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(54) Title: TOPICAL DOSAGE REGIMEN

(57) Abstract: Described herein is a novel dosage regimen, and related uses and methods, for a prostaglandin FP receptor agonist (PFPPRA) compound topically administered to the skin. The dosage regimen is useful for reduction of subcutaneous fat, for example, in patients who suffer from local excesses of subcutaneous fat. A particular advantage of the dosage regimen is the ability to reduce composition exposure and thereby promote convenience and comfort, while maintaining the desired exposure and therapeutic effect in subcutaneous fat. Further provided are kits according to the novel dosage regimen, comprising a PFPPRA composition and instructions for use.



TOPICAL DOSAGE REGIMEN

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application, U.S.S.N. 62/018,233, filed June 27, 2014, the entire contents of which are incorporated herein by reference.

Field of the Invention

[0002] This invention relates to a novel dosage regimen for a prostaglandin FP receptor agonist (a PFPPRA compound), *e.g.*, latanoprost, bimatoprost, tafluprost, travoprost, and prodrugs thereof, administered to the skin. The dosage regimen is useful for local reduction of subcutaneous fat, for example, in individuals with local excesses of subcutaneous fat. The dosage regimen improves a user's comfort and convenience while achieving the desired drug delivery.

Background of the Invention

[0003] Local excesses of body fat are an important cause of aesthetic dissatisfaction, reduced self-esteem, and psychosocial distress. These excesses may involve, for example, prominent and undesired deposits of fat on the face, periorbital area, cheeks, chin, neck, chest, breast, abdomen, buttocks, hips, thighs, legs, and/or arms. One approach to reduce local excesses of body fat is to administer a fat-reducing drug. Some fat-reducing drugs are administered topically, *i.e.*, to the skin surface.

[0004] Generally, the efficacy of a drug depends on the degree of drug exposure in the target tissue, *e.g.*, the excess adipose tissue, *e.g.*, subcutaneous fat. A standard measure of drug exposure is the area under the time-concentration curve (AUC) in the target tissue.

[0005] Many topical skin medications are used on a daily schedule, which is easy for users to remember. Furthermore, many daily skin medications, *e.g.*, retinoids, acne medications, corticosteroids, antibiotics, antimycotics, and moisturizers, are left on the skin indefinitely and removed only incidentally, *e.g.*, when the user next washes the skin.

[0006] Instructions that accompany many daily skin medications are silent as to whether and when the product should be removed. Thus, use of daily skin medications can routinely result in skin surface exposure for well over 12 hours, and in some cases 24 hours or more. These extended periods of skin surface exposure can be desirable when the therapeutic

purpose is to treat the skin *per se*, because they maximize skin exposure over the dosage interval.

[0007] However, when the efficacy of a topical medication is determined by exposure in tissue other than the skin surface, an opportunity can exist to modify exposure beneficially in one tissue without compromise to the other. For example, exposure on the skin surface may merely be incidental to the route of delivery when exposure in subcutaneous fat (and the dermis adjacent to it) is more relevant to efficacy.

[0008] Therefore, there is a need for topical PFPPRA dosage regimens to that improve patient comfort and convenience by reducing exposure on the skin surface without reducing exposure in subcutaneous fat and/or dermis.

Summary of the Invention

[0009] The inventors have previously found that compounds of the prostaglandin FP receptor agonist (PFPPRA compound) class can be administered to the skin to locally reduce adipose tissue under the skin, *i.e.*, subcutaneous fat. See, *e.g.*, U.S. Patent 8,426,471 and U.S. Publication No. 2010/0234466, incorporated herein by reference.

[0010] The present invention arises from the experimental discovery that PFPPRA compounds possess unexpectedly different pharmacokinetic properties in subcutaneous fat and dermis, compared to other previously studied compartments, such as plasma and the eye. Briefly, it has been discovered that when a PFPPRA compound is applied to surface of skin (for example, in certain ointment and gel formulations), most of the delivery into the dermis or across the skin is achieved within 4-12 hours. Furthermore, the compound (or its active metabolite) remains in the dermis or subcutaneous fat for 24 hours or more. This is surprising, because it is typical for PFPPRA compounds to be rapidly metabolized and cleared from the body. For example, when latanoprost is administered intravenously or ophthalmically, the active metabolite, latanoprost free acid, is eliminated with a half-life of about 9-85 minutes. However, it has now been discovered that when latanoprost is administered percutaneously to subcutaneous fat, the active metabolite, latanoprost free acid, is eliminated slowly, with a half-life of about 18-24 hours (Example 5).

[0011] Based on the above experimental results, the inventors have recognized that if certain topical compositions comprising a PFPPRA compound are removed after most of a daily dose is delivered (*e.g.*, about 4 to 8 hours after application), longer exposure on the skin surface is unnecessary, and the topical composition or residue thereof can be removed from the skin surface. Thus, patient comfort and convenience can be promoted without

compromising delivery of the drug to the dermis and fat. Removal of the topical composition, in this instance, means gross removal (*e.g.*, removal of at least 80%, 85%, 90%, 95%, 99%, or 100%) of the remaining topical composition or residue thereof, including any remaining PFPPRA compound and any remaining excipients, from the skin surface, *e.g.*, by washing, bathing, scrubbing, scraping, removing patches, and the like, and/or stripping from the skin. It should be understood that some ingredients of the topical composition can be volatile and can evaporate following application to the skin thereby leaving a residue. Other ingredients do not necessarily evaporate. For example, PFPPRA compounds are not volatile compounds.

[0012] Thus, in one aspect, provided is a prostaglandin FP receptor agonist compound for topical use in reducing body fat, whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours per dose of the composition.

[0013] In another aspect, provided is a method for locally reducing body fat in a subject in need thereof, the method comprising administering a topical composition comprising a PFPPRA compound to the skin surface, and removing the topical composition or residue thereof from the skin surface between about 4 hours and about 12 hours after said administering. In certain embodiments, the dermis has taken up at least 80% of maximal load by the PFPPRA compound (or active metabolite thereof) within about 4 to about 12 hours of administration (with maximal load as defined herein). In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after the dermis has taken up at least 80% of maximal load. In certain embodiments, more than about 60 percent of the 24-hour transcutaneous flux occurs within 4 to 12 hours after administration. In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60 percent of the 24-hour transcutaneous flux has occurred.

[0014] In another aspect, provided is a kit comprising a topical fat-reducing composition and instructions for use, wherein the composition comprises a PFPPRA compound, and wherein the instructions provide for a duration of skin surface exposure to the composition or residue thereof of between about 4 hours and about 12 hours per dose of the composition.

[0015] In certain embodiments of the uses, methods, and kits described herein, the dose frequency is about once every 24 hours.

[0016] In certain embodiments, the PFPPRA compound is selected from the group consisting of latanoprost, tafluprost, travoprost, bimatoprost, and pharmaceutically acceptable

salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, or prodrugs thereof. In certain embodiments, the PFPPRA compound is hydrolyzed in the skin to an active metabolite. For example, in certain embodiments, latanoprost is a prodrug that is hydrolyzed in the skin to yield latanoprost free acid. In certain embodiments, tafluprost is a prodrug that is hydrolyzed in the skin to yield tafluprost free acid. In certain embodiments, travoprost is a prodrug that is hydrolyzed in the skin to yield travoprost free acid (*aka* fluprostenol). In certain embodiments, bimatoprost is a prodrug that is hydrolyzed in the skin to yield bimatoprost free acid.

[0017] Other objects and advantages will become apparent to those skilled in the art from consideration of the ensuing Detailed Description, Examples, and Claims.

Definitions

Chemical definitions

[0018] 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.

[0019] Certain compounds as described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. The compounds provided 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. In certain embodiments, the compounds as described herein are enantiopure compounds. In certain other embodiments, mixtures of stereoisomers are provided.

[0020] Furthermore, certain compounds, as described herein may have one or more double bonds that can exist as either the *cis* or *trans*, or the E or Z isomer, unless otherwise indicated. The invention additionally encompasses the compounds as individual isomers

substantially free of other isomers, and alternatively, as mixtures of various isomers, *e.g.*, racemic mixtures of E/Z isomers or mixtures enriched in one E/Z isomer.

[0021] The terms “enantiomerically enriched,” “enantiomerically pure” and “non-racemic,” as used interchangeably herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (*e.g.*, greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, more preferably at least 75% by weight, and even more preferably at least 80% by weight. In some embodiments, the enrichment can be much greater than 80% by weight, providing a “substantially enantiomerically enriched,” “substantially enantiomerically pure” or a “substantially non-racemic” preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, more preferably at least 90% by weight, and even more preferably at least 95% by weight. In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, S.H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0022] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0023] As used herein, “aliphatic” refers to an alkyl, alkenyl, alkynyl, or carbocyclyl group, as defined herein.

[0024] As used herein, alone or as part of another group, “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 30 carbon atoms (“C₁₋₃₀ alkyl”). In some embodiments, an alkyl group has 1 to 20 carbon atoms (“C₁₋₂₀ alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In

some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ 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 (“C₂₋₆ alkyl”). Examples of C₁₋₆ 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). Unless otherwise specified, each instance of an alkyl group is independently unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) are substituted with one or more substituents. In certain embodiments, the alkyl group is an unsubstituted C₁₋₃₀ alkyl. In certain embodiments, the alkyl group is a substituted C₁₋₃₀ alkyl.

[0025] As used herein “perhaloalkyl” as defined herein refers to an alkyl group having from having from 1 to 30 carbon atoms wherein all of the hydrogen atoms are each independently replaced halogen, *e.g.*, selected from fluoro, bromo, chloro or iodo (“C₁₋₃₀ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 20 carbon atoms (“C₁₋₂₀ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 10 carbon atoms (“C₁₋₁₀ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 6 carbon atoms (“C₁₋₆ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 5 carbon atoms (“C₁₋₅ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 4 carbon atoms (“C₁₋₄ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 3 carbon atoms (“C₁₋₃ perhaloalkyl”). In some embodiments, the perhaloalkyl has 1 to 2 carbon atoms (“C₁₋₂ perhaloalkyl”). In some embodiments, all of the hydrogen atoms are each replaced with fluoro. In some embodiments, all of the hydrogen atoms are each replaced with chloro. Examples of perhaloalkyl groups include –CF₃, –CF₂CF₃, –CF₂CF₂CF₃, –CCl₃, –CFCl₂, –CF₂Cl and the like.

[0026] As used herein, “alkyloxy” refers to an alkyl group, as defined herein, substituted with an oxygen atom, wherein the point of attachment is the oxygen atom. In certain embodiments, the alkyl group has 1 to 30 carbon atoms (“C₁₋₃₀ alkyloxy”). In some embodiments, the alkyl group has 1 to 20 carbon atoms (“C₁₋₂₀ alkyloxy”). In some embodiments, the alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyloxy”). In some embodiments, the alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyloxy”). In some embodiments, the alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyloxy”). Examples of C₁₋₄

alkyloxy groups include methoxy (C₁), ethoxy (C₂), propoxy (C₃), isopropoxy (C₃), butoxy (C₄), *tert*-butoxy (C₅) and the like. Examples of C₁₋₆ alkyloxy groups include the aforementioned C₁₋₄ alkyloxy groups as well as pentyloxy (C₅), isopentyloxy (C₅), neopentyloxy (C₅), hexyloxy (C₆) and the like. Unless otherwise specified, each instance of the alkyl moiety of the alkyloxy group is independently unsubstituted (an “unsubstituted alkyloxy”) or substituted (a “substituted alkyloxy”) with one or more substituents. In certain embodiments, the alkyloxy group is an unsubstituted C₁₋₃₀ alkyloxy. In certain embodiments, the alkyloxy group is a substituted C₁₋₃₀ alkyloxy.

[0027] As used herein, “alkylcarboxy” refers to a group of the formula $-\text{C}(=\text{O})\text{OR}^a$ or $-\text{OC}(=\text{O})\text{R}^a$, wherein R^a is an alkyl group as defined herein. In certain embodiments, the alkyl of the alkylcarboxy group has 1 to 6 carbon atoms (“C₁₋₆ alkylcarboxy”). In some embodiments, the alkyl of the alkylcarboxy group has 1 to 5 carbon atoms (“C₁₋₅ alkylcarboxy”). In some embodiments, the alkyl of the alkylcarboxy group has 1 to 4 carbon atoms (“C₁₋₄ alkylcarboxy”). In some embodiments, the alkyl of the alkylcarboxy group has 1 to 3 carbon atoms (“C₁₋₃ alkylcarboxy”). In some embodiments, the alkyl of the alkylcarboxy group has 1 to 2 carbon atoms (“C₁₋₂ alkylcarboxy”). Unless otherwise specified, each instance of the alkyl of the alkylcarboxy group is independently unsubstituted (an “unsubstituted alkylcarboxy”) or substituted (a “substituted alkylcarboxy”) with one or more substituents. In certain embodiments, the alkylcarboxy group is an unsubstituted C₁₋₆ alkylcarboxy. In certain embodiments, the alkylcarboxy group is a substituted C₁₋₆ alkylcarboxy.

[0028] As used herein, alone or as part of another group, “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 30 carbon atoms and one or more carbon-carbon double bonds (“C₂₋₃₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 20 carbon atoms (“C₂₋₂₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ 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. 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 C₂₋₃₀ alkenyl. In certain embodiments, the alkenyl group is a substituted C₂₋₃₀ alkenyl.

[0029] As used herein, alone or as part of another group, “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 30 carbon atoms and one or more carbon-carbon triple bonds (“C₂₋₃₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 20 carbon atoms (“C₂₋₂₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ 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 atom (“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. 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 C₂₋₃₀ alkynyl. In certain embodiments, the alkynyl group is a substituted C₂₋₃₀ alkynyl.

[0030] 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”). Exemplary carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), 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”)) 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 1, 2, 3, 4, or 5 substituents as described herein. In certain embodiments, the carbocyclyl group is an unsubstituted C_{3–10} carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C_{3–10} carbocyclyl.

[0031] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 7 ring carbon atoms (“C_{3–7} cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C_{3–6} cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C_{5–6} cycloalkyl”). Examples of C_{5–6} cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C_{3–6} cycloalkyl groups include the aforementioned C_{5–6} cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C_{3–7} cycloalkyl groups include the aforementioned C_{3–6} cycloalkyl groups as well as cycloheptyl (C₇). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is an unsubstituted C_{3–7} cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C_{3–7} cycloalkyl.

[0032] As used herein, alone or as part of another group, “heterocyclyl” refers to a radical of a 3– to 8–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 (“3–8–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”)), 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 carbocycl or heterocycl ring, or ring systems wherein the heterocycl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocycl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocycl ring system.

[0033] In some embodiments, a heterocycl 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 heterocycl”). In some embodiments, a heterocycl 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 heterocycl”). In some embodiments, the 5–6-membered heterocycl has 1–3 ring heteroatoms selected from nitrogen, oxygen and sulfur. In some embodiments, the 5–6-membered heterocycl has 1–2 ring heteroatoms selected from nitrogen, oxygen and sulfur. In some embodiments, the 5–6-membered heterocycl has 1 ring heteroatom selected from nitrogen, oxygen and sulfur. Exemplary 3–membered heterocycls containing 1 heteroatom include, without limitation, azirdinyl, oxiranyl, thioenyl. Exemplary 4–membered heterocycls containing 1 heteroatom include, without limitation, azetidyl, oxetanyl and thietanyl. Exemplary 5–membered heterocycls containing 1 heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl–2,5–dione. Exemplary 5–membered heterocycls containing 2 heteroatoms include, without limitation, dioxolanyl, oxathiolanyl and dithiolanyl. Exemplary 5–membered heterocycls containing 3 heteroatoms include, without limitation, triazolanyl, oxadiazolanyl, and thiadiazolanyl. Exemplary 6–membered heterocycl groups containing 1 heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocycl groups containing 2 heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6–membered heterocycl groups containing 3 heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocycl groups containing 1 heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocycl groups containing 1 heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Unless otherwise specified, each instance of heterocycl is independently unsubstituted (an “unsubstituted heterocycl”) or substituted (a “substituted heterocycl”) with one or more substituents. In certain embodiments, the heterocycl group is an unsubstituted 3–8-

membered heterocyclyl. In certain embodiments, the heterocyclyl group is a substituted 3–8-membered heterocyclyl.

[0034] As used herein, alone or as part of another group, “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system having 6–10 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–10} 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). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more cycloalkyl 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 as described herein. In certain embodiments, the aryl group is an unsubstituted C_{6–10} aryl. In certain embodiments, the aryl group is a substituted C_{6–10} aryl.

[0035] As used herein, alone or as part of another group, “heteroaryl” refers to a radical of a 5–14-membered monocyclic or polycyclic (*e.g.*, bicyclic) $4n+2$ aromatic ring system having 4–10 ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10-membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl 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 carbocycl or heterocycl 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 on the 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). 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. Exemplary 5-membered heteroaryls containing 1 heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryls containing 2 heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryls containing 3 heteroatoms include, without limitation, triazolyl, oxadiazolyl, thiadiazolyl. Exemplary 5-membered heteroaryls containing 4 heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryls containing 1 heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryls containing 2 heteroatoms include, without limitation, pyridazinyl, pyrimidinyl and pyrazinyl. Exemplary 6-membered heteroaryls containing 3 or 4 heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7 membered heteroaryls containing 1 heteroatom include, without limitation, azepinyl, oxepinyl and thiepinyl. Exemplary 5,6-bicyclic heteroaryls include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl (*aka* benzothienyl), isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryls include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl and quinazolinyl. 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 5–10-membered heteroaryl. In certain embodiments, the heteroaryl group is a substituted 5–10-membered heteroaryl.

[0036] Alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl, referred to without the suffix “-ene,” describe a monoradical of alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, respectively, and as defined herein, wherein the monoradical is directly attached to a parent molecule or to another group by one bond (*e.g.*, one single or double bond). Monoradical groups, as defined herein, may also be optionally substituted. Groups referred to with the suffix “-ene”, such as alkylene, alkenylene, alkynylene, carbocyclylene, heterocyclylene, arylene and heteroarylene groups, describe a diradical of alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl, respectively, and as defined herein, wherein the diradical is between and directly attached to two groups (*e.g.*, between the parent molecule and another group) by two bonds (*e.g.*, single or double bonds). Diradical groups may also be optionally substituted.

