via syringe to a stirred suspension of sulfamide **2** (100 mg, 0.26 mmol) and DBU (55 mg, 0.36 mmol) in dry acetonitrile under nitrogen atmosphere. The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The pure compound **5** (187 mg, 0.20 mmol, 84% yield) obtained after column chromatography (silica gel, DCM/methanol 100:5; v/v) was then treated with TFA:H₂O (5:2) in presence of triisopropylsilane (5%) for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with ether afforded white solid as crude products. The final separation and purification of target pGlu-SA **4** was performed by preparative HPLC (218TP510, 10 mm × 250 mm, Grace Corporate, Columbia, MD, USA), using a linear gradient of 0%–1% acetonitrile in 0.1% trifluoroacetic acid. After lyophilization the 23 mg (25% yield from **5**) of white solid lactam **4** was obtained.



Scheme 2. Indirect Synthetic Route of the pGlu-SA **4**.

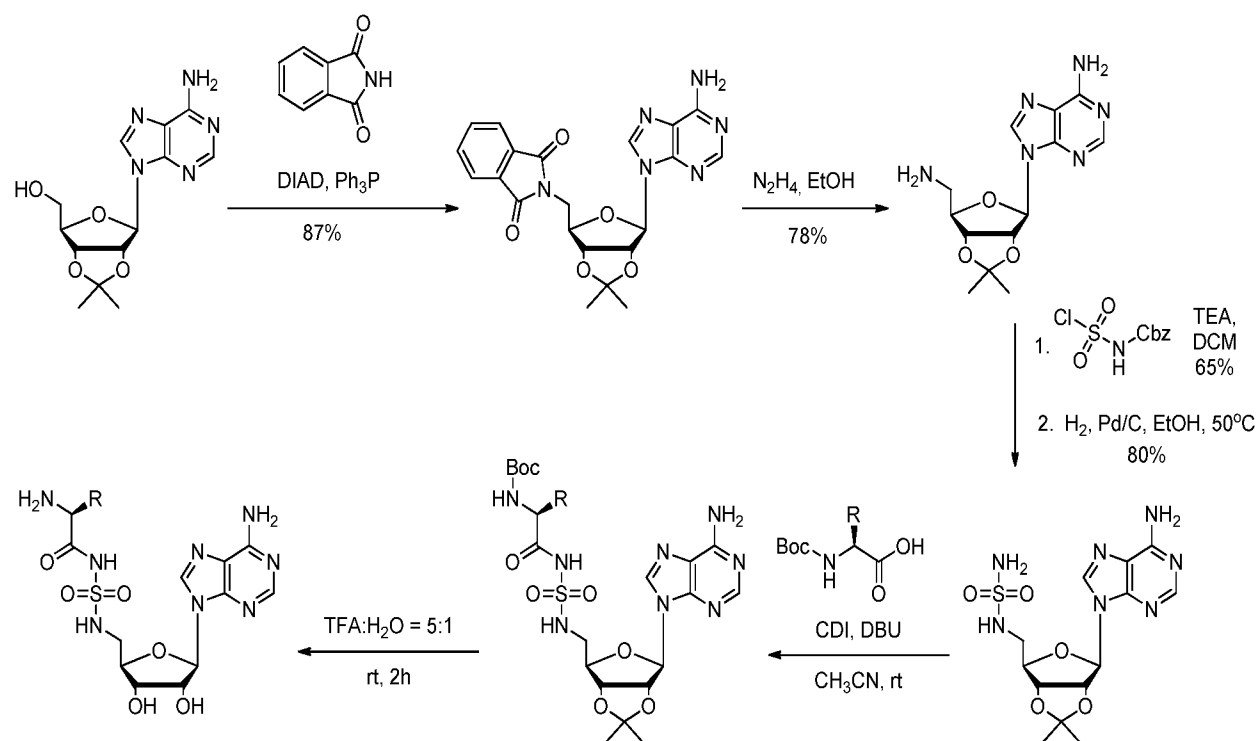
Compound **AA**



[000278] Similar to compound **4**, compound **AA** can be directly synthesized based on **Scheme 1** by substituting L-pyrogutamic acid with (S)-4-oxoazetidine-2-carboxylic acid. ^1H NMR (600 MHz, D_2O) δ 8.46 (s, 1H), 8.44 (s, 1H), 6.11 (d, $J = 4.7$ Hz, 1H), 4.86 (t, $J = 5.5$ Hz, 1H), 4.51 (t, $J = 5.2$ Hz, 1H), 4.50 – 4.47 (m, 1H), 4.43 – 4.34 (m, 1H), 3.55 – 3.42 (m, 2H), 3.00 (dd, $J = 17.3, 5.5$ Hz, 1H), 2.90 (dd, $J = 17.3, 4.5$ Hz, 1H); ^{13}C NMR (151 MHz, D_2O) δ 170.4, 168.6, 148.1, 146.8, 144.8, 143.2, 119.4, 89.5, 83.6, 73.5, 71.1, 51.0, 44.3, 38.2.

Synthesis of Compounds of Formula (II)

[000279] Exemplary compounds of Formula (II) were prepared according to the method shown in **Scheme 3**.



Scheme 3 ("R" denotes R¹¹)

Biological Evaluation

[000280] Exemplary sulfamides demonstrate potent inhibition to a panel of cancer cell lines with low micromolar IC₅₀ using CellTiter-Glo luminescence viability assays (Table 1).

Biological Materials

[000281] Dimethyl sulfoxide (DMSO), 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), and other chemical reagents were purchased from Sigma-Aldrich (St. Louis, USA). CellTiter-Glo[®] Luminescent Cell Viability Assay was purchased from Promega (Madison, USA). Dulbecco's Modified Eagle Medium (DMEM), RPMI 1640 medium, and fetal bovine serum (FBS) were purchased from Gibco (Grand Island, USA). All cell lines were purchased from ATCC (Manassas, USA).

Cell Culture and MTT Assay

[000282] The anti-proliferative activities of the sulfamide compounds were assessed by the tetrazolium-based MTT assay. Human lung cancer A549 cell line, human cervical cancer

HeLa cell line, human colorectal carcinoma HCT-116 cell line, and human breast carcinoma MCF-7 cell line and MDA 231 cell line were cultured in DMEM medium supplied with 10% FBS. Cells were seeded in 96 well plates at the density of 5000, 8000, 8000, 12,000 and 6000 cells per well, respectively. Cancer cells were treated with respective compounds for 72 h and then incubated with 100 μ L of 0.5 mg/mL 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) solution for 4 h. The supernatant was discarded and DMSO was added to each well. Absorbance at 570 nm was measured using a SpectraMax M2 reader (Molecular Devices, Sunnyvale, USA). The number of viable cells in the control group was assigned a relative value of 100%.

Cell Titer Glo Assay

[000283] The leukemia cell lines MOLT-4 was cultured in RPMI-1640 medium and HL-60 was cultured in DMEM medium, 10% FBS was supplied to both culture systems. For the growth assays, MOLT-4 cell and HL-60 were plated in 96-well plates at 9000 cells/well and 10,000 cells/well. Cells were treated with sulfamide compounds at various concentrations. On Day 3, cells were lysed with CellTiter-Glo[®] Luminescent Cell Viability Assay reagent (Promega) following manufacture's instruction and luminescence was read using the PerkinElmer Victor³ V plate reader (PerkinElmer, Waltham, USA). Percent cell growth was calculated relative to control cells.

Table 1. Inhibition of pGlu-SA **4** to a panel of cancer cell lines.

Cell Line	Cell Type	IC50/ μ M
MOLT-4	Human acute lymphoblastic leukemia	2.44
HL60	Human acute promyelocytic leukemia	0.46
MDA231	Breast cancer	11.03
A549	Lung cancer	7.93
HCT116	Colon cancer	1.48
HeLa	Cervical cancer	25.24
MCF-7	Breast cancer	0.19

Discovery of Novel Aminoacyl Sulfamides for Prostate Cancer Therapy

[000284] tRNA synthetase (aaRS) plays a very significant role in protein synthesis due to its crucial involvement in the translation process. Inhibiting the activity of aaRS would

decrease the protein producing ability of cells, thus destroying the protein supply for cell growth and causing cell apoptosis or other cell death. Research on aaRS inhibitors has focused on the development of compounds mimicking aminoacyl adenylates to deplete the charging endogenous tRNAs. Among such compounds, aminoacyl sulfamides stand out because of their potency to inhibit cancer cell growth. Here, the testing results of synthetic sulfamides on a panel of prostate cancer cell lines such as LNCaP and PC3 using cell viability assays with the range of nanomolar to low micromolar IC₅₀ are reported. Additionally, cell apoptosis staining and cell cycle/arrest assays on prostate cancer cells were performed. These results demonstrated that aminoacyl sulfamides induced apoptosis and shifted the cell cycle. Since aaRSs could directly link to tumorigenesis as a result of their non-canonical functions in angiogenesis, immune responses and signal transduction pathway, aminoacyl sulfamides are ideal drug leads for developing new anticancer agents leading to a potential application in regulating oncoprotein expression and modification for prostate cancer therapeutics.

Results and Discussion

[000285] In Vitro Cytotoxic Activity. Androgen receptor-dependent (LNCaP) and androgen independent (PC-3) cell lines were selected to evaluate aminoacyl sulfamides (aa-SA) (below) for their capability to inhibit prostate cancer cell growth *in vitro*. The cytotoxic activity of the synthesized compounds was evaluated using the CellTiter-Glo assay as described previously. The cytotoxic activities are expressed as the median growth inhibitory concentration (IC₅₀) and are provided in Table 2. From the results, it is evident that some of the tested compounds displayed potent growth inhibitory activity from nM to low uM range.

Table 2: IC₅₀ of aminoacyl sulfamides for PC3 and LNCaP cells with error bars

Compound Number	IC ₅₀ for LNCap (μM)	IC ₅₀ for PC3 (μM)
Phe-SA	3.4 ± 1.70	0.035 ± 0.0017
Met-SA	0.0015±0.000075	0.79 ± 0.039
Gly-SA	0.41 ± 0.020	0.057 ± 0.0028
Ile-SA	5.1 ± 0.25	9.6 ± 0.48
Cys-SA	27 ± 1.35	1.3 ± 0.065
Trp-SA	0.0093 ± 0.00046	0.56 ± 0.028
Ser-SA	1.6 ± 0.080	0.95 ± 0.047
Arg-SA	1.6 ± 0.080	0.53 ± 0.026
Ala-SA	3.4 ± 0.17	0.65 ± 0.033
Lys-SA	1.1 ± 0.055	0.83 ± 0.041

Compound Number	IC ₅₀ for LNCap (μM)	IC ₅₀ for PC3 (μM)
Pro-SA	0.26 ± 0.013	0.18 ± 0.0090
Val-SA	1.6 ± 0.080	1.2 ± 0.060
Leu-SA	0.022 ± 0.0011	0.28 ± 0.014
His-SA	0.072 ± 0.0036	10 ± 0.50
Thr-SA	1.5 ± 0.075	0.49 ± 0.024
Asp-SA	0.75 ± 0.037	0.0069 ± 0.00034
Tyr-SA	0.005 ± 0.00025	16 ± 0.80
Glu-SA	0.014 ± 0.00070	0.68 ± 0.034
Gln-SA	0.77 ± 0.038	0.014 ± 0.00074
L-Gln-lactam-SA	0.40 ± 0.020	0.0011 ± 0.000055
Asn-SA	3.8 ± 0.19	0.18 ± 0.0090
Arg-NO ₂ -SA	0.0022 ± 0.00011	1.3 ± 0.065
D-Gln-lactam-SA	0.077 ± 0.060	0.013 ± 0.011

[000286] Mechanism of Cell Death. Apoptosis is the primary mechanism through which prostate cancer cells are killed when exposed to treatments such as chemotherapy or radiotherapy. Most recent studies have shown that advanced stages of this disease exhibit a significant degree of resistance to certain therapies so new drug development is in urgent need. The tRNA synthetase inhibitors of 23 novel aminoacyl sulfamides have been evaluated for their induction of apoptosis on PC-3 and LNCap cell lines. The result in Figures 1 and 2 revealed that the mechanism of cytotoxicity of compound, was due to inducing apoptotic cell death on PC-3 cell lines.

[000287] Cell Cycle Analysis. Flow cytometry was used to explore the effects of the aminoacyl sulfamides on cell cycle. PC-3 cells were treated with the 10 μM concentration of the compound for 48h, fixed with ethanol and stained with propidium iodide. As shown in Figures 3 and 4, treatment of the cells with aminoacyl sulfamides increased cell cycle arrest at the sub G0/G1 and S phase, resulting in cell population increase in the subG0/G1 and S phase compared to the control cells. In line with this finding, the cell populations in G0/G1 phase decreased significantly after treatments. These results demonstrate that, in PC-3 cells, cell cycle arrest in the subG0/G1 and S phase contributes to the cytotoxicity of the aminoacyl sulfamides.

[000288] Aminoacyl Sulfamides Inhibit Prostate Cancer Cell Migration using Scratch Assay. Cell migration was determined using an *in vitro* “wound-healing” scratch assay. Briefly, cells were seeded in 6-well plates and grown for 48 h to allow them to reach confluences. The confluent monolayer was scratched using a sterilized 1 ml pipette tip and incubated with 10 μM aminoacyl sulfamides in fresh growth medium for 24 h. Cells moved

to the denuded area were photographed. As demonstrated in Figure 5, these compounds effectively inhibit cancer cell migration or motility. The compounds tested in this assay and the compounds shown in Figure 5 are selected from the compounds shown in the table below:

1	Phe-SA	13	Leu-SA
2	Met-SA	14	His-SA
3	Gly-SA	15	Thr-SA
4	Ile-SA	16	Asp-SA
5	Cys-SA	17	Tyr-SA
6	Trp-SA	18	Glu-SA
7	Ser-SA	19	Gln-SA
8	Arg-SA	20	L-Gln-lactam-SA
9	Ala-SA	21	Asn-SA
10	Lys-SA	22	Arg-NO ₂ -SA
11	Pro-SA	23	D-Gln-lactam-SA
12	Val-SA		

Conclusions

[000289] In summary, a panel of cell lines was tested using the CellTiter-Glo luminescence viability assay with nanomolar to low micromolar IC₅₀ values for the 23 different aminoacyl sulfamides we synthesized. Additionally, cell apoptosis staining and cell cycle/arrest assays were performed on LNCaP and PC3 cells. These results demonstrated that aminoacyl sulfamides induced apoptosis and shifted the cells to the sub G₀/G₁ and S phase. The corresponding results identified the potency of aminoacyl sulfamides as anticancer agents.

Experimental Procedures

[000290] Cell Line Maintenance. The LNCaP cancer cells were grown in RPMI-1460 and PC-3 cancer cells were grown in HAM media supplemented with 10% heat inactivated FBS, medium containing 50 units of penicillin/mL, 50 g/mL of streptomycin/mL, in T-75 cm² flasks at 37°C in a humidified atmosphere containing 5% CO₂ incubator. The cells were maintained as “monolayer culture” by serial sub-culturing.

[000291] Biological Materials. Dimethyl sulfoxide (DMSO), 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), and other chemical reagents were purchased from Sigma-Aldrich (St. Louis, USA). CellTiter-Glo® Luminescent Cell Viability Assay was purchased from Promega (Madison, USA). RPMI-1460, HAM media and fetal bovine serum (FBS) were purchased from Gibco (Grand Island, USA). All cell lines were purchased from ATCC (Manassas, USA).

[000292] Cell Titer Glo Assay. The cancer cells was cultured in medium, 10% FBS was supplied to the culture system. For the growth assays, cancer cells were plated in 96-well plates at 8,000 cells/well. Cells were treated with compounds at various concentrations. On Day 2, cells were lysed with CellTiter-Glo® Luminescent Cell Viability Assay reagent (Promega) following manufacture's instruction and luminescence was read using the PerkinElmer Victor3 V plate reader (PerkinElmer, Waltham, USA). Percent cell growth was calculated relative to control cells. The results reported are mean of at least three separate experiments. Significant differences were analyzed according the ANOVA wherein the differences were considered to be significant at $p < 0.05$.

[000293] Cell Cycle Analysis (Flow Cytometry). The cancer cells were treated with 10 μM of compounds for 48 h. After treatment, the cells were washed twice with ice-cold PBS, collected by centrifugation, and fixed in ice-cold 70% (v/v) ethanol, washed with PBS, re-suspended with 0.1 mg/mL RNase, stained with 40 mg/mL PI, and analyzed by flow cytometry using Accuri™ C6 (BD Biosciences). The cell cycle distributions were calculated using CFlow plus software.

[000294] Cell Migration "Wound-Healing" Scratch Assay. Cell migration was determined using an in vitro "wound-healing" scratch assay. Briefly, cells were seeded in 6-well plates and grown for 48 h to allow them to reach confluences. The confluent monolayer was scratched using a sterilized 1 ml pipette tip and incubated with aminoacyl sulfamides in fresh growth medium for 24 h. Cells moved to the denuded area were photographed.

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Equivalents and Scope

[000295] 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.

[000296] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[000297] 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

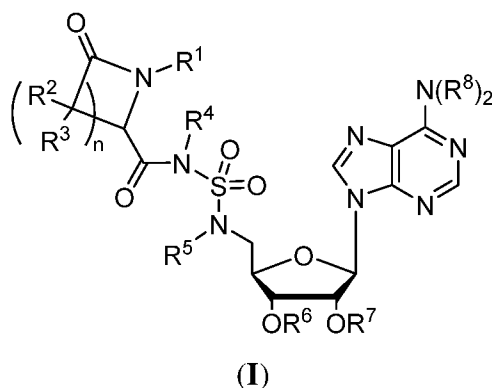
embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[000298] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

Claims

What is claimed is:

1. A compound of Formula (I)



or a pharmaceutically acceptable salt thereof,

wherein:

each of R¹, R⁴, and R⁵ is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

each instance of R⁸ is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or two R⁸ are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

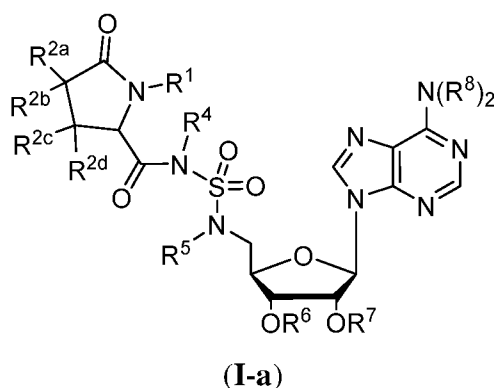
each of R⁶ and R⁷ is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group, or R⁶ and R⁷ are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

each instance of R² and R³ is independently hydrogen, halogen, -CN, -NO₂, -N₃, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl; and

n is 1, 2, 3, or 4.