[0037] Aliphatic, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, “substituted” or “unsubstituted” aliphatic, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group (*e.g.*, 1, 2, 3, 4, or 5 positions), and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. 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.

[0038] Exemplary carbon atom substituents include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$

$-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, 3–8-membered heterocyclyl, C_{6-10} aryl, and 5–10-membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group =O, =S, =NN(R^{bb})₂, =NNR^{bb}C(=O)R^{aa}, =NNR^{bb}C(=O)OR^{aa}, =NNR^{bb}S(=O)₂R^{aa}, =NR^{bb}, or =NOR^{cc};

each instance of R^{aa} is, independently, selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl, or two R^{aa} groups are joined to form a 3-8-membered heterocyclyl or 5-10-membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl, or two R^{bb} groups are joined to form a 3-8-membered heterocyclyl or 5-10-membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3–8-membered heterocyclyl, C₆₋₁₀ aryl, and 5–10-membered heteroaryl, or two R^{cc} groups are joined to form a 3–8-membered heterocyclyl or 5–10-membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-C(=O)OR^{ee}$, $-OC(=O)R^{ee}$, $-OC(=O)OR^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-$

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}SO₂R^{ee}, -SO₂N(R^{ff})₂, -SO₂R^{ee}, -SO₂OR^{ee}, -OSO₂R^{ee}, -S(=O)R^{ee}, -Si(R^{ee})₃, -OSi(R^{ee})₃, -C(=S)N(R^{ff})₂, -C(=O)SR^{ee}, -C(=S)SR^{ee}, -SC(=S)SR^{ee}, -P(=O)₂R^{ee}, -P(=O)(R^{ee})₂, -OP(=O)(R^{ee})₂, -OP(=O)(OR^{ee})₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

each instance of R^{ee} is, independently, selected from C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl, or two R^{ff} groups are joined to form a 3-8-membered heterocyclyl or 5-10-membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(OC₁₋₆ alkyl)(C₁₋₆ alkyl), -N(OH)(C₁₋₆ alkyl), -NH(OH), -SH, -SC₁₋₆ alkyl, -SS(C₁₋₆ alkyl), -C(=O)(C₁₋₆ alkyl), -CO₂H, -CO₂(C₁₋₆ alkyl), -OC(=O)(C₁₋₆ alkyl), -OCO₂(C₁₋₆ alkyl), -C(=O)NH₂, -C(=O)N(C₁₋₆ alkyl)₂, -OC(=O)NH(C₁₋₆ alkyl), -NHC(=O)(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)C(=O)(C₁₋₆ alkyl), -NHCO₂(C₁₋₆ alkyl), -NHC(=O)N(C₁₋₆ alkyl)₂, -NHC(=O)NH(C₁₋₆ alkyl), -NHC(=O)NH₂, -C(=NH)O(C₁₋₆ alkyl), -OC(=NH)(C₁₋₆ alkyl), -OC(=NH)OC₁₋₆ alkyl, -C(=NH)N(C₁₋₆ alkyl)₂, -C(=NH)NH(C₁₋₆ alkyl), -C(=NH)NH₂, -OC(=NH)N(C₁₋₆ alkyl)₂, -OC(NH)NH(C₁₋₆ alkyl), -OC(NH)NH₂, -NHC(NH)N(C₁₋₆ alkyl)₂, -NHC(=NH)NH₂, -NHCO₂(C₁₋₆ alkyl), -SO₂N(C₁₋₆ alkyl)₂, -SO₂NH(C₁₋₆ alkyl), -SO₂NH₂, -SO₂C₁₋₆ alkyl, -SO₂OC₁₋₆ alkyl, -OSO₂C₁₋₆ alkyl, -SOC₁₋₆ alkyl, -Si(C₁₋₆ alkyl)₃, -OSi(C₁₋₆ alkyl)₃, -C(=S)N(C₁₋₆ alkyl)₂, C(=S)NH(C₁₋₆ alkyl), C(=S)NH₂, -C(=O)S(C₁₋₆ alkyl), -C(=S)SC₁₋₆ alkyl, -SC(=S)SC₁₋₆ alkyl, -P(=O)₂(C₁₋₆ alkyl), -P(=O)(C₁₋₆ alkyl)₂, -OP(=O)(C₁₋₆ alkyl)₂, -OP(=O)(OC₁₋₆ alkyl)₂, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, 3-8-membered-heterocyclyl, C₆₋₁₀ aryl, and 5-10-membered heteroaryl; or two geminal R^{gg} substituents can be joined to form =O or =S.

[0039] In certain embodiments, the carbon atom substituent is selected from the group consisting of halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, 3–8-membered heterocyclyl, C_{6-10} aryl, and 5–10-membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3–8-membered heterocyclyl or 5–10-membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} and R^{dd} are as defined above.

[0040] As used herein, the term “hydroxyl” or “hydroxy” refers to the group $-\text{OH}$. The term “substituted hydroxyl” or “substituted hydroxy,” by extension, refers to a hydroxyl group wherein the oxygen atom is substituted with a group other than hydrogen, *e.g.*, selected from $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, and $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein.

[0041] As used herein, the term “thiol” or “thio” refers to the group $-\text{SH}$. The term “substituted thiol” or “substituted thio,” by extension, refers to a thiol group wherein the sulfur atom is substituted with a group other than hydrogen, and includes groups selected from $-\text{SR}^{\text{aa}}$, $-\text{S}=\text{SR}^{\text{cc}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, and $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, wherein R^{aa} and R^{cc} are as defined herein.

[0042] As used herein, the term, “amino” refers to the group $-\text{NH}_2$.

[0043] As used herein, the term “substituted amino” refers to a monosubstituted, disubstituted, or trisubstituted amino group, as defined herein.

[0044] As used herein, the term “monosubstituted amino” refers to an amino group substituted with one hydrogen and one group other than hydrogen, and includes groups selected from $-\text{NH}(\text{R}^{\text{bb}})$, $-\text{NHC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NHCO}_2\text{R}^{\text{aa}}$, $-\text{NHC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NHC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NHSO}_2\text{R}^{\text{aa}}$, $-\text{NHP}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{NHP}(=\text{O})(\text{NR}^{\text{bb}})_2$, wherein R^{aa} , R^{bb} and R^{cc} are as defined herein, and wherein R^{bb} of the group $-\text{NH}(\text{R}^{\text{bb}})$ is not hydrogen.

[0045] As used herein, the term “disubstituted amino” refers to an amino group substituted with two groups other than hydrogen, and includes groups selected from $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, and $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, 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.

[0046] As used herein, the term “halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

[0047] As used herein, “nitro” refers to the group -NO₂.

[0048] As used herein, “cyano” refers to the group -CN.

[0049] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, -OH, -OR^{aa}, -N(R^{cc})₂, -CN, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{bb})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, -P(=O)₂R^{aa}, -P(=O)(R^{aa})₂, -P(=O)₂N(R^{cc})₂, -P(=O)(NR^{cc})₂, C₁₋₁₀ alkyl, C₁₋₁₀ perhaloalkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl, or two R^{cc} groups attached to an N atom are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined above.

[0050] In certain embodiments, the substituent present on the nitrogen atom is an “amino protecting group”. Amino protecting groups include, but are not limited to, -OH, -OR^{aa}, -N(R^{cc})₂, -C(=O)R^{aa}, -C(=O)N(R^{cc})₂, -CO₂R^{aa}, -SO₂R^{aa}, -C(=NR^{cc})R^{aa}, -C(=NR^{cc})OR^{aa}, -C(=NR^{cc})N(R^{cc})₂, -SO₂N(R^{cc})₂, -SO₂R^{cc}, -SO₂OR^{cc}, -SOR^{aa}, -C(=S)N(R^{cc})₂, -C(=O)SR^{cc}, -C(=S)SR^{cc}, C₁₋₁₀ alkyl (*e.g.*, aralkyl, heteroaralkyl), C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₀ carbocyclyl, 3-14 membered heterocyclyl, C₆₋₁₄ aryl, and 5-14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa}, R^{bb}, R^{cc} and R^{dd} are as defined herein. Amino 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.

[0051] For example, amino protecting groups such as amide groups (*e.g.*, -C(=O)R^{aa}) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-

dithiobenzoyloxycarbonylamino)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.

[0052] Amino protecting groups such as carbamate groups (*e.g.*, $\text{—C(=O)OR}^{\text{aa}}$) 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), 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, alkylidithio 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-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Troc), *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-dimethoxycarbonylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-

dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0053] Amino protecting groups such as sulfonamide groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0054] Other amino protecting groups include, but are not limited to, phenothiazinyl-(10)-carbonyl derivative, *N*'-*p*-toluenesulfonylaminocarbonyl derivative, *N*'-phenylaminothiocarbonyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypropylamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-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]methyleamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N-p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentacarbonylchromium- or tungsten)carbonyl]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).

[0055] In certain embodiments, the substituent present on the oxygen atom is an “oxygen protecting group”. Oxygen protecting groups include, but are not limited to $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)R^{aa}$, $-C(=O)OR^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as 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, the entirety of which is incorporated herein by reference.

[0056] 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, tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl, 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, *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 -naphthylidiphenylmethyl, *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, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), isobutyl carbonate, vinyl carbonate, allyl carbonate, *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*-(methoxycarbonyl)benzoate, α -naphthoate, *N,N,N',N'*-tetramethylphosphorodiamidate, *N*-phenylcarbamate, dimethylphosphinothioyl, 2,4-dinitrophenylsulfenate, sulfate,

methanesulfonate (mesylate), benzyisulfonate, and tosylate (Ts). For protecting 1,2- or 1,3-diols, the protecting groups include methylene acetal, ethylidene acetal, 1-*t*-butylethylidene ketal, 1-phenylethylidene ketal, (4-methoxyphenyl)ethylidene acetal, 2,2,2-trichloroethylidene acetal, acetonide, cyclopentylidene ketal, cyclohexylidene ketal, cycloheptylidene ketal, benzylidene acetal, *p*-methoxybenzylidene acetal, 2,4-dimethoxybenzylidene ketal, 3,4-dimethoxybenzylidene acetal, 2-nitrobenzylidene acetal, methoxymethylene acetal, ethoxymethylene acetal, dimethoxymethylene ortho ester, 1-methoxyethylidene ortho ester, 1-ethoxyethylidene ortho ester, 1,2-dimethoxyethylidene ortho ester, α -methoxybenzylidene ortho ester, 1-(*N,N*-dimethylamino)ethylidene derivative, α -(*N,N'*-dimethylamino)benzylidene derivative, 2-oxacyclopentylidene ortho ester, di-*t*-butylsilylene group (DTBS), 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene) derivative (TIPDS), tetra-*t*-butoxydisiloxane-1,3-diylidene derivative (TBDS), cyclic carbonates, cyclic boronates, ethyl boronate, and phenyl boronate.

[0057] In certain embodiments, the substituent present on an sulfur atom is an sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0058] These and other exemplary substituents are described in more detail in the Detailed Description, the Examples and in the Claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

[0059] As used herein, the terms “salt”, “acceptable salt”, or “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. 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.

[0060] As used herein, the term “prodrug” means a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*e.g.*, *in vitro* or *in vivo* enzymatic conditions) to provide a pharmacologically active compound. In this instance, the “prodrug” is a compound administered to a subject, and the pharmacologically active compound is the “active metabolite thereof.” Exemplary prodrugs include esters, amides, and/or thioamides of the parent free acid, and compounds wherein a hydroxyl group on the parent compound (*e.g.*, a pentacyclic hydroxyl group of the PFPPRA compound) is acylated. In certain cases, a prodrug has improved physical and/or delivery properties over the parent compound. Prodrugs are typically designed to enhance pharmacologically, pharmaceutically and/or pharmacokinetically based properties associated with the parent compound. The advantage of a prodrug can lie in its physical properties, such as enhanced water solubility for parenteral administration at physiological pH compared to the parent compound, or it enhances absorption from the digestive tract, or it may enhance drug stability for long-term storage.

Other definitions

[0061] “Disease”, “disorder,” and “condition” are used interchangeably herein.

[0062] As used herein, an “individual” or “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.*, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)), other primates (*e.g.*, cynomolgus monkeys, rhesus monkeys) and commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs. In any aspect and/or embodiment of the invention, the mammal is a human.

[0063] As used herein, “local administration” or “administering locally” or “local effect” means administration/application of the active ingredient or active metabolite thereof directly, or in proximity to, a part of the body, tissue, or lesion where said active substance is intended to exert its action. This may include, for example, topical administration to a part of the skin.

[0064] As used herein, unless otherwise specified, “topical administration” or “topically” means application to the surface of the skin.

[0065] As used herein, and unless otherwise specified, a “therapeutically effective amount” “an amount sufficient” or “sufficient amount” of a compound means the level, amount or concentration of the compound needed to treat a disease, disorder or condition, or to reduce or lower a particular parameter (*e.g.*, body fat) in the body of a subject, without causing significant negative or adverse side effects to body or the treated tissue. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutically active agent.

[0066] As used herein, the terms “reduce”, “reduction”, “reducing”, “lower”, or “lowering” means to diminish or lessen the volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, body fat, adipose tissue) in the body of a subject.

[0067] As used herein, the term “eliminate” means to completely remove any unwanted or undesired volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, excess body fat, excess adipose tissue) in the body of a subject.

[0068] As used herein, “suffer,” “suffers” or “suffering from” refers to a subject diagnosed with a particular disease or condition. As used herein, “likely to suffer” refers to a subject who has not been diagnosed with a particular disease or condition by a medical practitioner, but has a predisposition (*e.g.*, genetic and/or physiologic predisposition), or exhibits signs or symptoms of the disease or condition.

[0069] As used herein, and unless otherwise specified, the terms “treat,” “treating” and “treatment” contemplate an action that occurs while a subject is suffering from the specified

disease or condition, which reduces the severity of the disease or condition, or retards or slows the progression of the disease or condition.

[0070] As used herein, unless otherwise specified, the terms “prevent,” “preventing” and “prevention” contemplate an action that occurs before a subject begins to suffer from the specified disease or condition, which inhibits or reduces the severity of the disease or condition.

[0071] Conditions for which treatment and prevention are contemplated may be further classified as a medical condition or a cosmetic condition. A “medical condition”, as used herein, refers to an abnormal condition that affects the body. A “cosmetic condition”, as used herein, refers to a condition other than a medical condition that affects the physical appearance of the body. A cosmetic condition can occur, for example, due to normal processes in a body, such as aging, pregnancy, puberty, and exposure to the sun or the elements, or due to normal features of a body, such as inherited facial features or body shapes that are found in healthy individuals. Various medical and cosmetic conditions are described herein. A “cosmetic method” refers to a method or procedure intended to ameliorate a cosmetic condition in the subject, *e.g.*, for the beautification of the subject’s body or a part thereof, *e.g.*, to ameliorate a “cosmetic condition in the subject” is contemplated useful for such purpose. A “therapeutic method” refers to a method or procedure intended to treat a medical condition, and a “pharmaceutical composition” is contemplated useful for such purpose. However, while pharmaceutical compositions are contemplated useful for therapeutic and prophylactic purposes, and cosmetic compositions are contemplated useful for cosmetic purposes, there may be overlap between the two compositions in terms of use of the composition. For example, a pharmaceutical composition is also contemplated useful for beautification purposes.

[0072] As used herein, the term “medicament” is used interchangeably with the term “pharmaceutical composition.”

[0073] As used herein, unless otherwise specified, “excess submental fat” means excess fat on the body region including the mentum, the underside of the jaw, and the anterior neck, for example to the level of the inferior border of the cricoid.

[0074] As used herein, unless otherwise specified, “steatoblepharon” refers to a condition characterized by excess fat of the eyelids and/or periorbital tissue. The excess fat can be due to prolapse of orbital or periorbital fat. Steatoblepharon can occur in the lower or upper eyelid, or both. Steatoblepharon can be considered a cause of “eye bags.”

[0075] The presence, amount, or severity of excess fat can be assessed objectively, *e.g.*, by magnetic resonance imaging, computed tomography, biopsy, or skin calipers, or subjectively, *e.g.*, by a clinician, a patient, or other observer, optionally with reference to a photonic, verbal, or descriptive scale or classification system, *e.g.*, a five-step severity scale.

Detailed Description of Certain Embodiments of the Invention

[0076] The inventors have previously found that compounds of the prostaglandin FP receptor agonist (PFPPRA compound) class can be administered to the skin to locally reduce adipose tissue under the skin, *i.e.*, subcutaneous fat. See, *e.g.*, U.S. Patent 8,426,471 and U.S. Publication No. 2010/0234466.

[0077] The present invention arises from the experimental discovery that PFPPRA compounds possess unexpectedly different pharmacokinetic properties in subcutaneous fat and dermis, compared to other previously studied compartments, such as plasma and the eye. Briefly, it has been discovered that when a PFPPRA compound is applied to surface of skin (for example, in certain ointment and gel formulations), most of the delivery into the dermis or across the skin is achieved within 4-12 hours. Furthermore, the compound (or its active metabolite) remains in the dermis or subcutaneous fat for 24 hours or more. This is surprising, because it is typical for PFPPRA compounds to be rapidly metabolized and cleared from the body. For example, when latanoprost is administered intravenously or ophthalmically, the active metabolite is eliminated with a half-life of about 9-85 minutes. However, it has now been discovered that when the compound is administered percutaneously to subcutaneous fat, the active metabolite is eliminated slowly, with a half-life of about 18-24 hours (Example 5).

[0078] Thus, the inventors have recognized that if a topical composition or residue thereof comprising a PFPPRA compound is removed from the skin surface after the dermis is maximally loaded (*e.g.*, removed about 4 to about 12 hours, *e.g.*, about 4 to about 8 hours, after application), further exposure on the skin surface can be avoided, and patient comfort and convenience can be promoted, without compromising delivery of the drug to the dermis and fat. Comforts and conveniences include the freedom to wash the skin for hygienic purposes, to apply cosmetics or fragrances to the skin, to wear certain clothing without risk of staining the clothing, and to interact with other persons without the odor or appearance (*e.g.*, sheen or greasiness) of a pharmaceutical composition on one's body. Examples of side effects that can occur with any topical composition, and that can be reduced or avoided by a

reduction in the exposure time of a topical composition, include greasy or oily skin, acne, dry skin, irritation, redness, and itch.