2. The compound of claim 1, wherein n is 1.
3. The compound of claim 1, wherein n is 2.

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

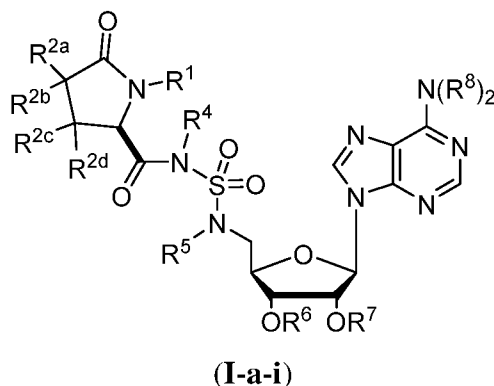


or a pharmaceutically acceptable salt thereof,

wherein:

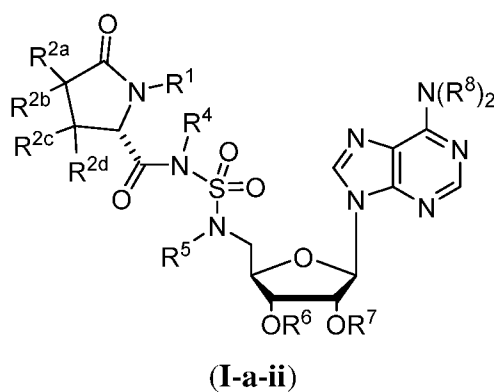
each of R^{2a} , R^{2b} , R^{2c} , and R^{2d} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-N_3$, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, optionally substituted hydroxyl, optionally substituted alkoxy, optionally substituted amino group, or optionally substituted acyl.

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



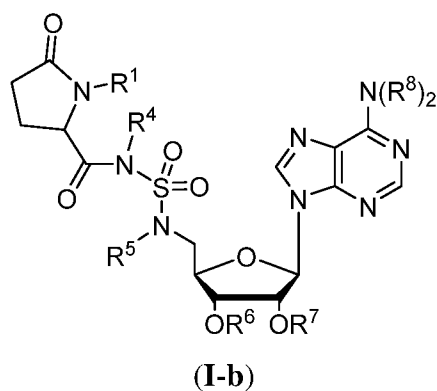
or a pharmaceutically acceptable salt thereof.

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



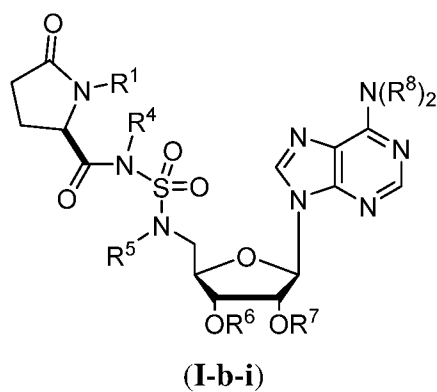
or a pharmaceutically acceptable salt thereof.

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



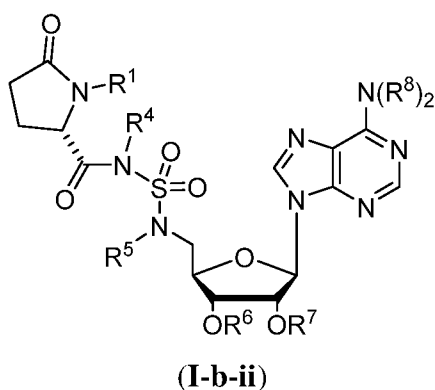
or a pharmaceutically acceptable salt thereof.

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



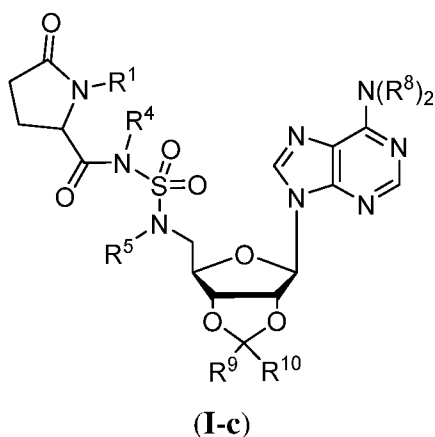
or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

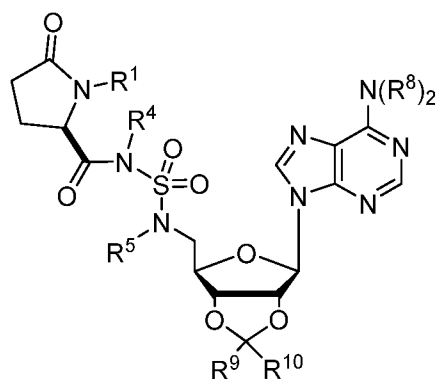
10. The compound of any one of claims 1-9, wherein R^6 is hydrogen.
11. The compound of any one of claims 1-9, wherein R^6 is optionally substituted alkyl.
12. The compound of any one of claims 1-11, wherein R^7 is hydrogen.
13. The compound of any one of claims 1-11, wherein R^7 is optionally substituted alkyl.
14. The compound of any one of claims 1-9, wherein R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.
15. The compound of any one of claims 1-9, wherein R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted 5-membered heterocyclic ring.
16. The compound of claim 1, wherein the compound is of Formula **(I-c)**:



or a pharmaceutically acceptable salt thereof,
wherein:

each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

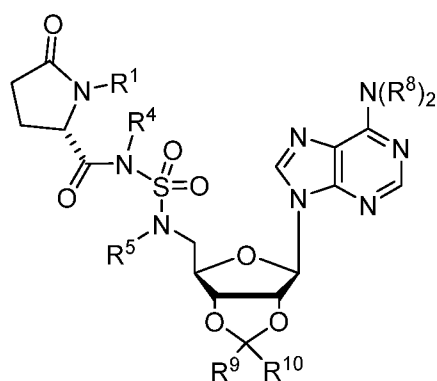
17. The compound of claim 16, wherein the compound is of Formula **(I-c-i)**:



(I-c-i)

or a pharmaceutically acceptable salt thereof.

18. The compound of claim 16, wherein the compound is of Formula **(I-c-ii)**:



(I-c-ii)

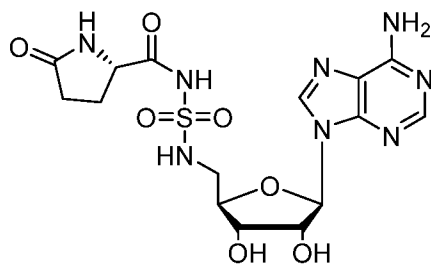
or a pharmaceutically acceptable salt thereof.

19. The compound of any one of claims 16-18, wherein R^9 is optionally substituted C_{1-6} alkyl.

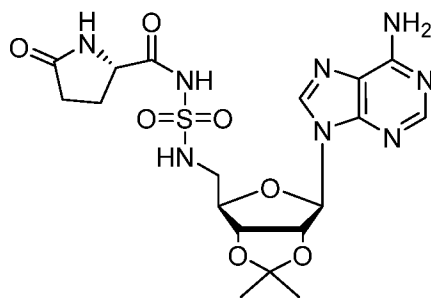
20. The compound of claim 19, wherein R^9 is unsubstituted C_{1-6} alkyl.

21. The compound of claim 20, wherein R^9 is methyl.

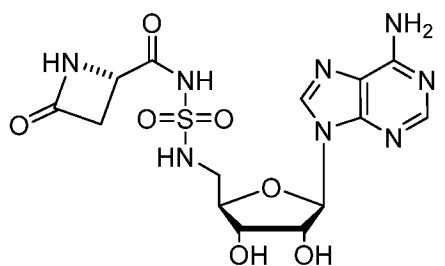
22. The compound of any one of claims 16-21, wherein R^{10} is optionally substituted C_{1-6} alkyl.
23. The compound of any one of claims 16-21, wherein R^{10} is unsubstituted C_{1-6} alkyl.
24. The compound of any one of claims 16-21, wherein R^{10} is methyl.
25. The compound of any one of claims 1-24, wherein R^1 is hydrogen.
26. The compound of any one of claims 1-25, wherein R^4 is hydrogen.
27. The compound of any one of claims 1-26, wherein R^5 is hydrogen.
28. The compound of any one of claims 1-27, wherein R^8 is hydrogen.
29. The compound of claim 1, wherein the compound is of the formula:



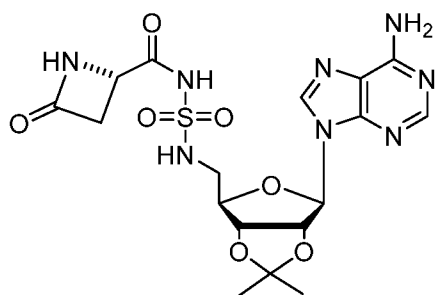
30. The compound of claim 1, wherein the compound is of the formula:



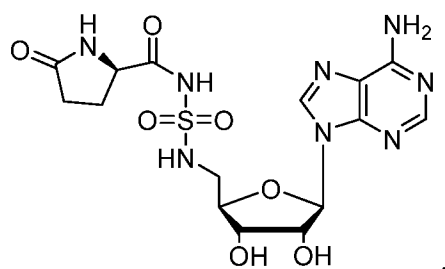
31. The compound of claim 1, wherein the compound is of the formula:



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

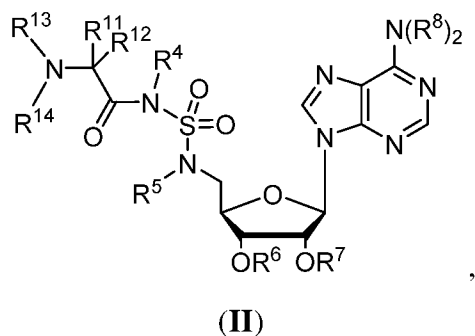


33. The compound of claim 1, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

34. A compound of Formula (II)



or a pharmaceutically acceptable salt thereof, wherein:

R¹¹ is hydrogen, halogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted carbocyclyl, optionally substituted

heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, or a side chain of a natural amino acid;

R^{12} is hydrogen, halogen, or optionally substituted alkyl;

R^{13} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

R^{14} is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

or R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

or R^{13} and R^{14} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

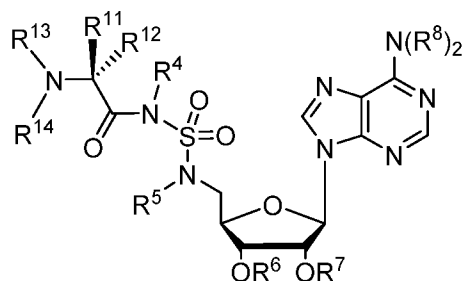
R^4 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

R^5 is hydrogen, optionally substituted alkyl, or a nitrogen protecting group;

each of R^6 and R^7 is independently hydrogen, optionally substituted alkyl, or an oxygen protecting group, or R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring; and

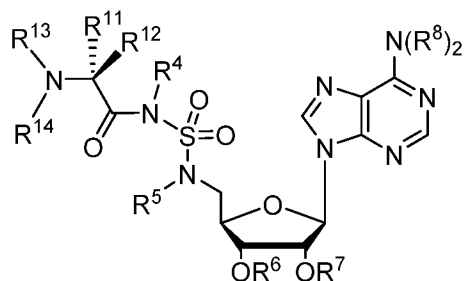
each instance of R^8 is independently hydrogen, optionally substituted alkyl, or a nitrogen protecting group, or two R^8 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.

35. The compound of claim 34, wherein the compound is of the formula:



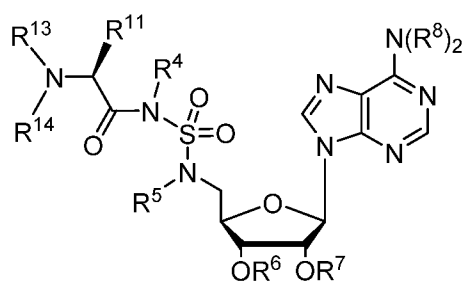
or a pharmaceutically acceptable salt thereof,

36. The compound of claim 34, wherein the compound is of the formula:



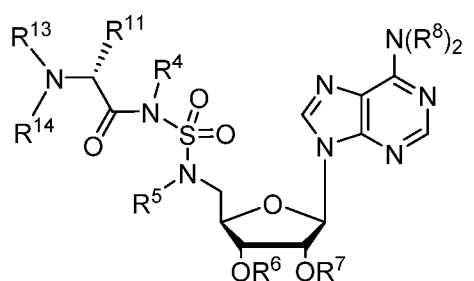
or a pharmaceutically acceptable salt thereof,

37. The compound of claim 34, wherein the compound is of the formula:



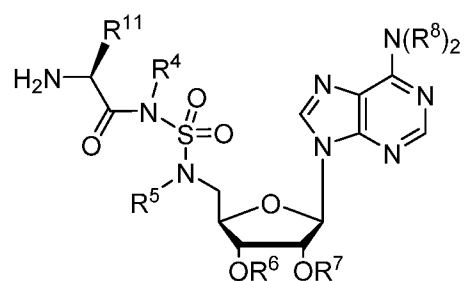
or a pharmaceutically acceptable salt thereof,

38. The compound of claim 34, wherein the compound is of the formula:



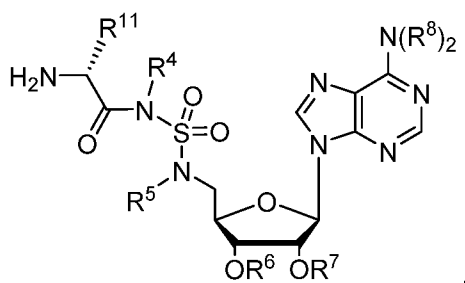
or a pharmaceutically acceptable salt thereof,

39. The compound of claim 34, wherein the compound is of the formula:



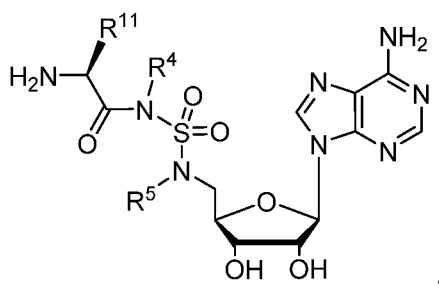
or a pharmaceutically acceptable salt thereof,

40. The compound of claim 34, wherein the compound is of the formula:



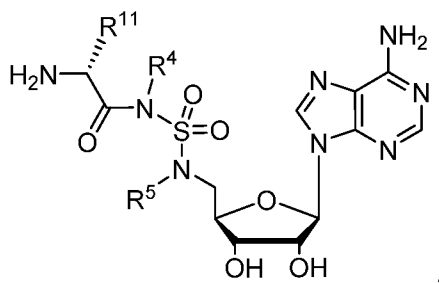
or a pharmaceutically acceptable salt thereof,

41. The compound of claim 34, wherein the compound is of the formula:



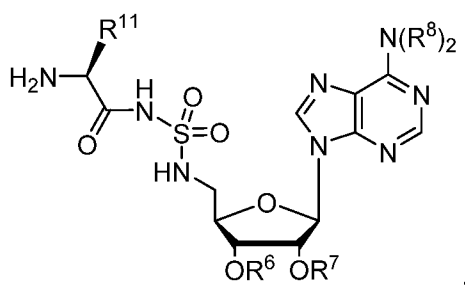
or a pharmaceutically acceptable salt thereof,

42. The compound of claim 34, wherein the compound is of the formula:



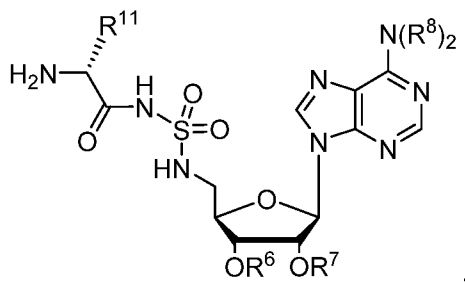
or a pharmaceutically acceptable salt thereof,

43. The compound of claim 34, wherein the compound is of the formula:



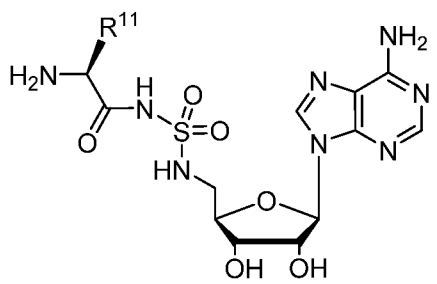
or a pharmaceutically acceptable salt thereof,

44. The compound of claim 34, wherein the compound is of the formula:



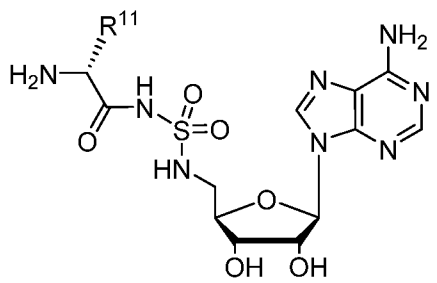
or a pharmaceutically acceptable salt thereof,

45. The compound of claim 34, wherein the compound is of the formula:



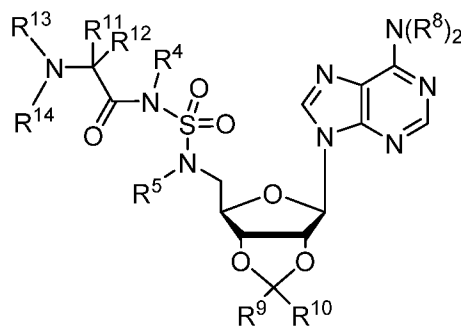
or a pharmaceutically acceptable salt thereof,

46. The compound of claim 34, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof,

47. The compound of claim 34, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof, wherein each of R^9 and R^{10} is independently hydrogen or optionally substituted alkyl.

48. The compound of any one of claims 34-47, wherein R^{11} is hydrogen.

49. The compound of any one of claims 34-47, provided that R^{11} is not hydrogen.

50. The compound of any one of claims 34-47, wherein R^{11} is optionally substituted alkyl.

51. The compound of any one of claims 34-47, wherein R^{11} is optionally substituted C_{1-6} alkyl.

52. The compound of any one of claims 34-47, wherein R^{11} is a side chain of a natural amino acid.

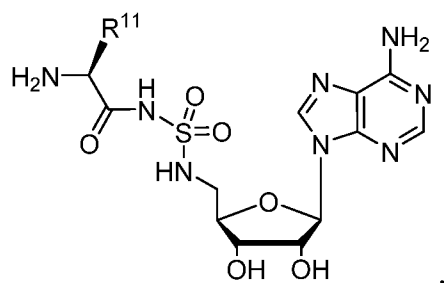
53. The compound of any one of claims 34-47, wherein R^{11} is Bn, $-\text{CH}_2\text{CH}_2\text{SMe}$, $-\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{SH}$, (1*H*-indol-3-yl)methyl, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$, Me, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, $-\text{CH}_2(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, (1*H*-imidazol-4-yl)methyl, $-\text{CH}(\text{OH})\text{Me}$, $-\text{CH}_2\text{COOH}$, (*para*-hydroxyphenyl)methyl, $-\text{CH}_2\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(=\text{O})\text{NH}_2$, or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})-\text{NH}-\text{NO}_2$.