[0079] Thus, in one aspect, provided is a prostaglandin FP receptor agonist compound for topical use in reducing body fat, whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours per dose of the composition.

[0080] In another aspect, provided is a method for locally reducing body fat in a subject in need thereof, the method comprising administering a topical composition comprising a PFPPRA compound to the skin surface and removing the topical composition or residue thereof from the skin surface between about 4 hour and about 12 hours, inclusive, after said administering. In certain embodiments, the dermis has taken up at least 80% of maximal load by the PFPPRA compound (or active metabolite thereof) within about 4 to about 12 hours of administration. In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after the dermis has taken up at least 80% of maximal load.

[0081] In another aspect, provided is a kit comprising a topical fat-reducing composition and instructions for use, wherein the composition comprises a PFPPRA compound, and wherein the instructions provide for a duration of skin surface exposure to the composition or residue thereof of between about 4 hours and about 12 hours per dose of the composition.

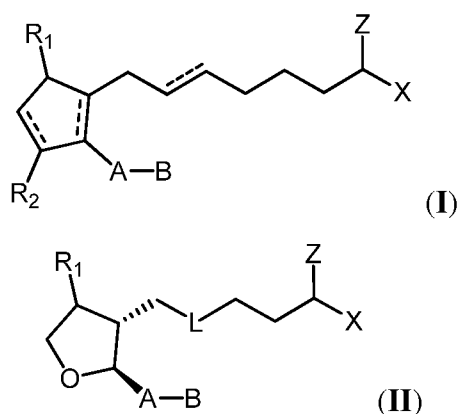
[0082] In certain embodiments of the uses, methods, and kits described herein, the dose frequency is about once every 24 hours.

PFPPRA compounds

[0083] As used herein, a “PFPPRA compound” can be any therapeutically relevant, naturally occurring or synthetic prostaglandin or prostaglandin analog, provided that it or its active metabolite (*e.g.*, if an ester, the parent acid) agonizes a prostaglandin FP receptor, *e.g.*, as determined using a functional assay. “Agonizes” or “agonism” may refer to, for example, a half maximal effective concentration (EC₅₀) of 1 micromolar or less, preferably 100 nanomolar or less. A functional assay may be, for example, assessment of phosphoinositide turnover in HEK293 cells expressing a cloned FP prostaglandin receptor. See, *e.g.*, Sharif *et al.*, *J. Ocular Pharmacol. Ther.* 2002;18:313-324. Many PFPPRA compounds can be classified as prostaglandins, prostanoids, or prostamides. Naturally occurring prostaglandins are a class of structurally related eicosanoid hormones that are derived enzymatically from arachidonic acid. An example of a naturally occurring prostaglandin PFPPRA compound is

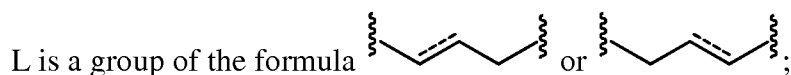
prostaglandin F2 α . Exemplary synthetic prostaglandins, which are prostaglandin F2 α analogs, include, but are not limited to, latanoprost, latanoprost free acid, bimatoprost, bimatoprost free acid, tafluprost, tafluprost free acid, travoprost, travoprost free acid (*a.k.a.* fluprostenol), and prodrugs (*e.g.*, 9-, 11-, and/or 15-ester derivatives) thereof.

[0084] In certain embodiments, the PFPPRA compound is a compound of Formula (I) or (II):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof;

wherein:



each instance of independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration;

A is optionally substituted C₁₋₁₀alkylene, optionally substituted C₂₋₁₀alkenylene, or optionally substituted C₂₋₁₀alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one or more –O– or –S– groups;

B is hydrogen, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3–8–membered–heterocyclyl, optionally substituted 5–14–membered–heteroaryl, optionally substituted C₆₋₁₀aryl, optionally substituted C₁₋₃₀alkyl, optionally substituted C₂₋₃₀alkenyl, or optionally substituted C₂₋₃₀alkynyl;

X is –OR₄, –SR₄, or –N(R₄)₂, wherein each instance of R₄ is independently hydrogen, optionally substituted C₁₋₃₀alkyl, optionally substituted C₂₋₃₀alkenyl, optionally substituted C₂₋₃₀alkynyl, –C(=O)R₅, or –C(=O)OR₅, wherein R₅ is optionally substituted C₁₋₃₀alkyl, optionally substituted C₂₋₃₀alkenyl, or optionally substituted C₂₋₃₀alkynyl, or two R₄ groups are joined to form an optionally substituted 3–8–membered–heterocyclyl or optionally substituted 5–14–membered–heteroaryl ring;

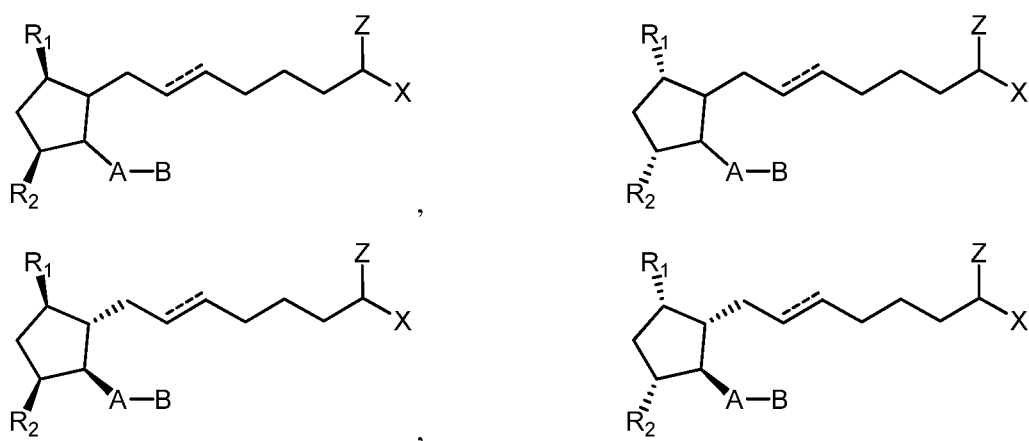
Z is =O, =S, or =NR_Z, wherein R_Z is selected from hydrogen, an amino protecting group, -OH, substituted hydroxyl, optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-8-membered-heterocyclyl, optionally substituted C₆₋₁₀aryl, or optionally substituted 5-14-membered-heteroaryl, or Z represents two hydrogen atoms;

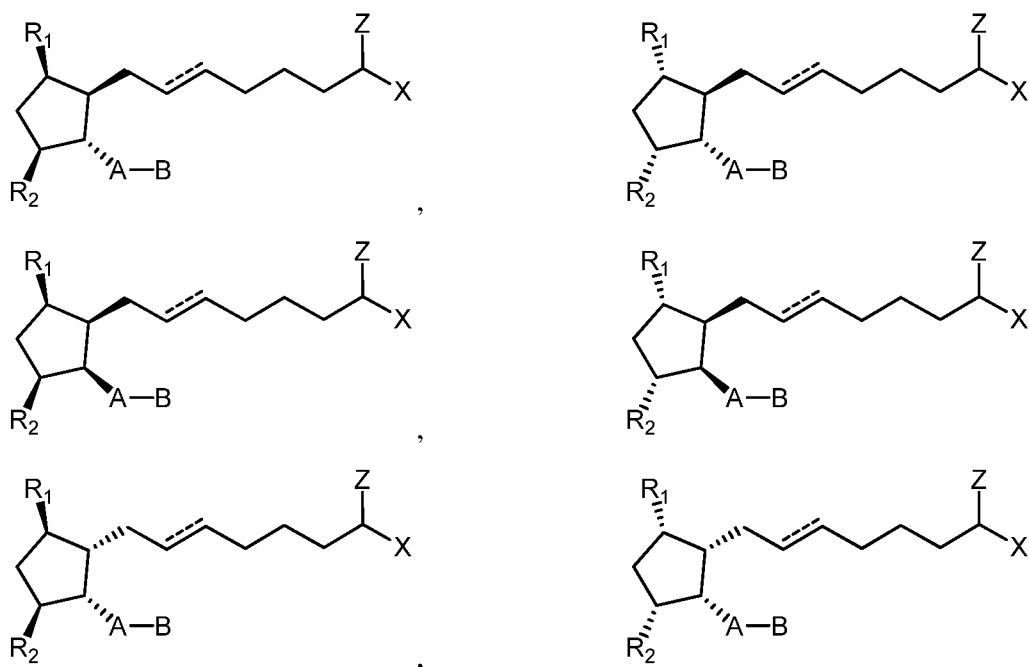
with regard to the compound of Formula (I), one of R₁ and R₂ is =O, -OH, or a -O(CO)R₆ group and the other one is -OH or -O(CO)R₆, or R₁ is =O and R₂ is H, wherein R₆ is an optionally substituted C₁₋₂₀alkyl, optionally substituted C₂₋₂₀alkenyl, optionally substituted C₂₋₂₀alkynyl, or -(CH₂)_mR₇ wherein m is 0 or an integer of between 1-10, inclusive, and R₇ is optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-8-membered-heterocyclyl, optionally substituted C₆₋₁₀aryl, or optionally substituted 5-14-membered-heteroaryl; and

with regard to the compound of Formula (II), R₁ is =O, -OH, or -O(CO)R₆, wherein R₆ is an optionally substituted C₁₋₂₀alkyl, optionally substituted C₂₋₂₀alkenyl, optionally substituted C₂₋₂₀alkynyl, or -(CH₂)_mR₇ wherein m is 0 or an integer of between 1-10, inclusive, and R₇ is optionally substituted C₃₋₇carbocyclyl, optionally substituted 3-8-membered-heterocyclyl, optionally substituted C₆₋₁₀aryl, or optionally substituted 5-14-membered-heteroaryl.

[0085] In certain embodiments, the endocyclic dotted lines of Formula (I) (*i.e.*, depicted in the 5-membered ring) each represent a single bond.

[0086] For example, in certain embodiments, wherein the endocyclic dotted lines of Formula (I) each represent a single bond, provided is a compound having any one of the following stereochemistry:





pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof, wherein ----- , R_1 , R_2 , A, B, Z and X are as defined herein.

[0087] In certain embodiments, the exocyclic dotted line ----- (*i.e.*, depicted outside of the 5-membered ring) of Formula (I) or (II) or a subset thereof represents a double bond in the *cis* or *trans* configuration. In certain embodiments, the exocyclic dotted line ----- represents a double bond in the *cis* configuration.

[0088] In certain embodiments, each instance of ----- independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration.

[0089] As generally defined above, one of R_1 and R_2 is =O, -OH, or a -O(CO) R_6 group and the other one is -OH or -O(CO) R_6 , or R_1 is =O and R_2 is H, wherein R_6 is an optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_7$ wherein m is 0 or an integer of between 1-10, inclusive, and R_7 is optionally substituted C_{3-7} carbocyclyl, optionally substituted 3-8-membered-heterocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5-14-membered-heteroaryl.

[0090] In certain embodiments, R_1 is =O; and R_2 is H.

[0091] In certain embodiments, one of R_1 and R_2 is -OH, substituted hydroxyl, or -O(CO) R_6 , and the other one is -OH, substituted hydroxyl, or -O(CO) R_6 .

[0092] In certain embodiments, both R_1 and R_2 are -OH.

[0093] In certain embodiments, one of R_1 and R_2 is -OH, and the other one is -O(CO) R_6 . In certain embodiments, R_1 is -OH, and R_2 is -O(CO) R_6 . In certain embodiments, R_2 is -OH,

and R_1 is $-O(CO)R_6$. In certain embodiments, R_6 is an optionally substituted C_{1-20} alkyl, *e.g.*, optionally substituted C_{1-15} alkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-5} alkyl, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-2} alkyl. In certain embodiments, R_6 is $-(CH_2)_rCH_3$ wherein r is 0, 1, 2, 3, 4, 5, or 6, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, or $-C(CH_3)_3$.

[0094] As generally defined above, A is optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene or optionally substituted C_{2-10} alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one or more $-O-$ or $-S-$ groups.

[0095] In certain embodiments, A is optionally substituted C_{1-10} alkylene, optionally substituted C_{2-10} alkenylene or optionally substituted C_{2-10} alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one $-O-$ group.

[0096] In certain embodiments, A is optionally substituted C_{4-6} alkylene, optionally substituted C_{4-6} alkenylene or optionally substituted C_{4-6} alkynylene, wherein the alkylene, alkenylene, or alkynylene group is optionally interrupted by one $-O-$ group.

[0097] In certain embodiments, A is optionally substituted C_{4-6} alkylene optionally interrupted by one $-O-$ group. In certain embodiments, A is optionally substituted C_{4-6} alkenylene optionally interrupted by one $-O-$ group. In certain embodiments, A is optionally substituted C_{4-6} alkynylene optionally interrupted by one $-O-$ group.

[0098] In certain embodiments, A is substituted with one or more groups selected from the group consisting of halogen, $-OH$, substituted hydroxyl, or $-O(CO)R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, and optionally substituted 5–14-membered-heteroaryl.

[0099] In certain embodiments, A is substituted with $=O$.

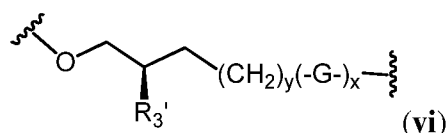
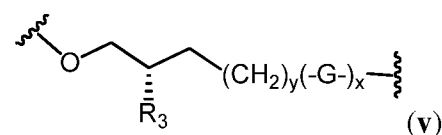
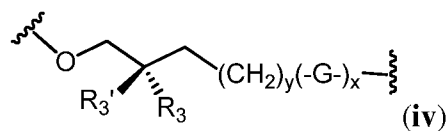
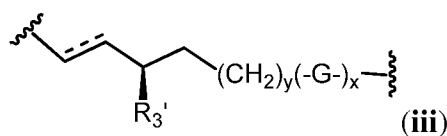
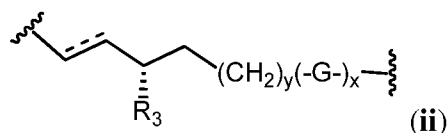
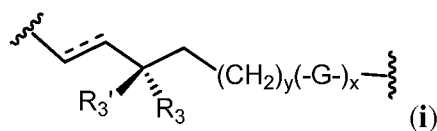
[00100] In certain embodiments, A is substituted with $-OC(=O)R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_9$, wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14-membered-heteroaryl.

[00101] In certain embodiments, A is substituted with $-OH$ or substituted hydroxyl.

[00102] In certain embodiments, A is substituted with substituted hydroxyl.

[00103] In certain embodiments, A is substituted with $-OH$.

[00104] In certain embodiments, A is a group of the Formula (i), (ii), (iii), (iv), (v), or (vi):



wherein each instance of ===== independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration;

each instance of R_3 and $R_{3'}$ is hydrogen, halogen, $-\text{OH}$, substituted hydroxyl, or $-\text{O}(\text{CO})R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(\text{CH}_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14-membered-heteroaryl, or R_3 and $R_{3'}$ are joined to form $=\text{O}$;

G is $-\text{O}-$ or $-\text{S}-$;

y is 0, 1, or 2; and

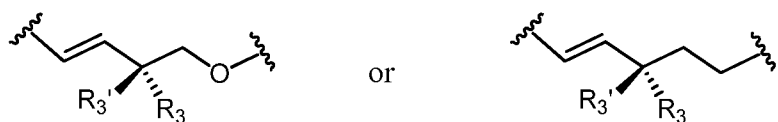
x is 0 or 1.

[00105] In certain embodiments, G is $-\text{O}-$. In certain embodiments, G is $-\text{S}-$.

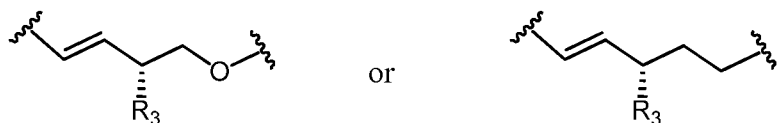
[00106] In certain embodiments, ===== of Formula (i), (ii), or (iii) represents a double bond in the *cis* configuration.

[00107] In certain embodiments, ===== of Formula (i), (ii), or (iii) represents a double bond in the *trans* configuration.

[00108] In certain embodiments, the group of the Formula (i) is of the formula:

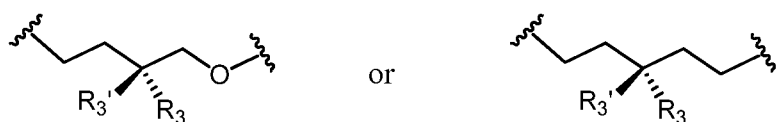


[00109] In certain embodiments, the group of the Formula (ii) is of the formula:

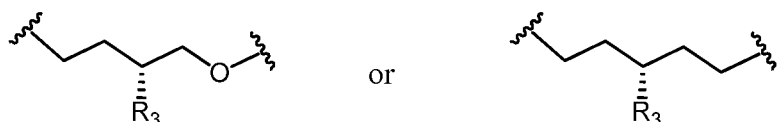


[00110] In certain embodiments, $\equiv$ of Formula (i), (ii), or (iii) represents a single bond.

[00111] In certain embodiments, the group of the Formula (i) is of the formula:



[00112] In certain embodiments, the group of the Formula (ii) is of the formula:



[00113] As generally defined above, each instance of R_3 and R_3' is independently hydrogen, halogen, $-OH$, substituted hydroxyl, or $-O(CO)R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14-membered-heteroaryl; or R_3 and R_3' are joined to form $=O$.

[00114] In certain embodiments, R_3 is hydrogen. In certain embodiments, R_3' is hydrogen. In certain embodiments, R_3 is hydrogen and R_3' is a non-hydrogen group. In certain embodiments, R_3' is hydrogen and R_3 is a non-hydrogen group. In certain embodiments, however, neither R_3 nor R_3' is hydrogen.

[00115] In certain embodiments, R_3 and R_3' are joined to form $=O$.

[00116] In certain embodiments, R_3 and R_3' are the same group. In certain embodiments, R_3 and R_3' are different groups.

[00117] In certain embodiments, R_3 is $-OH$, substituted hydroxyl, or $-O(CO)R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or

optionally substituted 5–14–membered–heteroaryl. In certain embodiments, R_3 is $-\text{O}(\text{CO})R_8$. In certain embodiments, R_3 is $-\text{O}(\text{CO})R_8$, and R_8 is optionally substituted C_{1-20} alkyl, *e.g.*, optionally substituted C_{1-15} alkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-5} alkyl, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-2} alkyl. In certain embodiments, R_3 is $-\text{O}(\text{CO})R_8$, and R_8 is $-(\text{CH}_2)_q\text{CH}_3$ wherein q is 0, 1, 2, 3, 4, 5, or 6, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, or $-\text{C}(\text{CH}_3)_3$. In certain embodiments, R_3 is $-\text{OH}$ or substituted hydroxyl. In certain embodiments, R_3 is substituted hydroxyl. In certain embodiments, R_3 is $-\text{OH}$.

[00118] In certain embodiments, R_3' is $-\text{OH}$, substituted hydroxyl, or $-\text{O}(\text{CO})R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(\text{CH}_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14–membered–heteroaryl. In certain embodiments, R_3' is $-\text{O}(\text{CO})R_8$. In certain embodiments, R_3' is $-\text{O}(\text{CO})R_8$, and R_8 is optionally substituted C_{1-20} alkyl, *e.g.*, optionally substituted C_{1-15} alkyl, optionally substituted C_{1-10} alkyl, optionally substituted C_{1-8} alkyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-5} alkyl, optionally substituted C_{1-4} alkyl, optionally substituted C_{1-3} alkyl, or optionally substituted C_{1-2} alkyl. In certain embodiments, R_3' is $-\text{O}(\text{CO})R_8$, and R_8 is $-(\text{CH}_2)_q\text{CH}_3$ wherein q is 0, 1, 2, 3, 4, 5, or 6, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, or $-\text{C}(\text{CH}_3)_3$. In certain embodiments, R_3' is $-\text{OH}$ or substituted hydroxyl. In certain embodiments, R_3' is substituted hydroxyl. In certain embodiments, R_3' is $-\text{OH}$.

[00119] In certain embodiments, R_3 is halogen, *e.g.*, selected from fluoro, chloro, bromo, and iodo. In certain embodiments, R_3' is halogen, *e.g.*, selected from fluoro, chloro, bromo, and iodo. In certain embodiments, R_3 is halogen and R_3' is halogen, *e.g.*, each independently selected from fluoro, chloro, bromo, and iodo. In certain embodiments, both R_3 and R_3' are fluoro.

[00120] In certain embodiments, y is 0; and x is 1. In certain embodiments, y is 0; and x is 0. In certain embodiments, y is 1; and x is 1. In certain embodiments, y is 1; and x is 0. In certain embodiments, y is 2; and x is 0. In certain embodiments, y is 2; and x is 1.

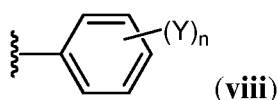
[00121] As defined generally above, B is hydrogen, optionally substituted C_{3-7} carbocyclyl, optionally substituted 3–8–membered–heterocyclyl, optionally substituted 5–14–membered–heteroaryl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-30} alkyl, optionally substituted C_{2-30} alkenyl, or optionally substituted C_{2-30} alkynyl.

[00122] In certain embodiments, B is hydrogen.

[00123] In certain embodiments, B is optionally substituted C_{1-30} alkyl. In certain embodiments, B is optionally substituted C_{2-30} alkenyl. In certain embodiments, B is optionally substituted C_{2-30} alkynyl.

[00124] In certain embodiments, B is optionally substituted C_{3-7} carbocyclyl, *e.g.*, optionally substituted cyclohexyl. In certain embodiments, B is optionally substituted 3–8–membered–heterocyclyl. In certain embodiments, B is optionally substituted C_{6-10} aryl. In certain embodiments, B is optionally substituted C_6 aryl (*i.e.*, phenyl). In certain embodiments, B is optionally substituted C_{10} aryl (*i.e.*, naphthyl). In certain embodiments, B is optionally substituted 5–to 14–membered heteroaryl. In certain embodiments, B is a monocyclic heteroaryl. In certain embodiments, B is optionally substituted monocyclic 5–membered heteroaryl. In certain embodiments, B is optionally substituted thienyl, *e.g.*, optionally substituted 2-thienyl or optionally substituted 3-thienyl. In certain embodiments, B is 3-(2-methyl)thienyl, 4-(2-methyl)thienyl, 2-(5-methyl)thienyl, 3-(2-chloro)thienyl, 2-(4-bromo)thienyl, 2-(5-bromo)thienyl, 3-(2,5-dichloro)thienyl, or 2-(3-chloro)thienyl. In certain embodiments, B is optionally substituted furanyl, *e.g.*, optionally substituted 2-furanyl or optionally substituted 3-furanyl. In certain embodiments, B is a bicyclic heteroaryl. In certain embodiments, B is an optionally substituted 5,6–bicyclic heteroaryl. In certain embodiments, B is 2-benzofuranyl. In certain embodiments, B is 2-benzothienyl. See, for example, U.S. Patent 5,834,498, the contents of which are incorporated herein by reference.

[00125] For example, in certain embodiments, B is an optionally substituted phenyl of the Formula (viii):



wherein:

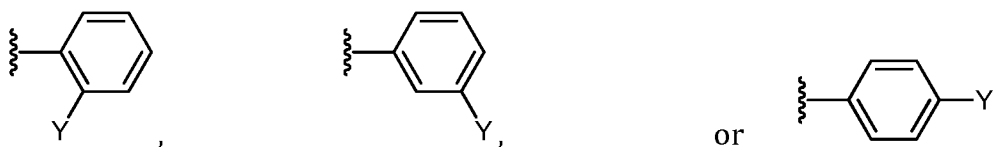
Y is selected from the group consisting of optionally substituted C_{1-10} alkyl, C_{1-10} perhaloalkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, halo, nitro, cyano, thiol, substituted thiol, hydroxyl, substituted hydroxyl, amino, monosubstituted amino, and disubstituted amino; and n is 0 or an integer of from 1 to 5, inclusive.

[00126] In certain embodiments, n is 0 or an integer from 1 to 3, inclusive.

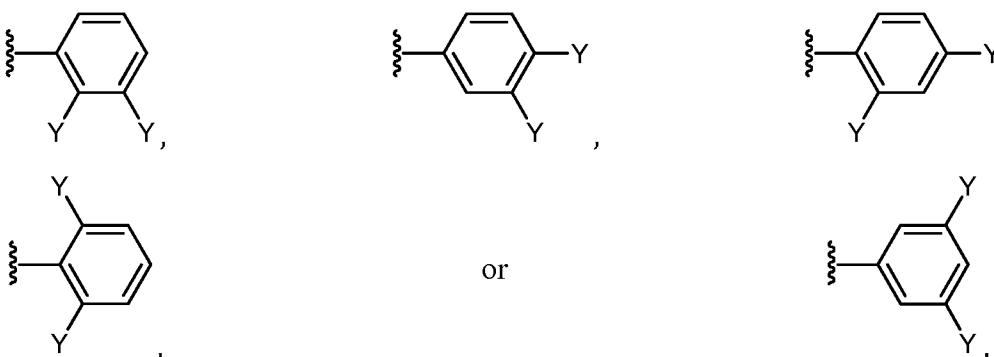
In certain embodiments, n is 0 or an integer from 1 to 2, inclusive.

In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2. In certain embodiments, n is 3.

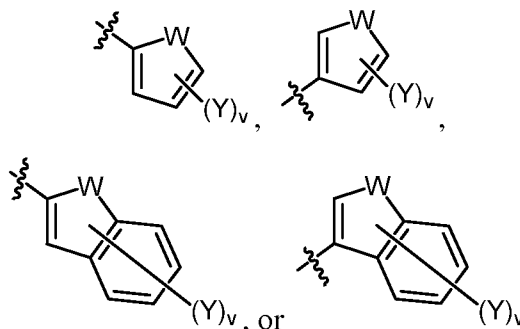
[00127] For example, in certain embodiments, wherein n is 1, the group of the Formula (viii) is of the formula:



[00128] In certain embodiments, wherein n is 2, the group of the Formula (viii) is of the formula:



[00129] In other embodiments, B is an optionally substituted heteroaryl of the Formula:



wherein:

W is O or S;

Y is selected from the group consisting of optionally substituted C₁₋₁₀alkyl, C₁₋₁₀perhaloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, halo, nitro, cyano, thiol, substituted thiol, hydroxyl, substituted hydroxyl, amino, monosubstituted amino, and disubstituted amino; and

v is 0 or an integer of from 1 to 3, inclusive.

[00130] In certain embodiments, v is 0 or an integer from 1 to 2, inclusive. In certain embodiments, v is 0 or 1. In certain embodiments, v is 0. In certain embodiments, v is 1. In certain embodiments, v is 2. In certain embodiments, v is 3.

[00131] In certain embodiments, Y is halo, *i.e.* selected from fluoro, iodo, bromo, or

chloro. In certain embodiments Y is chloro. In certain embodiments Y is fluoro.

[00132] In certain embodiments, Y is optionally substituted C₁₋₁₀alkyl or C₁₋₁₀perhaloalkyl.

[00133] In certain embodiments, Y is optionally substituted C₁₋₁₀alkyl. In certain embodiments, Y is optionally substituted C₁₋₆alkyl. In certain embodiments, Y is optionally substituted C₁₋₄alkyl. In certain embodiments, Y is optionally substituted C₁₋₃alkyl. In certain embodiments, Y is optionally substituted C₁₋₂alkyl. In certain embodiments, Y is –CH₃, –CH₂F, or –CHF₂.

[00134] In certain embodiments, Y is C₁₋₁₀perhaloalkyl. In certain embodiments, Y is C₁₋₆perhaloalkyl. In certain embodiments, Y is C₁₋₄perhaloalkyl. In certain embodiments, Y is C₁₋₃perhaloalkyl. In certain embodiments, Y is C₁₋₂perhaloalkyl. In certain embodiments, Y is –CF₃, –CF₂Cl, or –CFCl₂.

[00135] As generally defined above, Z is =O, =S, or =NR_Z, wherein R_Z is selected from hydrogen, an amino protecting group, –OH, substituted hydroxyl, optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3–8–membered–heterocyclyl, optionally substituted C₆₋₁₀aryl, or optionally substituted 5–14–membered–heteroaryl, or Z represents two hydrogen atoms.

[00136] In certain embodiments, Z is =O.

[00137] In certain embodiments, Z is =S.

[00138] In certain embodiments, Z is =NR_Z, wherein R_Z is selected from hydrogen, an amino protecting group, –OH, substituted hydroxyl, optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, optionally substituted C₃₋₇carbocyclyl, optionally substituted 3–8–membered–heterocyclyl, optionally substituted C₆₋₁₀aryl, or optionally substituted 5–14–membered–heteroaryl. In certain embodiments, Z is =NR_Z and R_Z is hydrogen.

[00139] In certain embodiments, Z represents two hydrogen atoms.

[00140] As generally defined above, X is –OR₄, –SR₄, or –N(R₄)₂, wherein each instance of R₄ is independently hydrogen, optionally substituted C₁₋₃₀alkyl, optionally substituted C₂₋₃₀alkenyl, optionally substituted C₂₋₃₀alkynyl, –C(=O)R₅, or –C(=O)OR₅, wherein R₅ is optionally substituted C₁₋₃₀alkyl, optionally substituted C₂₋₃₀alkenyl, or optionally substituted C₂₋₃₀alkynyl, or two R₄ groups are joined to form an optionally substituted 3–8–membered–heterocyclyl or optionally substituted 5–14–membered–heteroaryl ring.

[00141] In certain embodiments, X is –OR₄. In certain embodiments, X is –OR₄, and R₄ is

hydrogen. In certain embodiments, X is $-OR_4$, and R_4 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_4 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_4 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_4 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_4 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00142] In certain embodiments, X is $-OR_4$, wherein R_4 is $-C(=O)R_5$, or $-C(=O)OR_5$.

[00143] In certain embodiments, X is $-OR_4$, and R_4 is $-C(=O)R_5$, and R_5 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00144] In certain embodiments, X is $-OR_4$, and R_4 is $-C(=O)OR_5$ and R_5 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00145] In certain embodiments, X is $-SR_4$. In certain embodiments, X is $-SR_4$, and R_4 is hydrogen. In certain embodiments, X is $-SR_4$, and R_4 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_4 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_4 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_4 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_4 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00146] In certain embodiments, X is $-\text{SR}_4$, wherein R_4 is $-\text{C}(=\text{O})\text{R}_5$, or $-\text{C}(=\text{O})\text{OR}_5$.

[00147] In certain embodiments, X is $-\text{SR}_4$, and R_4 is $-\text{C}(=\text{O})\text{R}_5$, and R_5 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00148] In certain embodiments, X is $-\text{SR}_4$, and R_4 is $-\text{C}(=\text{O})\text{OR}_5$ and R_5 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, R_5 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl.

[00149] In certain embodiments, X is $-\text{N}(\text{R}_4)_2$. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 group is hydrogen. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and neither of the two R_4 groups are hydrogen. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is optionally substituted C_{1-10} alkyl, optionally substituted C_{2-10} alkenyl, or optionally substituted C_{2-10} alkynyl. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is optionally substituted C_{1-6} alkyl, *e.g.*, C_{1-3} alkyl, C_{3-4} alkyl, or C_{4-6} alkyl. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is optionally substituted C_{2-6} alkenyl, *e.g.*, C_{2-3} alkenyl, C_{3-4} alkenyl, or C_{4-6} alkenyl. In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is optionally substituted C_{2-6} alkynyl, *e.g.*, C_{2-3} alkynyl, C_{3-4} alkynyl, or C_{4-6} alkynyl. However, in certain embodiments, X is not $-\text{NH}(\text{iPr})$.

[00150] In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is $-\text{C}(=\text{O})\text{R}_5$, or $-\text{C}(=\text{O})\text{OR}_5$.

[00151] In certain embodiments, X is $-\text{N}(\text{R}_4)_2$ and at least one R_4 is $-\text{C}(=\text{O})\text{R}_5$, and R_5 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, or optionally substituted C_{2-20} alkynyl. In certain embodiments, R_5 is optionally substituted C_{1-10} alkyl, optionally

substituted C₂₋₁₀alkenyl, or optionally substituted C₂₋₁₀alkynyl. In certain embodiments, R₅ is optionally substituted C₁₋₆alkyl, *e.g.*, C₁₋₃alkyl, C₃₋₄alkyl, or C₄₋₆alkyl. In certain embodiments, R₅ is optionally substituted C₂₋₆alkenyl, *e.g.*, C₂₋₃alkenyl, C₃₋₄alkenyl, or C₄₋₆alkenyl. In certain embodiments, R₅ is optionally substituted C₂₋₆alkynyl, *e.g.*, C₂₋₃alkynyl, C₃₋₄alkynyl, or C₄₋₆alkynyl.

[00152] In certain embodiments, X is -N(R₄)₂ and at least one R₄ is -C(=O)OR₅ and R₅ is optionally substituted C₁₋₂₀alkyl, optionally substituted C₂₋₂₀alkenyl, or optionally substituted C₂₋₂₀alkynyl. In certain embodiments, R₅ is optionally substituted C₁₋₁₀alkyl, optionally substituted C₂₋₁₀alkenyl, or optionally substituted C₂₋₁₀alkynyl. In certain embodiments, R₅ is optionally substituted C₁₋₆alkyl, *e.g.*, C₁₋₃alkyl, C₃₋₄alkyl, or C₄₋₆alkyl. In certain embodiments, R₅ is optionally substituted C₂₋₆alkenyl, *e.g.*, C₂₋₃alkenyl, C₃₋₄alkenyl, or C₄₋₆alkenyl. In certain embodiments, R₅ is optionally substituted C₂₋₆alkynyl, *e.g.*, C₂₋₃alkynyl, C₃₋₄alkynyl, or C₄₋₆alkynyl.

[00153] In other embodiments, X is -N(R₄)₂ and the two R₄ groups are joined to form an optionally substituted 3–8–membered–heterocyclyl or optionally substituted 5–14–membered–heteroaryl ring.

[00154] In certain embodiments, wherein X is -OR₄, -SR₄, or -N(R₄)₂, any one of R₄ or R₅ is optionally substituted C₁₋₃₀alkyl (*e.g.*, C₁₋₁₀alkyl, C₁₋₆alkyl, C₁₋₃alkyl, C₇₋₃₀alkyl, C₁₀₋₃₀alkyl, C₇₋₂₅alkyl, C₁₀₋₂₅alkyl, C₁₅₋₂₅alkyl). In certain embodiments, any one of R₄ or R₅ is optionally substituted C₂₋₃₀alkenyl (*e.g.*, C₂₋₁₀alkenyl, C₂₋₆alkenyl, C₁₋₃alkenyl, C₇₋₃₀alkenyl, C₁₀₋₃₀alkenyl, C₇₋₂₅alkenyl, C₁₀₋₂₅alkenyl, C₁₅₋₂₅alkenyl). In certain embodiments, any one of R₄ or R₅ is optionally substituted C₂₋₃₀alkynyl (*e.g.*, C₂₋₁₀alkynyl, C₂₋₆alkynyl, C₁₋₃alkynyl, C₇₋₃₀alkynyl, C₁₀₋₃₀alkynyl, C₇₋₂₅alkynyl, C₁₀₋₂₅alkynyl, C₁₅₋₂₅alkynyl).

[00155] In any of the above embodiments, when R₄ or R₅ are defined as a C₇₋₃₀alkyl or C₇₋₃₀alkenyl groups, such groups may also be referred to as “lipid tails.” Lipid tails present in these lipid groups can be saturated and unsaturated, depending on whether or not the lipid tail comprises double bonds. The lipid tail can also comprise different lengths, often categorized as medium (*i.e.*, with tails between 7–12 carbons, *e.g.*, C₇₋₁₂ alkyl or C₇₋₁₂ alkenyl), long (*i.e.*, with tails greater than 12 carbons and up to 22 carbons, *e.g.*, C₁₃₋₂₂ alkyl or C₁₃₋₂₂ alkenyl), or very long (*i.e.*, with tails greater than 22 carbons, *e.g.*, C₂₃₋₃₀ alkyl or C₂₃₋₃₀ alkenyl).