54. The compound of any one of claims 34-53, wherein R^{12} is hydrogen.

55. The compound of any one of claims 34-54, wherein R^{13} is hydrogen.

56. The compound of any one of claims 34-47 and 54, wherein R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.
57. The compound of any one of claims 34-47 and 54, wherein R^{13} and R^{11} are taken together with their intervening atoms to form an optionally substituted pyrrolidinyl ring.
58. The compound of any one of claims 34-57, wherein R^{14} is hydrogen.
59. The compound of any one of claims 34-54, wherein R^{13} and R^{14} are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.
60. The compound of any one of claims 34-59, wherein R^4 is hydrogen.
61. The compound of any one of claims 34-60, wherein R^5 is hydrogen.
62. The compound of any one of claims 34-61, wherein R^6 is hydrogen.
63. The compound of any one of claims 34-61, wherein R^6 is optionally substituted alkyl.
64. The compound of any one of claims 34-63, wherein R^7 is hydrogen.
65. The compound of any one of claims 34-64, wherein R^7 is optionally substituted alkyl.
66. The compound of any one of claims 34-61, wherein R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted heterocyclic ring.
67. The compound of any one of claims 34-61, wherein R^6 and R^7 are taken together with their intervening atoms to form an optionally substituted, monocyclic, 5-membered heterocyclic ring.
68. The compound of any one of claims 34-67, wherein R^8 is hydrogen.

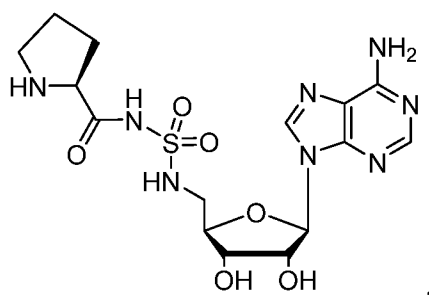
69. The compound of claim 34, wherein the compound is of the formula:



R^{11}
Bn
$-\text{CH}_2\text{CH}_2\text{SMe}$
H
$-\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$
$-\text{CH}_2\text{SH}$
(1 <i>H</i> -indol-3-yl)methyl
$-\text{CH}_2\text{OH}$
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$
Me
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$
$-\text{CH}_2(\text{CH}_3)_2$
$-\text{CH}_2\text{CH}(\text{CH}_3)_2$
(1 <i>H</i> -imidazol-4-yl)methyl
$-\text{CH}(\text{OH})\text{Me}$
$-\text{CH}_2\text{COOH}$
(<i>para</i> -hydroxyphenyl)methyl
$-\text{CH}_2\text{CH}_2\text{COOH}$
$-\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{NH}_2$
$-\text{CH}_2\text{C}(=\text{O})\text{NH}_2$
$-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})-\text{NH}-\text{NO}_2$

or a pharmaceutically acceptable salt thereof.

70. The compound of claim 34, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof.

71. A pharmaceutical composition comprising a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.
72. The pharmaceutical composition of claim 71, wherein the pharmaceutical composition comprises a therapeutically effective amount of the compound.
73. The pharmaceutical composition of claim 71 or 72, wherein the pharmaceutical composition is for use in treating a proliferative disease in a subject.
74. The pharmaceutical composition of claim 73, wherein the proliferative disease is cancer.
75. The pharmaceutical composition of claim 71 or 72, wherein the pharmaceutical composition is for use in treating an infectious disease in a subject.
76. The pharmaceutical composition of claim 71 or 72, wherein the infectious disease is a bacterial infection.
77. The pharmaceutical composition of claim 76, wherein the infectious disease is a viral infection.
78. A method of treating a proliferative disease in a subject, the method comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72.
79. The method of claim 78, wherein the subject is a mammal.
80. The method of claim 79, wherein the subject is human.
81. The method of claim 78, wherein the proliferative disease is cancer.

82. The method of claim 81, wherein the cancer is leukemia, breast cancer, lung cancer, colon cancer, or cervical cancer.

83. The method of claim 78, wherein the proliferative disease is an autoimmune disease.

84. A method of treating an infectious disease in a subject, the method comprising: administering to the subject a therapeutically effective amount of a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72.

85. The method of claim 84, wherein the infectious disease is a bacterial infection.

86. The method of claim 84, wherein the infectious disease is a viral infection.

87. A method of modulating aminoacyl tRNA synthetase activity in a biological sample or a subject, the method comprising:

contacting the biological sample with a therapeutically effective amount of a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72.

88. A method of inhibiting cell growth in a biological sample or subject, the method comprising:

administering to the subject or contacting the biological sample with a therapeutically effective amount of a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72.

89. A method of inducing apoptosis of a cell in a biological sample, the method comprising:

administering to the subject or contacting the biological sample with a therapeutically effective amount of a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72.

90. The method of any one of claims 78-89, further comprising:
administering to the subject a therapeutically effective amount of another pharmaceutical agent in combination with the compound, the pharmaceutically acceptable salt thereof, or the pharmaceutical composition.
91. The method of claim 90, wherein the pharmaceutical agent is an anti-proliferative agent.
92. A kit comprising a compound of any one of claims 1-70, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 71 or 72; and instructions for administering the compound, the pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