[00156] Exemplary unsaturated lipid tails include, but are not limited to:

Myristoleic $-(CH_2)_7CH=CH(CH_2)_3CH_3$,

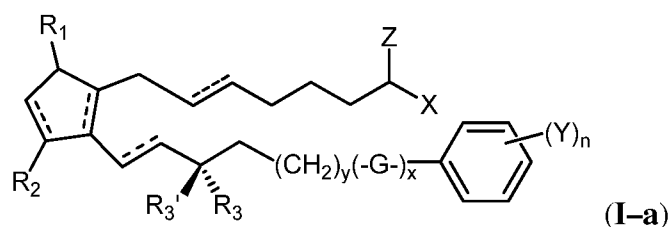
Palmitoleic $-(CH_2)_7CH=CH(CH_2)_5CH_3$,

Sapienic	$-(\text{CH}_2)_4\text{CH}=\text{CH}(\text{CH}_2)_8\text{CH}_3$,
Oleic	$-(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$,
Linoleic	$-(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$,
α -Linolenic	$-(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3$,
Arachinodonic	$-(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$,
Eicosapentaenoic	$-(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3$,
Erucic	$-(\text{CH}_2)_{11}\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$, and
Docosahexaenoic	$-(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}-\text{CH}_2\text{CH}_3$.

[00157] Exemplary saturated lipid tails include, but are not limited to:

Lauric	$-(\text{CH}_2)_{10}\text{CH}_3$,
Myristic	$-(\text{CH}_2)_{12}\text{CH}_3$,
Palmitic	$-(\text{CH}_2)_{14}\text{CH}_3$,
Stearic	$-(\text{CH}_2)_{16}\text{CH}_3$,
Arachidic	$-(\text{CH}_2)_{18}\text{CH}_3$,
Behenic	$-(\text{CH}_2)_{20}\text{CH}_3$,
Lignoceric	$-(\text{CH}_2)_{22}\text{CH}_3$, and
Cerotic	$-(\text{CH}_2)_{24}\text{CH}_3$.

[00158] In certain embodiments of Formula (I), the compound is of Formula (I-a):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_1 , R_2 , Z , and X are as defined herein;

each instance of ----- independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration;

each instance of R_3 and R_3' is independently hydrogen, halogen, $-\text{OH}$, substituted hydroxyl, or $-\text{O}(\text{CO})R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(\text{CH}_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14-membered-heteroaryl, or R_3 and R_3' are joined to form $=\text{O}$;

Y is selected from the group consisting of optionally substituted C₁₋₁₀alkyl, C₁₋₁₀perhaloalkyl, optionally substituted C₂₋₁₀alkenyl, optionally substituted C₂₋₁₀alkynyl, halo, nitro, cyano, thiol, substituted thiol, hydroxyl, substituted hydroxyl, amino, monosubstituted amino, and disubstituted amino;

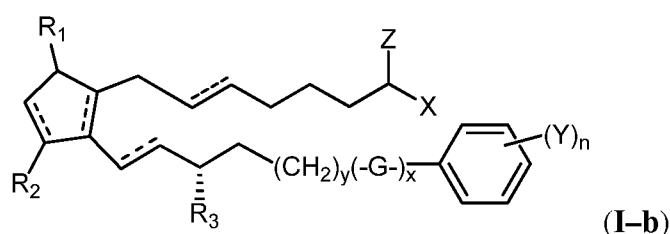
G is -O- or -S-;

y is 0, 1, or 2;

x is 0 or 1; and

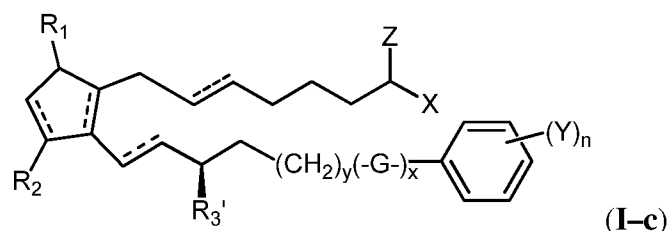
n is 0 or an integer of from 1 to 5, inclusive.

[00159] In certain embodiments of Formula (I-a), wherein R₃' is hydrogen, the compound is of Formula (I-b):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R₁, R₂, R₃, Z, X, Y, G, y, x, and n are as defined herein.

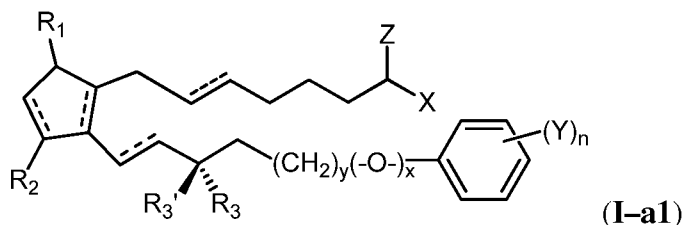
[00160] In certain embodiments of Formula (I-a), wherein R₃ is hydrogen, the compound is of Formula (I-c):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R₁, R₂, R₃', Z, X, Y, G, y, x, and n are as defined herein.

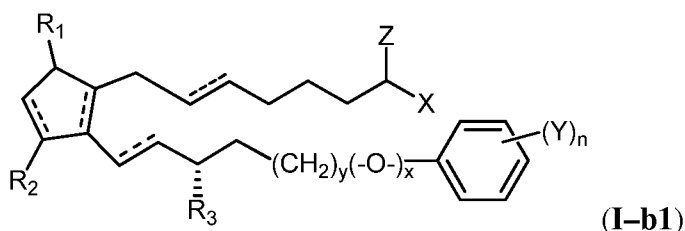
[00161] In certain embodiments, G is -O-. In certain embodiments, G is -S-.

[00162] In certain embodiments of Formula (I-a), wherein G is -O-, provided is a compound of Formula (I-a1):



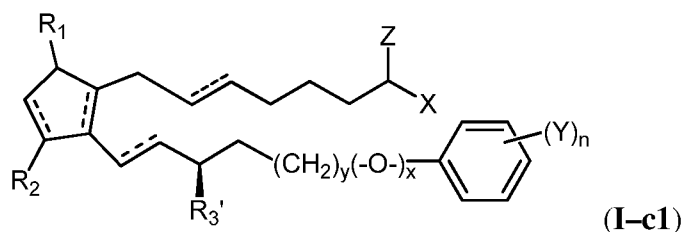
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_1 , R_2 , Z , and X are as defined herein; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , y , x , and n are as defined herein.

[00163] In certain embodiments of Formula (I-b), wherein G is -O-, the compound is of Formula (I-b1):



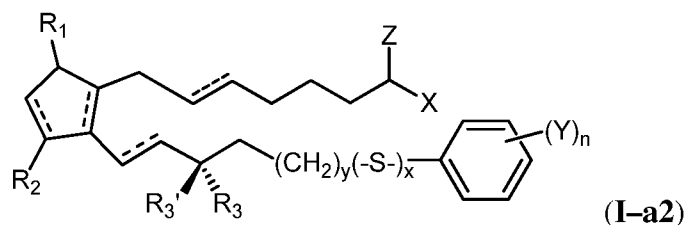
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , y , x , and n are as defined herein.

[00164] In certain embodiments of Formula (I-c), wherein G is -O-, the compound is of Formula (I-c1):



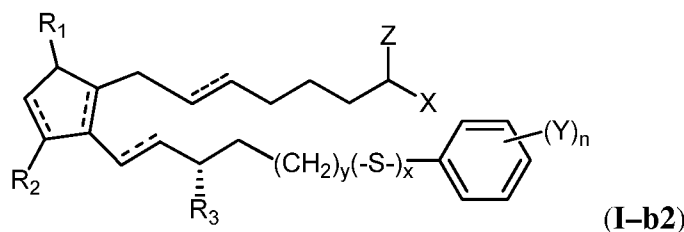
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00165] In certain embodiments of Formula (I-a), wherein G is -S-, provided is a compound of Formula (I-a2):



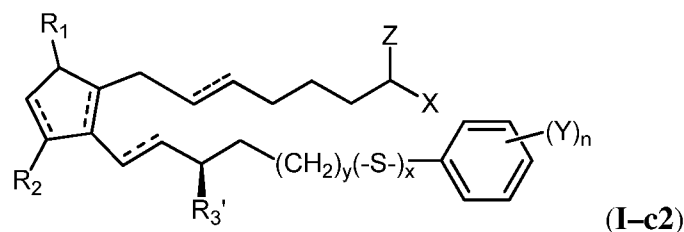
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_1 , R_2 , Z , and X are as defined herein; wherein ----- , R_1 , R_2 , R_3 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00166] In certain embodiments of Formula (I-b), wherein G is -S-, the compound is of Formula (I-b2):



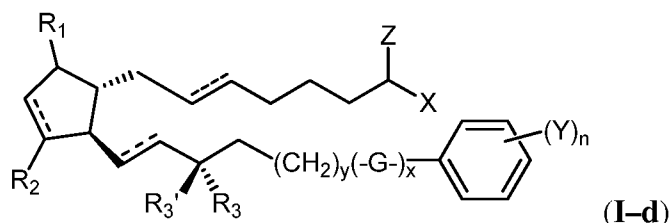
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , y , x , and n are as defined herein.

[00167] In certain embodiments of Formula (I-c), wherein G is -S-, the compound is of Formula (I-c2):



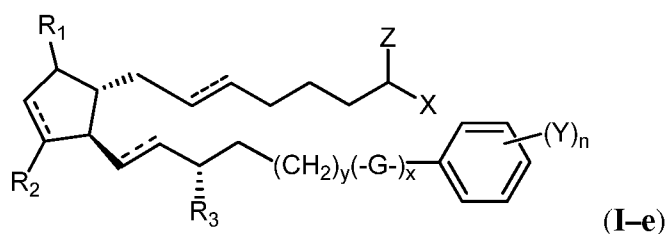
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00168] In certain embodiments, the compound of Formula (I-a) has the following stereochemistry, also referred to herein as a compound of Formula (I-d):



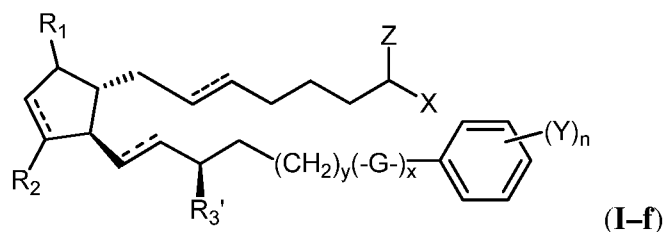
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , Z , Y , G , X , y , x , and n are as defined herein.

[00169] In certain embodiments of Formula (I-d), wherein R_3' is hydrogen, the compound is of Formula (I-e):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , G , y , x , and n are as defined herein.

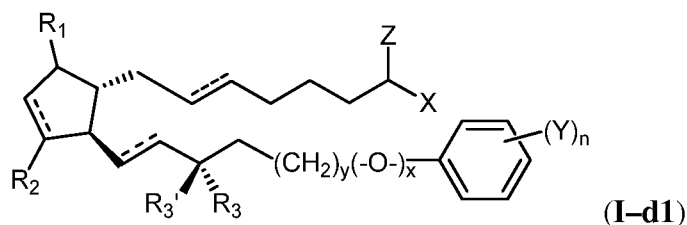
[00170] In certain embodiments of Formula (I-d), wherein R_3 is hydrogen, the compound is of Formula (I-f):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , G , y , x , and n are as defined herein.

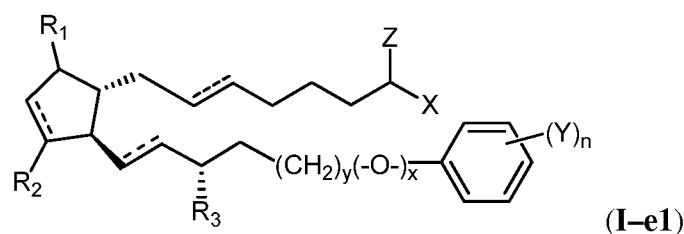
[00171] In certain embodiments, G is $-O-$. In certain embodiments, G is $-S-$.

[00172] In certain embodiments of Formula (I-d), wherein G is -O-, the compound is of Formula (I-d1):



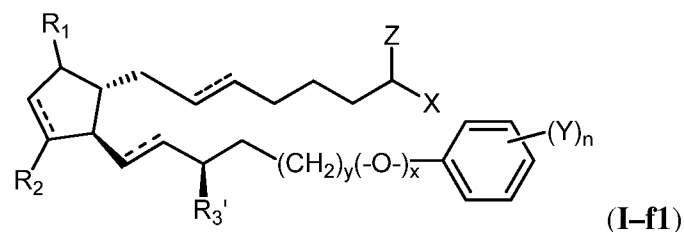
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , Z , Y , X , y , x , and n are as defined herein.

[00173] In certain embodiments of Formula (I-e), wherein G is -O-, the compound is of Formula (I-e1):



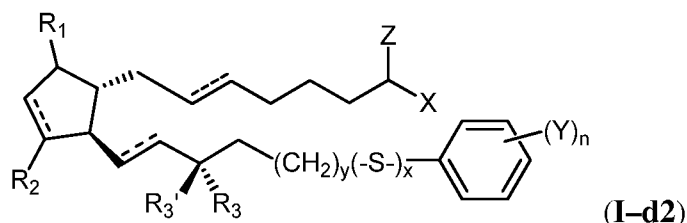
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , y , x , and n are as defined herein.

[00174] In certain embodiments of Formula (I-f), wherein G is -O-, the compound is of Formula (I-f1):



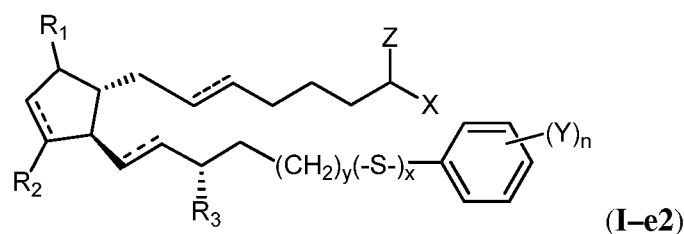
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00175] In certain embodiments of Formula (I-d), wherein G is -S-, the compound is of Formula (I-d2):



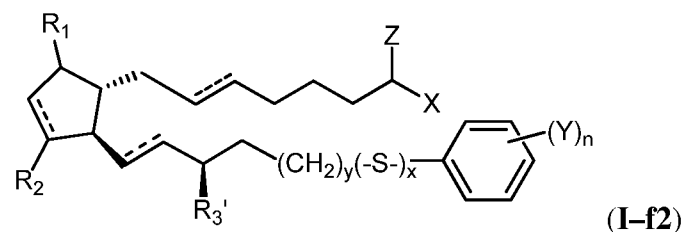
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , Z , Y , X , y , x , and n are as defined herein.

[00176] In certain embodiments of Formula (I-e), wherein G is -S-, the compound is of Formula (I-e2):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , Z , X , Y , y , x , and n are as defined herein.

[00177] In certain embodiments of Formula (I-f), wherein G is -S-, the compound is of Formula (I-f2):

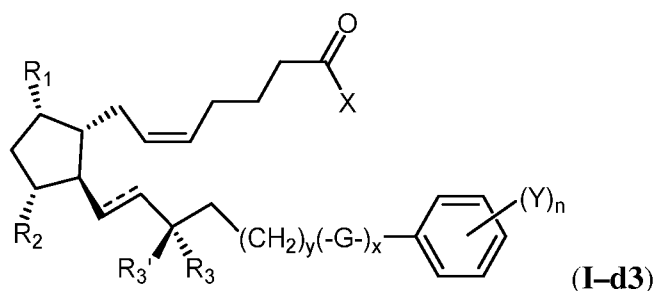


or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00178] In certain embodiments, Z is =O. In certain embodiments, each ----- represents a single bond. In certain embodiments, each endocyclic ----- represents a single bond. In certain embodiments at least one exocyclic ----- represents a *cis*-double bond. In certain embodiments, each instance of R_1 and R_2 is -OH. In certain embodiments, each instance of R_1 and R_2 is -O(CO) R_6 . In certain embodiments, one of R_1 and R_2 is -OH, and the other one

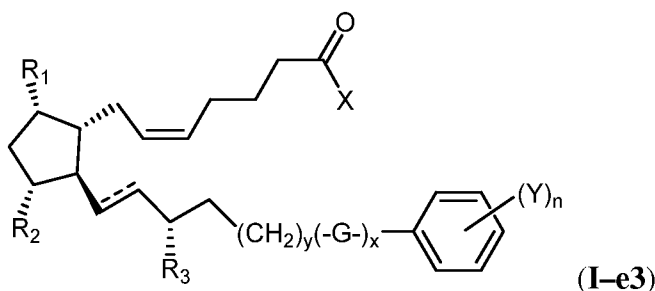
is $-\text{O}(\text{CO})\text{R}_6$. In certain embodiments, one of R_3 and $\text{R}_3'\text{R}_3'$ is $-\text{O}(\text{CO})\text{R}_8$, and the other is hydrogen. In certain embodiments, R_1 is $-\text{OH}$, R_2 is $-\text{O}(\text{CO})\text{R}_6$, one of R_3 and $\text{R}_3'\text{R}_3'$ is $-\text{OH}$, and the other is hydrogen. In certain embodiments, R_2 is $-\text{OH}$, R_1 is $-\text{O}(\text{CO})\text{R}_6$, one of R_3 and $\text{R}_3'\text{R}_3'$ is $-\text{OH}$, and the other is hydrogen. In certain embodiments, each of R_1 and R_2 is $-\text{OH}$, and one of R_3 and $\text{R}_3'\text{R}_3'$ is $-\text{O}(\text{CO})\text{R}_8$, and the other is hydrogen. In certain embodiments, each instance of R_1 and R_2 is $-\text{O}(\text{CO})\text{R}_6$, and one of R_3 and $\text{R}_3'\text{R}_3'$ is $-\text{O}(\text{CO})\text{R}_8$, and the other is hydrogen. In certain embodiments, $-\text{O}(\text{CO})\text{R}_6$ and $-\text{O}(\text{CO})\text{R}_8$ attached to the compound are the same group. In certain embodiments, $-\text{O}(\text{CO})\text{R}_6$ and $-\text{O}(\text{CO})\text{R}_8$ attached to the compound are different groups.

[00179] In certain embodiments of Formula (**I-d**), wherein Z is $=\text{O}$, each endocyclic ----- represents a single bond, and at least one exocyclic ----- represents a *cis*-double bond, provided is a compound of Formula (**I-d3**) having the following stereochemistry:



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , G , Y , X , y , x , and n are as defined herein.

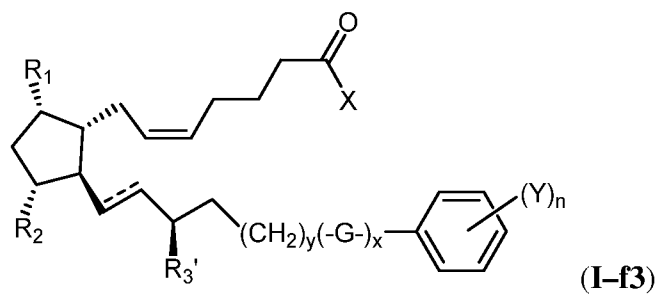
[00180] In certain embodiments of Formula (**I-e**), wherein Z is $=\text{O}$, each endocyclic ----- represents a single bond, and at least one exocyclic ----- represents a *cis*-double bond, provided is a compound of Formula (**I-e3**) having the following stereochemistry:



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , G , X , Y , y , x , and n are as defined herein.

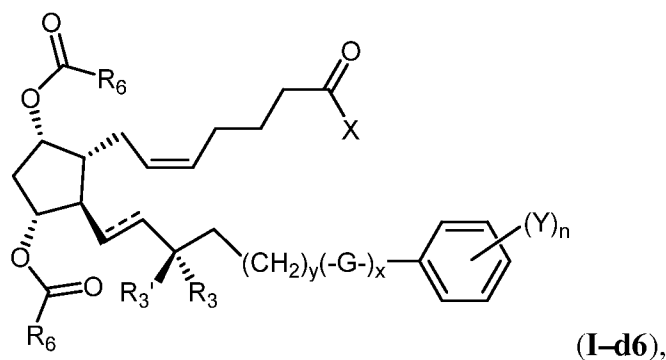
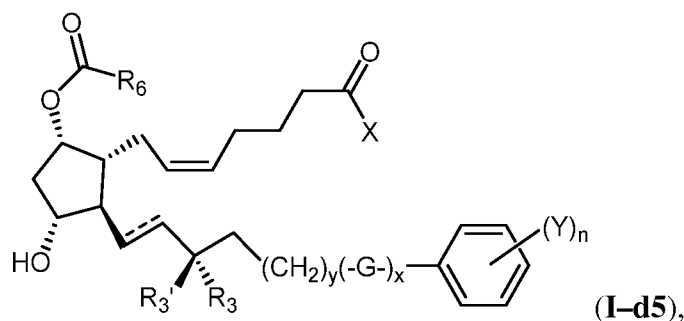
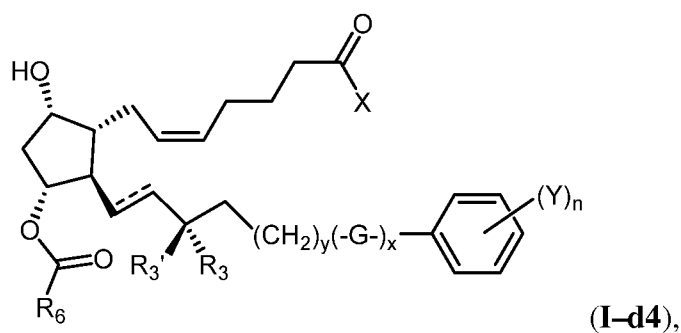
[00181] In certain embodiments of Formula (**I-f**), wherein Z is $=\text{O}$, each endocyclic

===== represents a single bond, and at least one exocyclic ===== represents a *cis*-double bond, provided is a compound of Formula (I-f3) having the following stereochemistry:



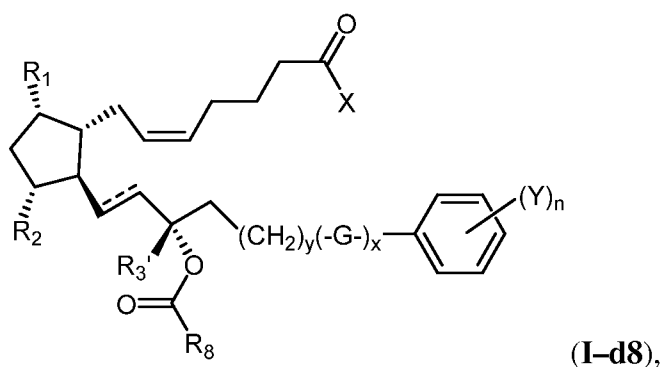
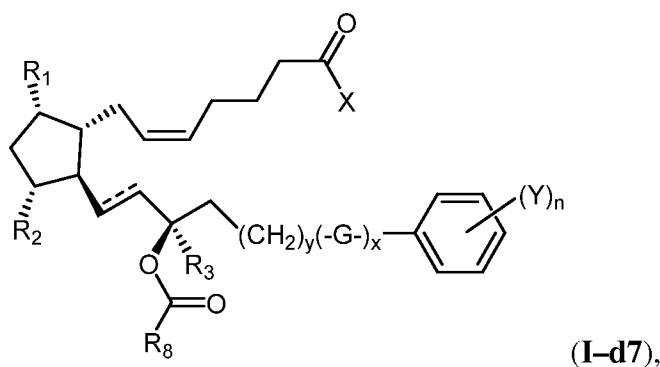
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein =====, R_1 , R_2 , R_3' , G, X, Y, y, x, and n are as defined herein.

[00182] In certain embodiments of Formula (I-d3), wherein R_1 is $-OH$ and R_2 is $-O(CO)R_6$, or wherein R_2 is $-OH$ and R_1 is $-O(CO)R_6$, or wherein both R_1 and R_2 are $-O(CO)R_6$, provided is a compound of Formula (I-d4), (I-d5), and (I-d6) having the following stereochemistry:



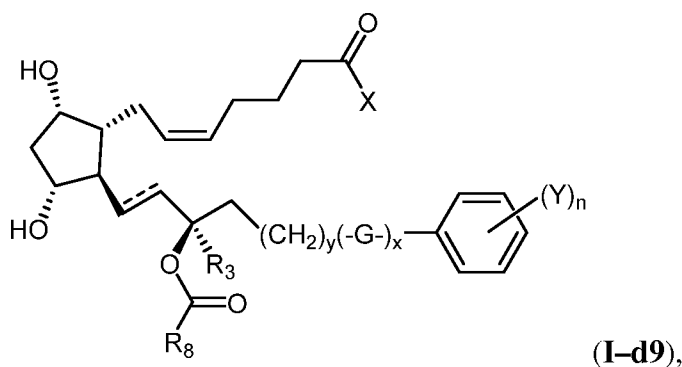
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_6 , R_3 , R_3' , G , Y , X , y , x , and n are as defined herein.

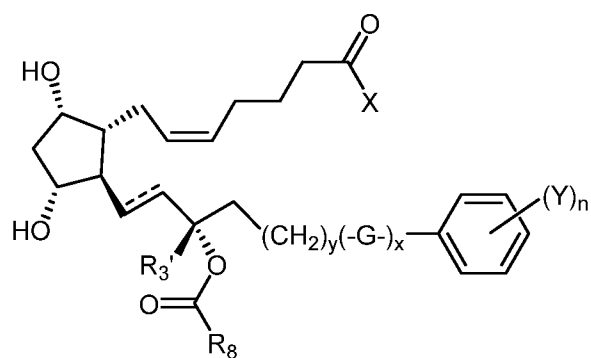
[00183] In certain embodiments of Formula (I-d3), wherein R_3 is $-\text{O}(\text{CO})R_8$ or R_3' is $-\text{O}(\text{CO})R_8$, provided is a compound of Formula (I-d7) and (I-d8) having the following stereochemistry:



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3 , R_3' , R_8 , G , Y , X , y , x , and n are as defined herein.

[00184] In certain embodiments of Formula (I-d3), wherein R_1 and R_2 are each $-\text{OH}$ and R_3 is $-\text{O}(\text{CO})R_8$, or wherein R_1 and R_2 are each $-\text{OH}$ and R_3' is $-\text{O}(\text{CO})R_8$, provided is a compound of Formula (I-d9) and (I-d10) having the following stereochemistry:

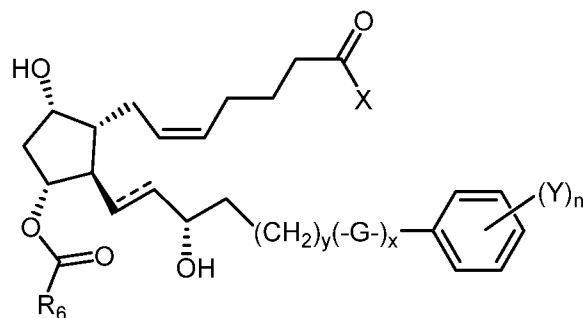




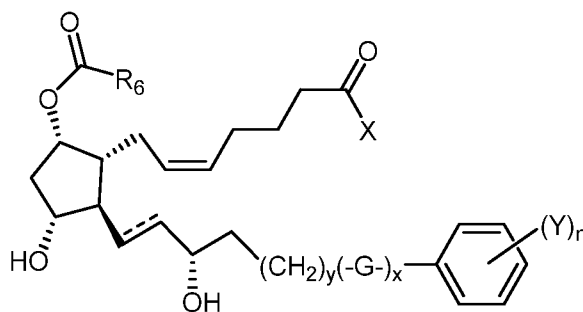
(I-d10),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R₃, R₃', R₈, G, Y, X, y, x, and n are as defined herein.

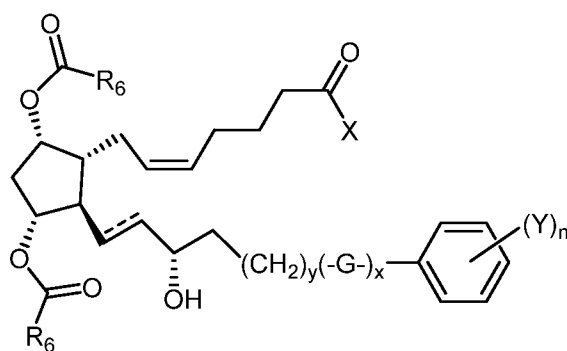
[00185] In certain embodiments of Formula (I-e3), wherein R₁ is -OH and R₂ is -O(CO)R₆, or wherein R₂ is -OH and R₁ is -O(CO)R₆, or wherein both R₁ and R₂ are -O(CO)R₆, and R₃' is hydrogen and R₃ is -OH, provided is a compound of Formula (I-d11), (I-d12), and (I-d13) having the following stereochemistry:



(I-d11),



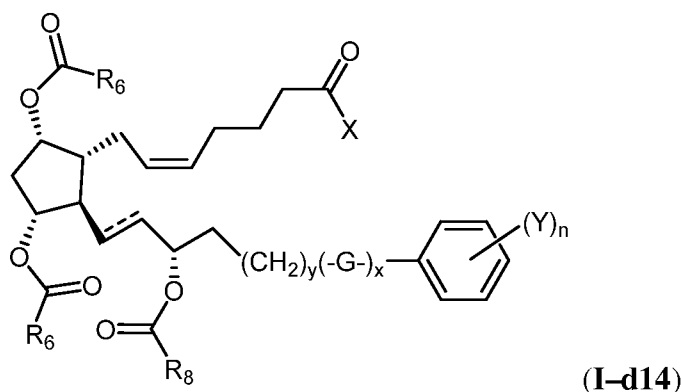
(I-d12),



(I-d13),

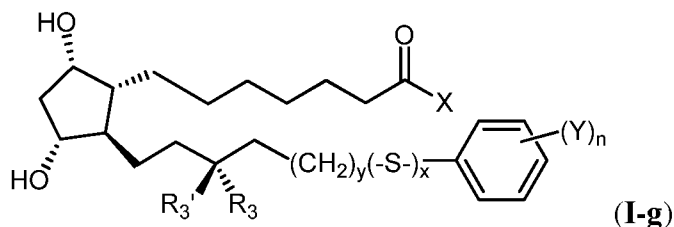
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_6 , R_3 , R_3' , G , Y , X , y , x , and n are as defined herein.

[00186] In certain embodiments of Formula (I-d8), wherein each of R_1 and R_2 are $-\text{O}(\text{CO})R_6$ and R_3' is hydrogen, provided is a compound of Formula (I-d14) having the following stereochemistry:



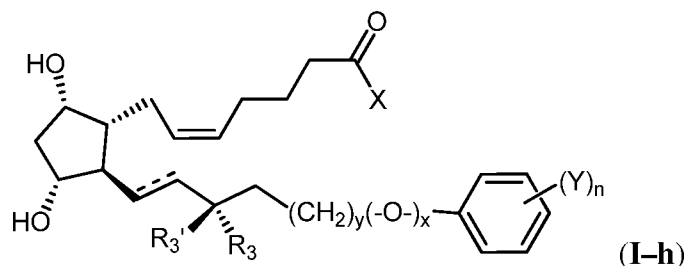
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_6 , R_8 , G , Y , X , y , x , and n are as defined herein.

[00187] In certain embodiments of Formula (I-d2), wherein Z is $=\text{O}$, each instance of R_1 and R_2 is $-\text{OH}$, and each ----- represents a single bond, provided is a compound of Formula (I-g):



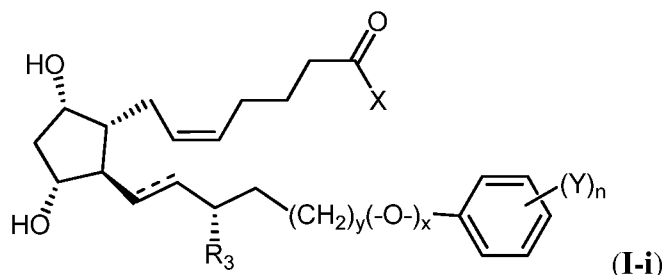
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein X , Y , R_3 , R_3' , y , x , and n are as defined herein.

[00188] In certain embodiments of Formula (I-d1), wherein each instance of R_1 and R_2 is $-\text{OH}$, and Z is $=\text{O}$, provided is a compound of Formula (I-h):



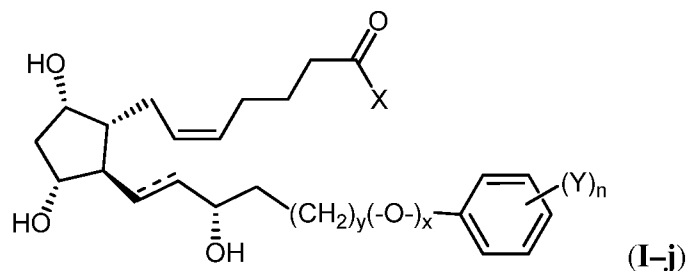
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_3 , R_3' , Y , X , y , x , and n are as defined herein.

[00189] In certain embodiments of Formula (I-h), wherein R_3' is hydrogen, provided is a compound of Formula (I-i):



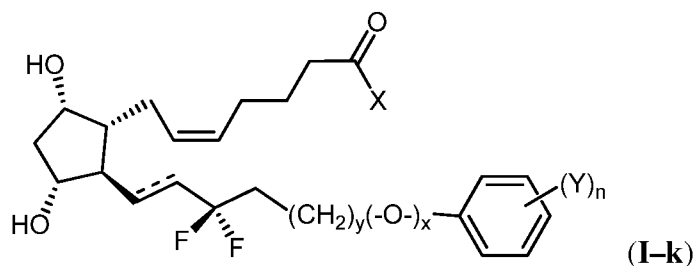
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_3 , Y , X , y , x , and n are as defined herein.

[00190] In certain embodiments of Formula (I-i), wherein R_3 is $-\text{OH}$, provided is a compound of Formula (I-j):



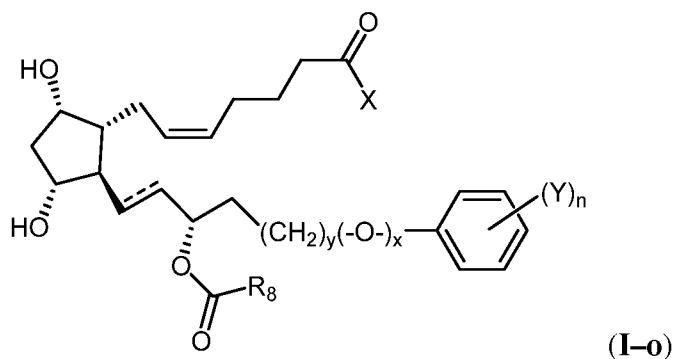
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein Y , X , y , x , and n are as defined herein.

[00191] In certain embodiments of Formula (I-h), wherein R_3 is F and R_3' is F , provided is a compound of Formula (I-k):



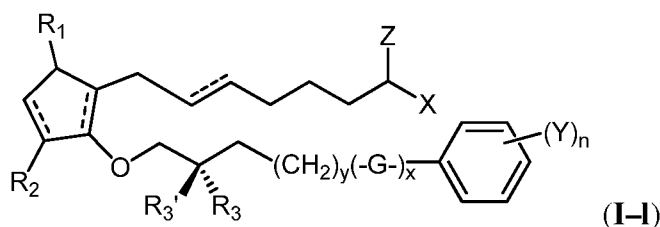
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , Y , X , y , x , and n are as defined herein.

[00192] In certain embodiments of Formula (I-i), wherein R_3 is $-O(CO)R_8$, provided is a compound of Formula (I-o):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_8 , Y, X, y, x, and n are as defined herein.