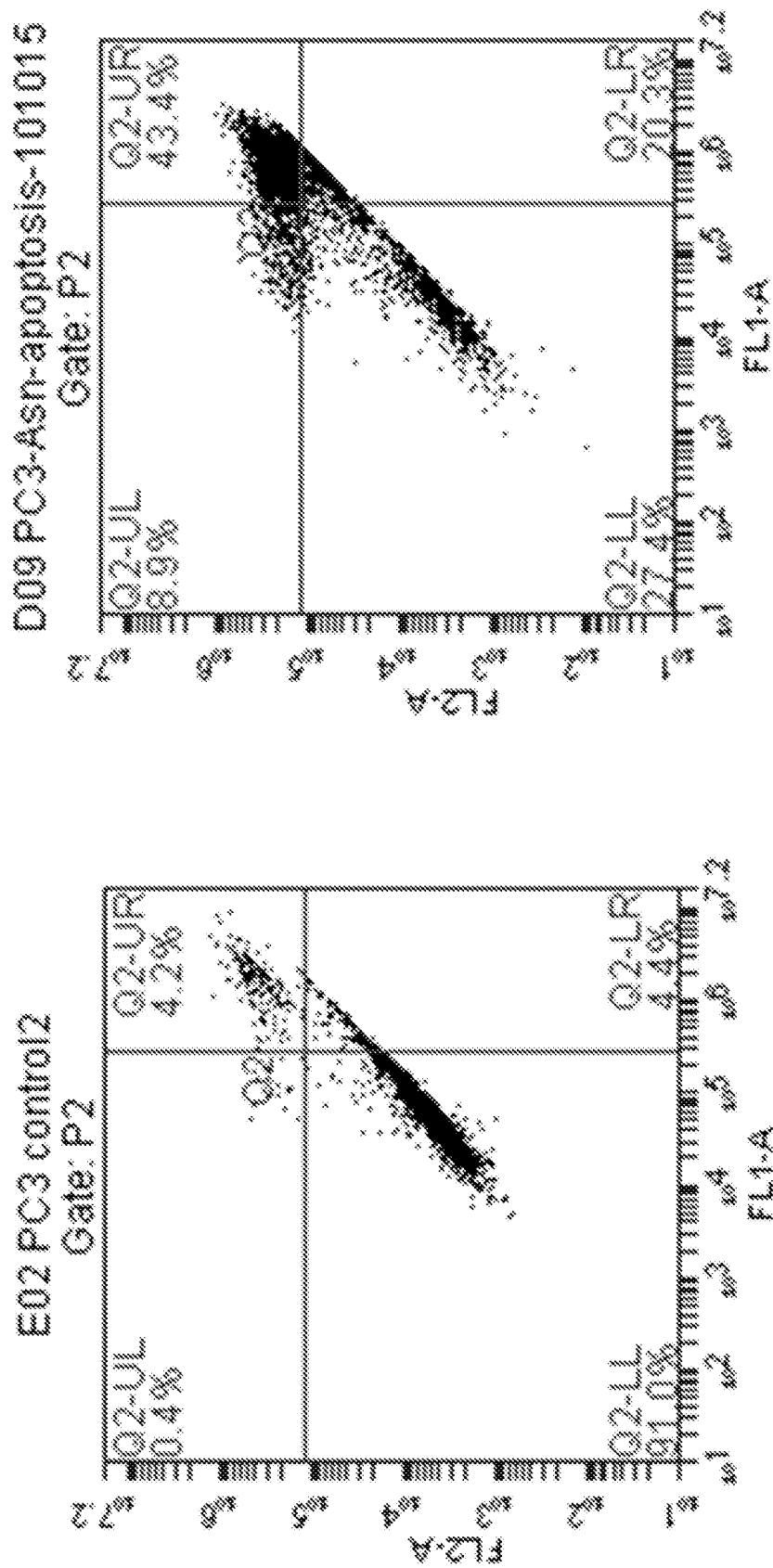


Figure 1

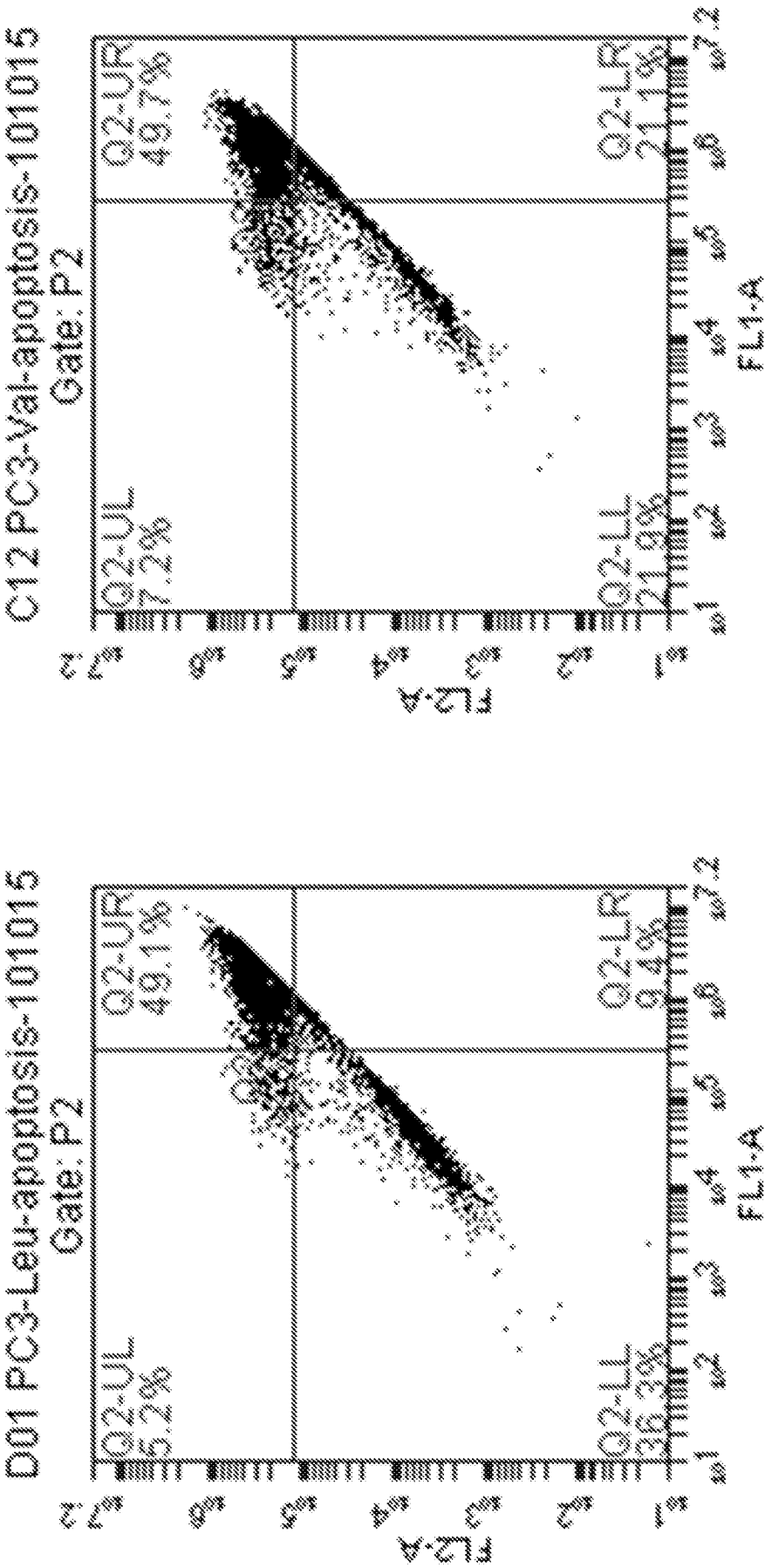


Figure 1 (continued)

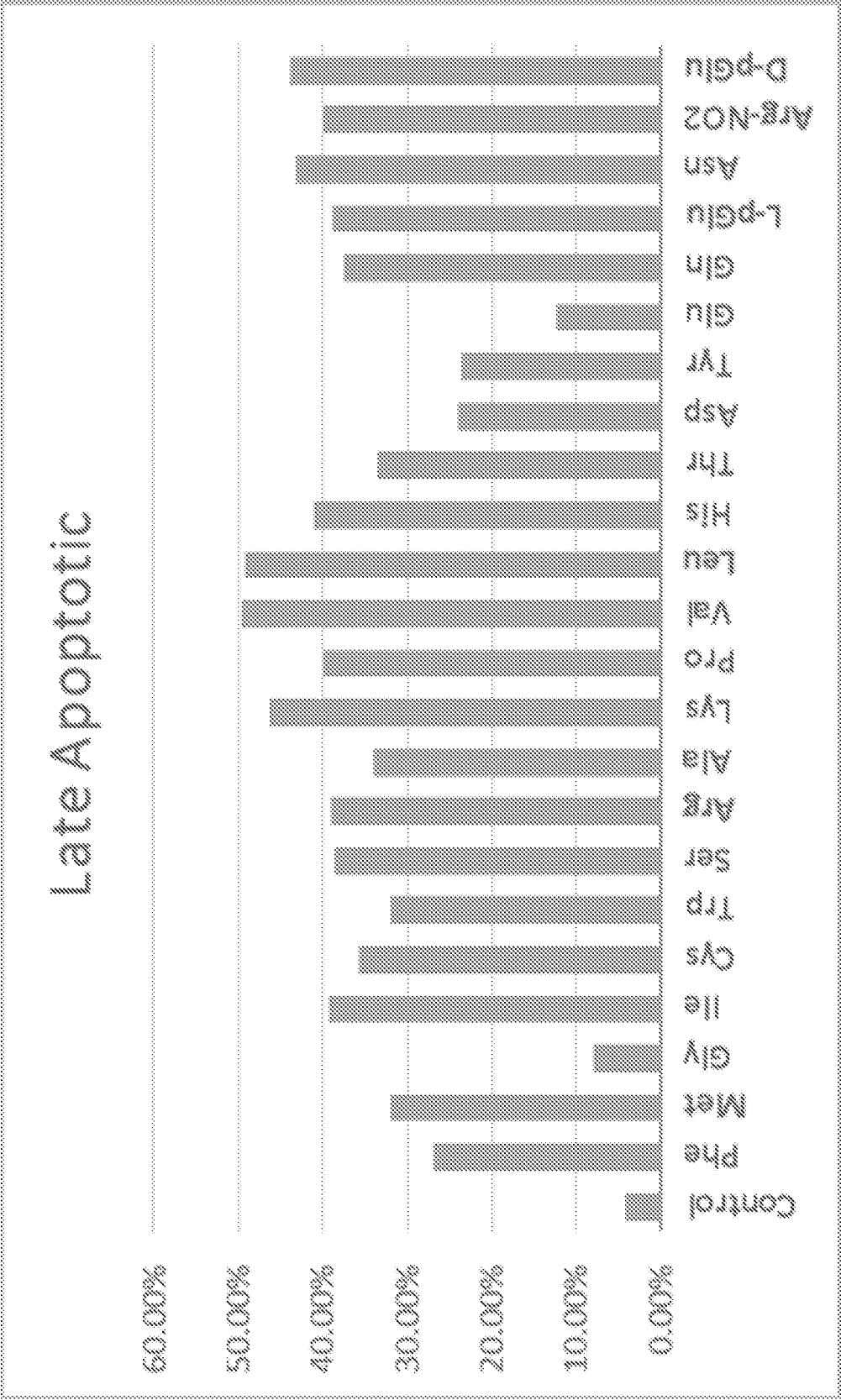


Figure 2

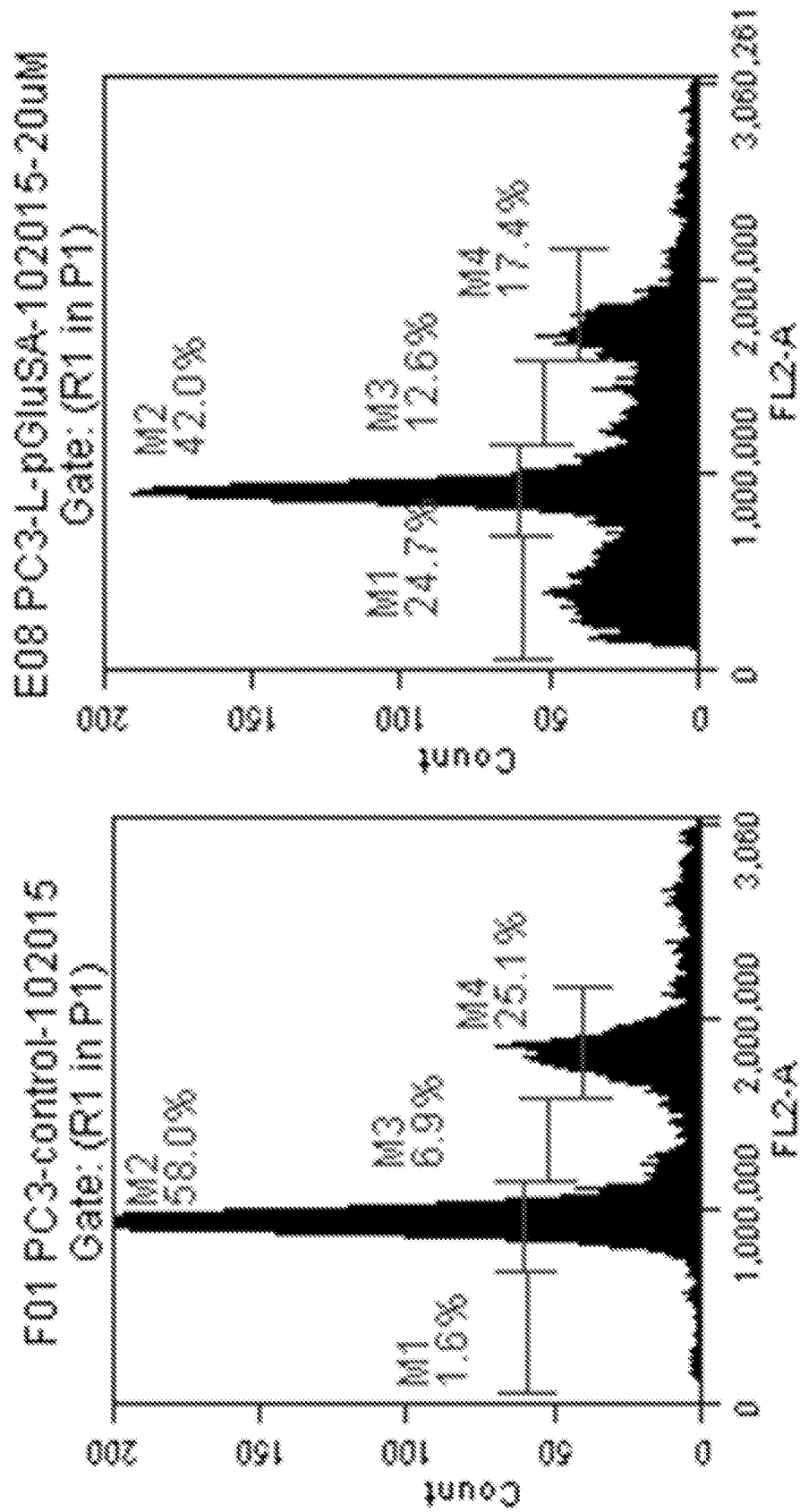


Figure 3

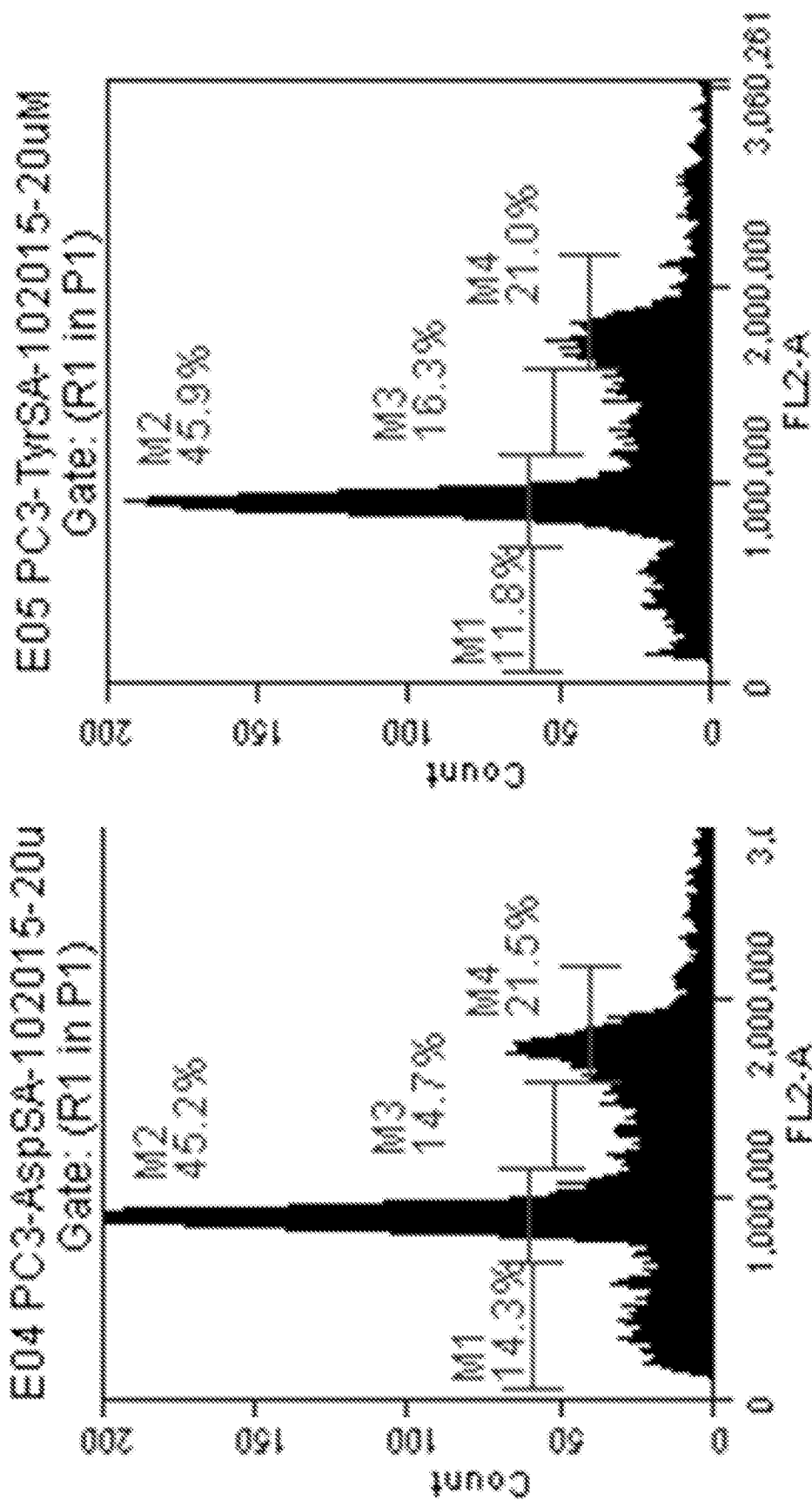


Figure 3 (continued)

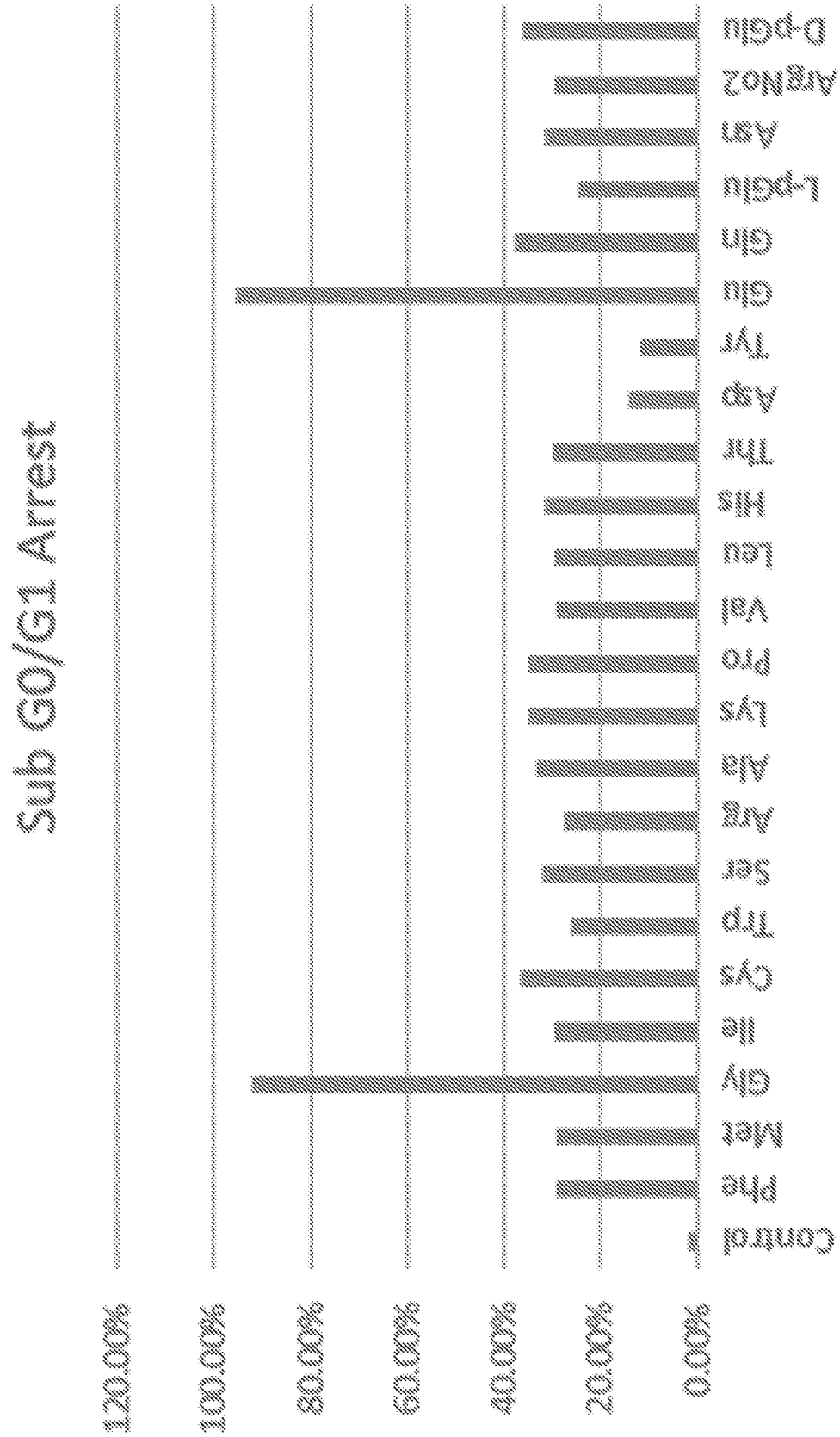


Figure 4

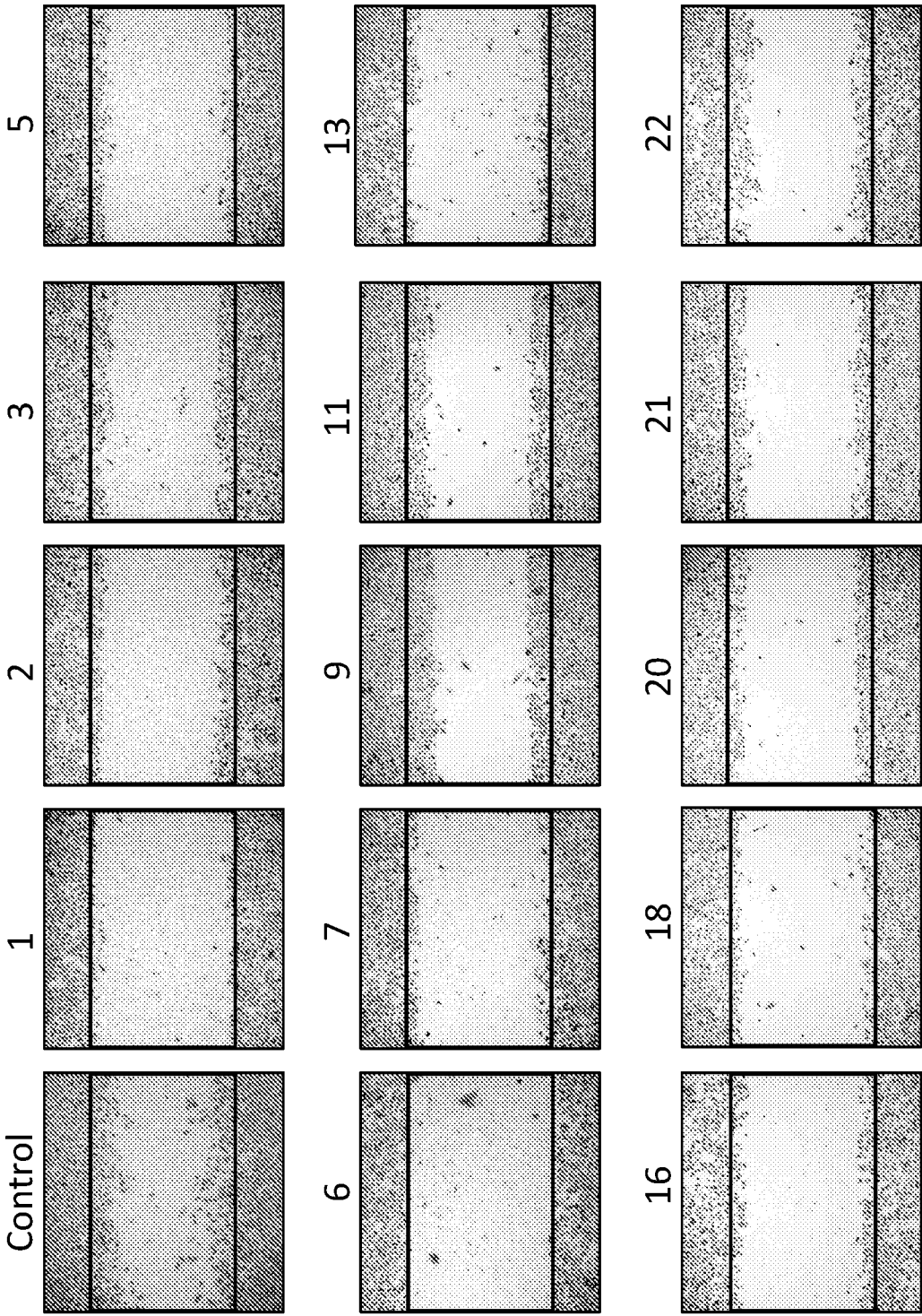


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/37092

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07H 19/16; A61K 31/7076 (2016.01)

CPC - C07H19/16

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): C07H 19/16; A61K 31/7076 (2016.01)

CPC: C07H19/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/46; 536/27.62; 536/27.23

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

PatBase, Google Scholar, PubWEST

adenosine sulfamide, derivative, sulfamoyl adenosine, 2-oxo-azetidin-4-yl, aminoacyl tRNA synthetase, inhibit, modulate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,824,657 A (HILL et al.) 20 October 1998 (20.10.1998) col 6, ln 10-12; col 18, ln 49-55; col 23-24; col 23-24, Table 1	1-2, 10, 31
Y	US 5,498,601 A (SATO et al.) 12 March 1996 (12.03.1996) col 5, ln 26 to col 6, ln 1; col 6, ln 19-24	1-2, 10, 31
A	US 8,927,533 B2 (GIANNINI et al.) 06 January 2015 (06.01.2015) Entire Document	1-2, 10, 31
A	US 2009/0170805 A1 (TAN et al.) 02 July 2009 (02.07.2009) Entire Document	1-2, 10, 31
A	PUBCHEM-CID 23647961 Create Date: 19 January 2008 (19.01.2008) pg 3, Fig	1-2, 10, 31
A	PUBCHEM-CID 24866955 Create Date: 11 August 2008 (11.08.2008) pg 3, Fig	1-2, 10, 31
A	BERNIER et al. 'Glutamylsulfamoyl adenosine and pyroglutamylsulfamoyl adenosine are competitive inhibitors of E. coli glutamyl-tRNA synthetase', J Enzyme Inhib Med Chem. 2005, Vol.20(1), pp 617. Abstract	1-2, 10, 31
A	US 2008/0293666 A1 (ALDRICH et al.) 27 November 2008 (27.11.2008) Entire Document	1-2, 10, 31

☐ Further documents are listed in the continuation of Box C.

* 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

16 October 2016

Date of mailing of the international search report

16 NOV 2016

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/37092

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.: 12-13, 22-28, 54-68 and 71-92
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:

--Please see attached sheet--

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.:
1-2, 10 and 31

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/US 16/37092

Attachment to Box. No.III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-11, 14-21, 29-53 and 69-70 directed to an adenosine sulfamide compound of Formula I or Formula II.

The adenosine sulfamide compound will be searched to the extent that the compound encompasses the first species of claim 1, represented by Formula (I) wherein

n is 1; and

each of R1, R2, R3, R4, R5, R6, R7 and R8 is H.

It is believed that claims 1-2, 10 and 31 read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1 described above.

Applicant is invited to elect additional adenosine sulfamide compounds of Formula (I) or Formula (II), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected composition. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched.

Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula (I), wherein

n is 2; each of R1, R2, R3, R4, R5 and R8 is H and R6 and R7 are taken together with their intervening atoms to form an unsubstituted heterocyclic ring (i.e., claims 1, 3-9, 14-15 and 16-18).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique adenosine sulfamide compound, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound having the core structure of Formula (I) or Formula (II).

This shared technical feature, however, does not provide a contribution over the prior art, as being obvious over PubChem-CID-23647961 (Create Date: 19 January 2008) (hereinafter 'Pubchem') in view of US 7,989,430 B2 to Aldrich et al. published on 02 August 2011 (hereinafter 'Aldrich').

Pubchem discloses a sulfamoyl analog of Formula (I), where a -O-SO₂-NH- linkage replaces the -NH-SO₂-NH- linkage of Formula (I), wherein n is 2; R1, R2, R3, R4, R5, R6, R7 and R8 are each H (pg 3, Fig), as a compound having antibacterial activity (pg 9, title of PubMed citation - Glutamylsulfamoyladenine and pyroglutamylsulfamoyladenine are competitive inhibitors of E. coli glutamyl-tRNA synthetase- Abstract of PubMed article attached separately).

Pubchem does not disclose the sulfamide linkage of Formula (I).

However, Aldrich teaches analogs of Formula (I) where a substituted phenyl replaces the 2-oxo-pyrrolidine ring of Formula (I), having a -O-SO₂-NH- linkage or a -NH-SO₂-NH- linkage as having antibacterial activity in a salt form (Fig 1, Example 1, Example 4; col 36, ln 10-15; col 4, ln 26-46).

It would have been obvious to one of ordinary skill in the art to combine the structure-activity studies disclosed in Aldrich with the compound of Pubchem, because both Pubchem and Aldrich are directed to adenosine compounds having antibacterial activity, and to substitute a -NH-SO₂-NH- linkage in place of the -O-SO₂-NH- linkage of the Pubchem compound, to thus design a compound of Formula (I) as a potent antibacterial agent.

As said compound was known at the time of the invention, this cannot be considered a special technical feature which would otherwise unify the inventions of Groups I+.

The inventions of Group I+, thus lack unity under PCT Rule 13.

Note: Claims 12-13, 22-28, 54-68 and 71-92 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are, therefore, not included in the above analysis.