[00193] In certain embodiments of Formula (I), the compound of Formula (I-l):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_1 , R_2 , Z, and X are as defined herein;

each instance of ===== independently represents a single bond or a double bond which can be in the *cis* or *trans* configuration;

each instance of R_3 and $R_{3'}$ is independently hydrogen, halogen, $-OH$, substituted hydroxyl, or $-O(CO)R_8$, wherein R_8 is optionally substituted C_{1-20} alkyl, optionally substituted C_{2-20} alkenyl, optionally substituted C_{2-20} alkynyl, or $-(CH_2)_mR_9$ wherein m is 0 or an integer between 1–10, inclusive, and R_9 is optionally substituted C_{3-7} carbocyclyl, optionally substituted C_{6-10} aryl, or optionally substituted 5–14-membered-heteroaryl, or R_3 and $R_{3'}$ are joined to form $=O$;

Y is selected from the group consisting of optionally substituted C_{1-10} alkyl, C_{1-10} perhaloalkyl, optionally substituted C_{2-10} alkenyl, optionally substituted C_{2-10} alkynyl, halo, nitro, cyano, thiol, substituted thiol, hydroxyl, substituted hydroxyl, amino, monosubstituted amino, and disubstituted amino;

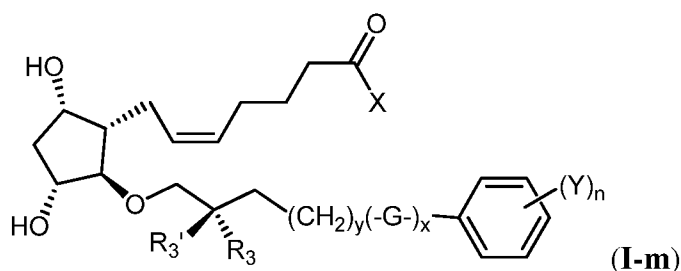
G is $-O-$ or $-S-$;

y is 0, 1, or 2;

x is 0 or 1; and

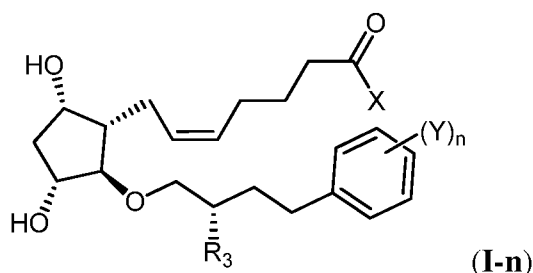
n is 0 or an integer of from 1 to 5, inclusive.

[00194] In certain embodiments of Formula (I-I), wherein Z is =O, and R₁ and R₂ are each -OH, provided is a compound of Formula (I-m):



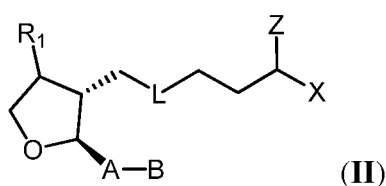
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R₁, R₂, Z, and X are as defined herein.

[00195] In certain embodiments of Formula (I-m), wherein R₃' is hydrogen, y is 2 and x is 0, provided is a compound of Formula (I-n):



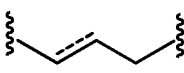
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R₁, R₂, Z, and X are as defined herein.

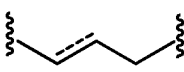
[00196] As generally defined above, in certain embodiments, provided is a compound of Formula (II):

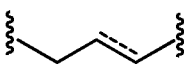


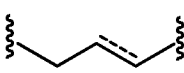
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; , wherein A, B, X, Z, L, and R₁ are as defined herein are as defined herein.

wherein A, B, X, Z, L, and R₁ are as defined herein. are as defined herein.

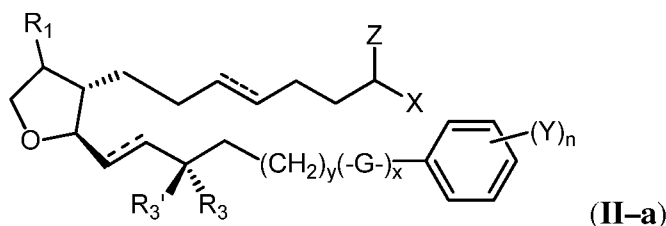
[00197] In certain embodiments, L is a group of the formula  wherein ===== represents a single bond.

[00198] In certain embodiments, L is a group of the formula  wherein ===== represents a double bond which can be in the *cis* or *trans* configuration. In certain embodiments, the double bond is in the *cis* configuration. In certain embodiments, the double bond is in the *trans* configuration

[00199] In certain embodiments, L is a group of the formula  wherein ===== represents a single bond.

[00200] In certain embodiments, L is a group of the formula  wherein ===== represents a double bond which can be in the *cis* or *trans* configuration. In certain embodiments, the double bond is in the *cis* configuration. In certain embodiments, the double bond is in the *trans* configuration

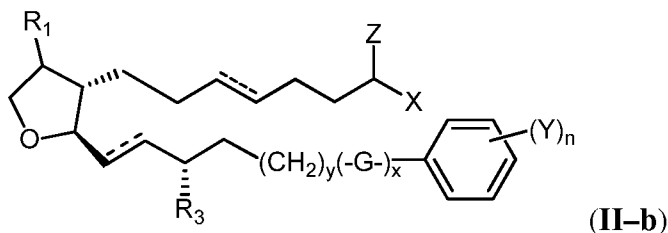
[00201] In certain embodiments of Formula (II), the compound of Formula (II-a):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof, wherein ===== , R_1 , Z, X, Y, G, R_3 , R_3' , y, x and n are as defined herein.

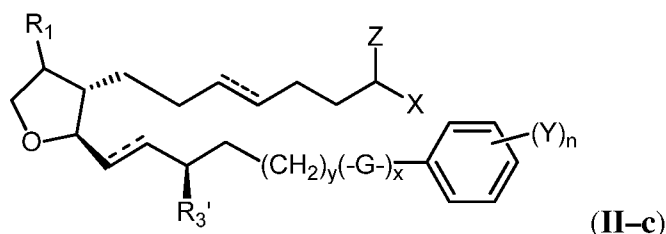
wherein ===== , R_1 , Z, X, Y, G, R_3 , R_3' , y, x, and n are as defined herein.

[00202] In certain embodiments of Formula (II-a), wherein R_3' is hydrogen, the compound is of Formula (II-b):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ===== , R_1 , R_3 , Z, X, Y, G, y, x, and n are as defined herein.

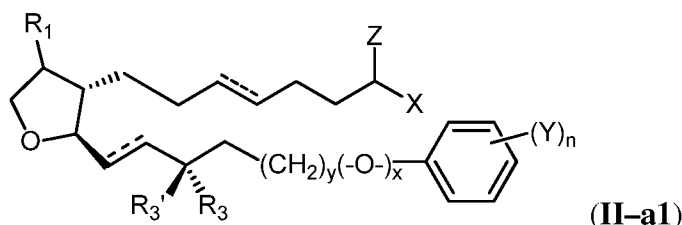
[00203] In certain embodiments of Formula (II-a), wherein R_3 is hydrogen, the compound is of Formula (II-c):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , G , y , x , and n are as defined herein.

[00204] In certain embodiments, G is $-O-$. In certain embodiments, G is $-S-$.

[00205] In certain embodiments of Formula (II-a), wherein G is $-O-$, provided is a compound of Formula (II-a1):

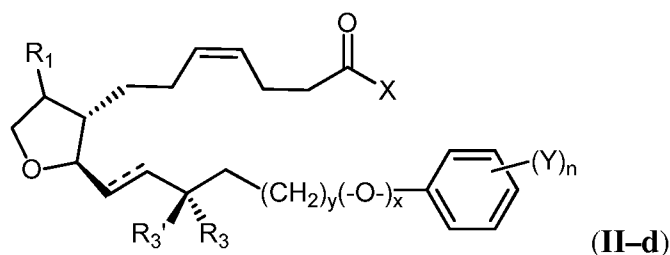


or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein R_1 , R_2 , Z , and X are as defined herein; wherein ----- , R_1 , R_2 , R_3' , Z , X , Y , y , x , and n are as defined herein.

[00206] In certain embodiments, Z is $=O$.

[00207] In certain embodiments at least one exocyclic ----- represents a *cis*-double bond.

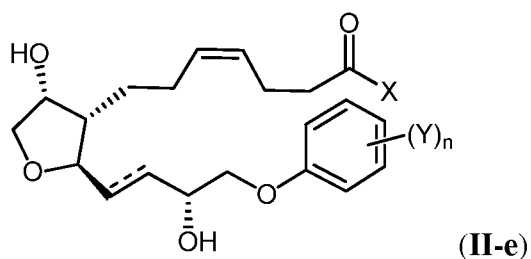
[00208] For example, in certain embodiments of Formula (II-a1), wherein Z is $=O$, provided is a compound of Formula (II-d):



or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein ----- , R_1 , R_3 , R_3' , Y , X , y , x , and n are as defined herein.

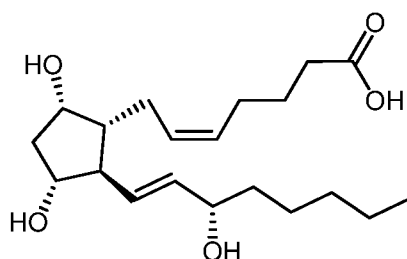
[00209] In certain embodiments of Formula (II-d), wherein R_1 is OH , R_3' is hydrogen, R_3

is -OH, y is 0, and x is 1, provided is a compound of Formula (II-e):

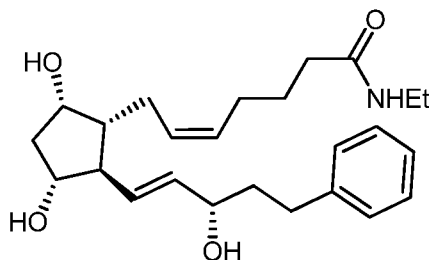


or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, isotopically enriched derivative, or prodrug thereof; wherein --- , Y, X, and n are as defined herein.

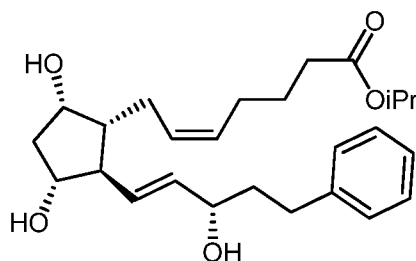
[00210] Exemplary compounds of Formula (I) include, but are not limited to:



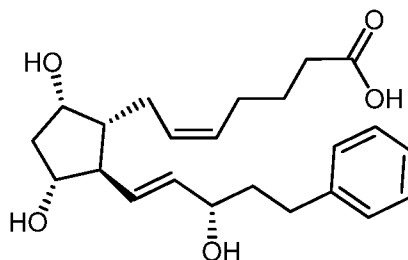
referred to herein as Prostaglandin F2α;



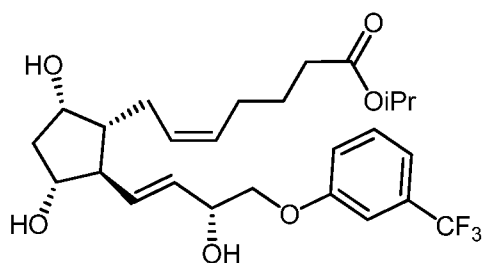
also referred to herein as bimatoprost;



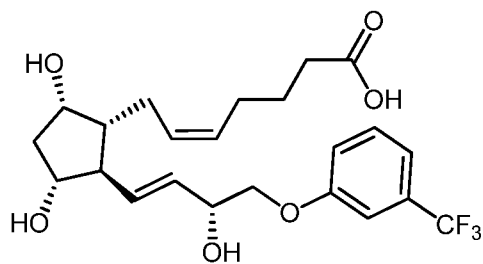
also referred to herein as bimatoprost isopropyl ester;



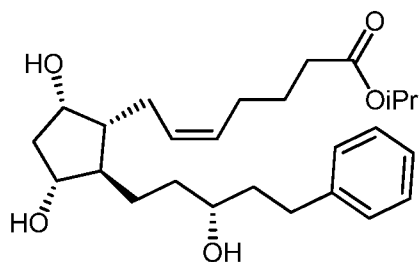
also referred to herein as bimatoprost free acid;



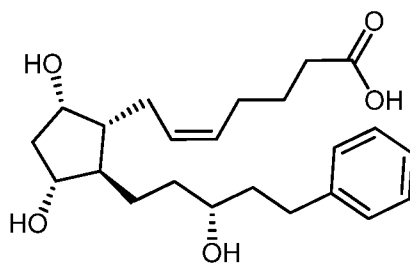
also referred to herein as travoprost;



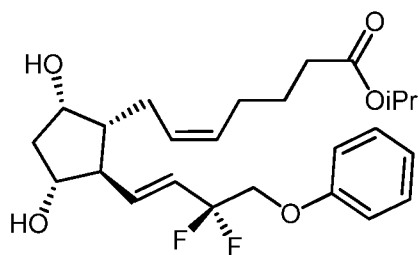
also referred to herein as travoprost free acid or fluprostenol;



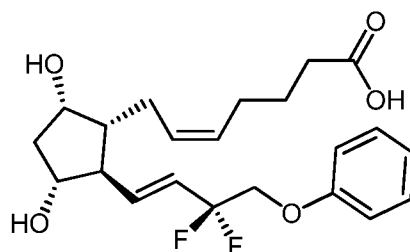
also referred to herein as latanoprost free acid;



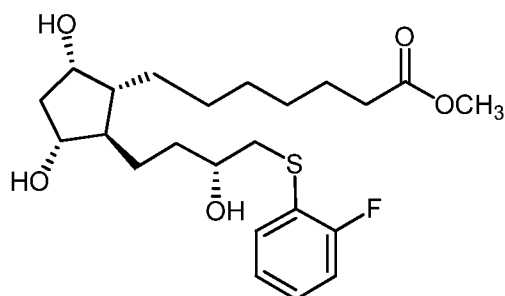
also referred to herein as latanoprost free acid;



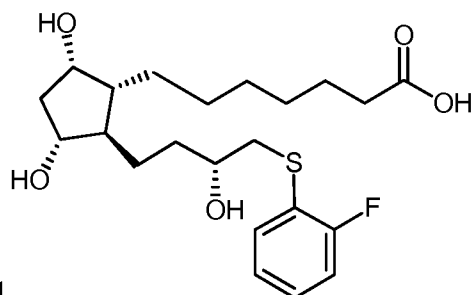
also referred to herein as tafluprost;



also referred to herein as tafluprost free acid or AFP-172;

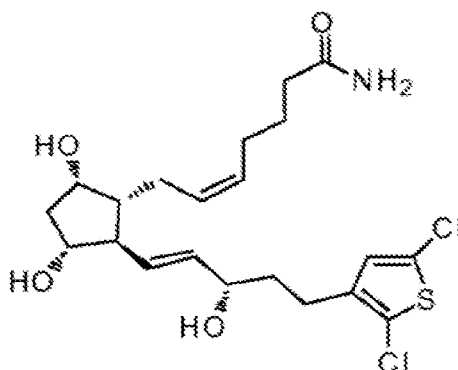


also referred to herein as CAY10509;



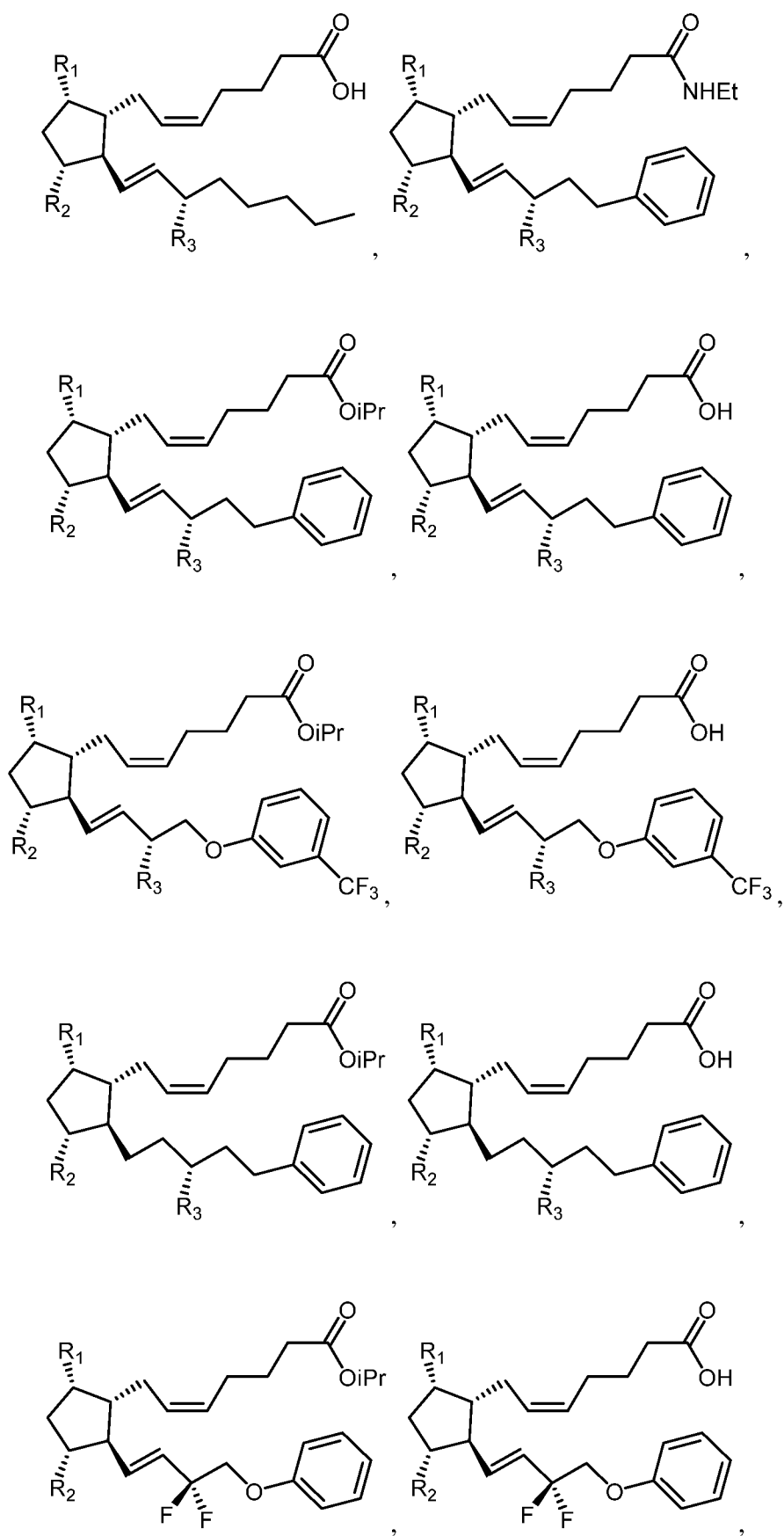
and

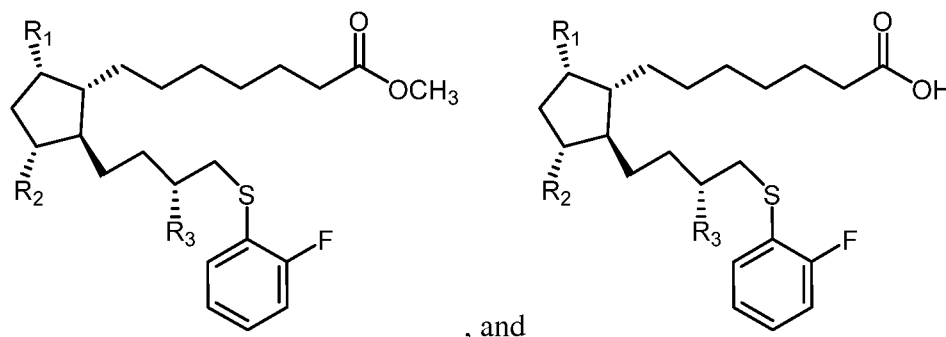
also referred to herein as CAY10509 free acid;



also referred to herein as 7-[3 α ,5 α -dihydroxy-2-(3 α -hydroxy-5-(3-(2,5-dichloro)thienyl)-1E-pentenyl)cyclopentyl]-5Z-heptenamide;

and 9-, 11-, and/or 15-ester derivatives (*e.g.*, prodrugs) of the above, *e.g.*, of formula:





wherein:

R_1 is $-\text{O}(\text{CO})R_6$ and R_2 is $-\text{OH}$, or

R_1 is $-\text{OH}$, R_2 is $-\text{O}(\text{CO})R_6$, or

R_1 is $-\text{OH}$, R_2 is $-\text{OH}$, and R_3 is $-\text{O}(\text{CO})R_8$, or

R_1 is $-\text{OH}$, R_2 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{OH}$, or

R_1 is $-\text{O}(\text{CO})R_6$, R_2 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{OH}$, or

R_1 is $-\text{O}(\text{CO})R_6$, R_2 is $-\text{OH}$, and R_3 is $-\text{O}(\text{CO})R_8$, or

R_1 is $-\text{OH}$, R_2 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{O}(\text{CO})R_8$, or

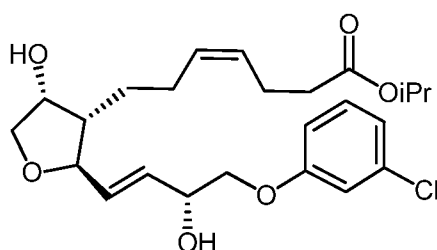
R_1 is $-\text{O}(\text{CO})R_6$, R_2 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{O}(\text{CO})R_8$,

wherein R_6 and R_8 are as defined herein, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, R_8 is $-(\text{CH}_2)_q\text{CH}_3$ wherein q is 0, 1, 2, 3, 4, 5, or 6, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, or $-\text{C}(\text{CH}_3)_3$. In certain embodiments, R_6 is $-(\text{CH}_2)_r\text{CH}_3$ wherein r is 0, 1, 2, 3, 4, 5, or 6, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, or $-\text{C}(\text{CH}_3)_3$.

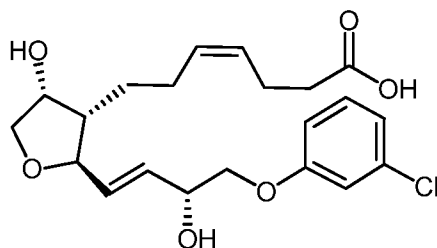
[00211] In certain embodiments, the compound of Formula (I) is selected from the group consisting of latanoprost, latanoprost free acid, tafluprost, tafluprost free acid, travoprost, fluprostenol, bimatoprost, bimatoprost free acid, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is selected from the group consisting of latanoprost, latanoprost free acid, tafluprost, tafluprost free acid, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is selected from the group consisting of latanoprost and pharmaceutically acceptable hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is selected from the group consisting of latanoprost free acid and

pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is latanoprost. In certain embodiments, the compound of Formula (I) is selected from the group consisting of tafluprost and pharmaceutically acceptable hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is selected from the group consisting of tafluprost free acid and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, the compound of Formula (I) is tafluprost.

[00212] Exemplary compounds of Formula (II) include, but are not limited to,

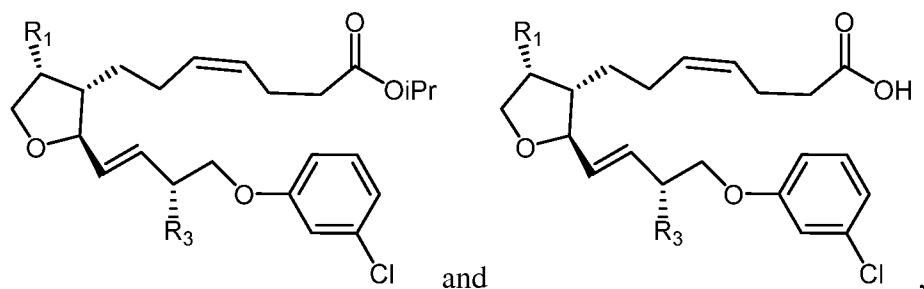


also referred to as AL-12182;.



also referred to as AL-12182 free acid;

and ester derivatives (*e.g.*, prodrugs) of the above, *e.g.*, of formula:



wherein:

R_1 is $-\text{OH}$ and R_3 is $-\text{O}(\text{CO})R_8$, or

R_1 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{OH}$, or

R_1 is $-\text{O}(\text{CO})R_6$, and R_3 is $-\text{O}(\text{CO})R_8$,

wherein R_6 and R_8 are as defined herein, and pharmaceutically acceptable salts, hydrates, solvates, stereoisomers, polymorphs, tautomers, isotopically enriched derivatives, and prodrugs thereof. In certain embodiments, R_8 is $-(CH_2)_qCH_3$ wherein q is 0, 1, 2, 3, 4, 5, or 6, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, or $-C(CH_3)_3$. In certain embodiments, R_6 is $-(CH_2)_rCH_3$ wherein r is 0, 1, 2, 3, 4, 5, or 6, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2C(CH_3)_3$, or $-C(CH_3)_3$.

[00213] In certain embodiments, the compound of Formula (I) or (II) is a prodrug of any one of the compounds described herein. Exemplary prodrugs include esters, amides, and/or thioamides of the parent free acid, and compounds wherein a hydroxyl group on the parent compound (*e.g.*, a pentacyclic hydroxyl group R_1 and/or R_2 or the hydroxyl group at the R_3 /and/or R_3' position) is esterified, *e.g.*, 9-, 11-, and/or 15-ester derivatives as described herein, *e.g.*, wherein the ester at said position is a C_{1-6} ester, *e.g.*, 9-propionyl bimatoprost, 11-propionyl bimatoprost, 15-propionyl bimatoprost, 9-butyryl bimatoprost, 11-butyryl bimatoprost, 15-butyryl bimatoprost, and the like.

Compositions and Formulations

[00214] As generally described herein, provided are topical compositions for use in any of the inventive methods, described herein, comprising a PFPFRA compound (the “active ingredient”), and optionally a pharmaceutically acceptable excipient.

[00215] Topical compositions, as used herein, encompass pharmaceutical compositions as well as cosmetic compositions. While pharmaceutical compositions are useful for therapeutic and prophylactic purposes, and cosmetic compositions are useful for beautification purposes.

[00216] In addition to the PFPFRA compound, the topical composition may additionally comprise one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients include, but are not limited to, any and all solvents, diluents or other liquid vehicles, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, thickening agents, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as coloring agents, coating agents, perfuming agents, and sunscreens may also be present in the composition. General considerations in the formulation and/or manufacture of the topical compositions can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00217] In some embodiments, the composition is a non-emulsion, *i.e.*, is not an emulsion.

In certain embodiments, the composition is not irritating to the skin.

[00218] Exemplary solvents and liquid vehicles include, but are not limited to, organic solvents (*e.g.*, polar protic solvents, polar aprotic solvents), water, saline, buffered aqueous solutions, and mixtures thereof. Exemplary polar protic solvents include, but are not limited to, organic alcohols such as methanol, ethanol, propanol, isopropanol, 1,3-butanediol, ethylene glycol, or propylene glycol, or mixture thereof. However, in certain embodiments, 1,3-butanediol is excluded. Exemplary polar aprotic solvents include, but are not limited to, dimethylsulfoxide (DMSO), and ethers such as diethyl ether and diethylene glycol monoethyl ether (DEGEE).

[00219] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and combinations thereof.

[00220] Exemplary surface active agents and/or emulsifiers include lipids/natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monolaurate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid

esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, *etc.* and/or combinations thereof.

[00221] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, *etc.*, and/or combinations thereof.

[00222] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[00227] 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.

[00228] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

[00229] 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, *etc.*, and combinations thereof.

[00230] 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, *etc.*, and combinations thereof.

[00231] Exemplary 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,

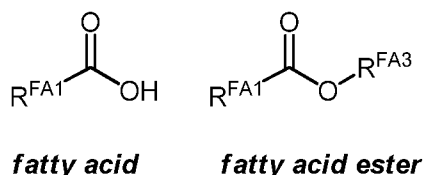
meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[00232] In some embodiments, the composition further comprises a viscosity enhancing agent. A viscosity enhancing agent, as used herein, is a substance which increases the viscosity of a solution or liquid/solid mixture. Exemplary viscosity enhancing agents include, but are not limited to, glycerin; cellulose derivatives (*e.g.*, methylcellulose (MC); hydroxypropylmethylcellulose (HPMC); carboxymethylcellulose (CMC); microcrystalline cellulose (CC); ethyl cellulose; hydroxyethyl cellulose (HEC); hydroxypropyl cellulose (HPC); cellulose); gelatin; starch; hetastarch; poloxamers; pluronics; sodium CMC; sorbitol; acacia; povidone; carbopol; polycarbophil; chitosan; alginate; chitosan glutamate; hyaluronic acid; elastin; hyaluronan; maltodextrin DE; deoxyglycocholate (GDC); polymethacrylic acid; glycols (*e.g.*, polymethylene glycol; polyethylene glycol); cyclodextrins (*e.g.*, sulfobutylether B cyclodextrin); sodium tauro-dihydrofusidate (STDHF); and N-trimethyl chitosan chloride (TMC). In certain embodiments, the viscosity enhancing agent is a cellulose derivative, *e.g.*, hydroxypropyl cellulose (HPC). In certain embodiments, the composition comprises a viscosity enhancing agent between about 0.5% and about 5% by weight, inclusive. In certain embodiments, the composition comprises a viscosity enhancing agent in between about 0.5% and about 4%, between about 0.5% and about 3%, between about 0.5% and about 2%, between about 0.5% and about 1%, between about 0.8% and about 5%, between about 0.8% and about 4%, between about 0.8% and about 3%, between about 0.5% and about 2%, or between about 0.5% and about 1%, inclusive. In certain embodiments, the composition comprises a viscosity enhancing agent in about 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, or 5% (by weight). In certain embodiments, the composition comprises hydroxypropylcellulose in about 1% by weight.

[00233] In certain embodiments, the composition further comprises an antioxidant, *e.g.*, 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. In certain embodiments, the composition comprises an antioxidant in between about 0.001% and about

0.1% by weight, inclusive. In certain embodiments, the composition comprises an antioxidant in between about 0.001% and about 0.05%, 0.001% and about 0.04%, 0.001% and about 0.03%, 0.001% and about 0.02%, 0.001% and about 0.01%, inclusive. In certain embodiments, the composition comprises an antioxidant in about 0.001%, 0.002%, 0.003%, 0.004%, 0.005%, 0.006%, 0.007%, 0.008%, 0.009%, 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% by weight. In certain embodiments, the composition comprises alpha tocopherol in about 0.002% by weight.

[00234] In certain embodiments, the composition further comprises a fatty acid and/or fatty acid ester, *e.g.*, of the below formulae:



wherein the alcohol moiety of the ester (R^{FA3}) is optionally substituted C_1 - C_6 alkyl, and the acyl moiety of the ester or acid (R^{FA1}) is optionally substituted C_{10} - C_{20} alkyl or optionally substituted C_{10} - C_{20} alkenyl.

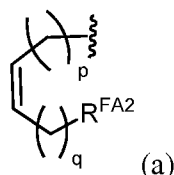
[00235] In certain embodiments, R^{FA3} is an optionally substituted C_{1-5} alkyl, C_{1-4} alkyl, C_{1-3} alkyl, C_{1-2} alkyl, C_{2-6} alkyl, C_{2-5} alkyl, C_{2-4} alkyl, C_{2-3} alkyl, C_{3-6} alkyl, C_{3-5} alkyl, C_{3-4} alkyl, C_{4-6} alkyl, C_{4-5} alkyl, or C_{5-6} alkyl. In certain embodiments, R^{FA3} is a branched alkyl group, *e.g.*, for example, isopropyl, isobutyl, sec-butyl, tert-butyl, or neopentyl. In certain embodiments, R^{FA3} is an unbranched alkyl group, *e.g.*, for example, methyl, ethyl, n-propyl, n-butyl, n-pentyl, or n-hexyl. In certain embodiments, R^{FA3} is an unsubstituted alkyl group, *i.e.*, comprising only carbon and hydrogen atoms. In certain embodiments, R^{FA3} is a substituted alkyl group, *e.g.*, substituted by halogen atoms.

[00236] In certain embodiments, R^{FA1} is an optionally substituted C_{10} - C_{19} alkyl, C_{10} - C_{18} alkyl, C_{10} - C_{17} alkyl, C_{10} - C_{16} alkyl, C_{10} - C_{15} alkyl, C_{10} - C_{14} alkyl, C_{10} - C_{13} alkyl, C_{11} - C_{20} alkyl, C_{11} - C_{19} alkyl, C_{11} - C_{18} alkyl, C_{11} - C_{17} alkyl, C_{11} - C_{16} alkyl, C_{11} - C_{15} alkyl, C_{11} - C_{14} alkyl, C_{11} - C_{13} alkyl, C_{12} - C_{19} alkyl, C_{12} - C_{18} alkyl, C_{12} - C_{17} alkyl, C_{12} - C_{16} alkyl, C_{12} - C_{15} alkyl, C_{12} - C_{14} alkyl, C_{12} - C_{13} alkyl, C_{13} - C_{20} alkyl, C_{13} - C_{19} alkyl, C_{13} - C_{18} alkyl, C_{13} - C_{17} alkyl, C_{13} - C_{16} alkyl, C_{13} - C_{15} alkyl, C_{13} - C_{14} alkyl, C_{14} - C_{20} alkyl, C_{14} - C_{19} alkyl, C_{14} - C_{18} alkyl, C_{14} - C_{17} alkyl, C_{14} - C_{16} alkyl, C_{14} - C_{15} alkyl, C_{15} - C_{20} alkyl, C_{15} - C_{19} alkyl, C_{15} - C_{18} alkyl, C_{15} - C_{17} alkyl, or C_{15} - C_{16} alkyl. In certain embodiments, R^{FA1} is a straight chain (unbranched) alkyl group. In certain embodiments, R^{FA1} is an unsubstituted alkyl group, *i.e.*, comprising only carbon and

hydrogen atoms. In certain embodiments, R^{FA1} is a substituted alkyl group, *e.g.*, substituted by halogen atoms.

[00237] In certain embodiments, R^{FA1} is an optionally substituted C_{10} - C_{19} alkenyl, C_{10} - C_{18} alkenyl, C_{10} - C_{17} alkenyl, C_{10} - C_{16} alkenyl, C_{10} - C_{15} alkenyl, C_{10} - C_{14} alkenyl, C_{10} - C_{13} alkenyl, C_{11} - C_{20} alkenyl, C_{11} - C_{19} alkenyl, C_{11} - C_{18} alkenyl, C_{11} - C_{17} alkenyl, C_{11} - C_{16} alkenyl, C_{11} - C_{15} alkenyl, C_{11} - C_{14} alkenyl, C_{11} - C_{13} alkenyl, C_{12} - C_{19} alkenyl, C_{12} - C_{18} alkenyl, C_{12} - C_{17} alkenyl, C_{12} - C_{16} alkenyl, C_{12} - C_{15} alkenyl, C_{12} - C_{14} alkenyl, C_{12} - C_{13} alkenyl, C_{13} - C_{20} alkenyl, C_{13} - C_{19} alkenyl, C_{13} - C_{18} alkenyl, C_{13} - C_{17} alkenyl, C_{13} - C_{16} alkenyl, C_{13} - C_{15} alkenyl, C_{13} - C_{14} alkenyl, C_{14} - C_{20} alkenyl, C_{14} - C_{19} alkenyl, C_{14} - C_{18} alkenyl, C_{14} - C_{17} alkenyl, C_{14} - C_{16} alkenyl, C_{14} - C_{15} alkenyl, C_{15} - C_{20} alkenyl, C_{15} - C_{19} alkenyl, C_{15} - C_{18} alkenyl, C_{15} - C_{17} alkenyl, C_{15} - C_{16} alkenyl. In certain embodiments, R^{FA1} is a unbranched alkenyl group. In certain embodiments, R^{FA1} is an unsubstituted alkenyl group, *i.e.*, comprising only carbon and hydrogen atoms. In certain embodiments, R^{FA1} is a substituted alkenyl group, *e.g.*, substituted by halogen atoms. In certain embodiments, R^{FA1} is an alkenyl group comprising 1, 2, 3, or 4 double bonds, each independently *cis* or *trans*.

[00238] In certain embodiments, R^{FA1} is an alkenyl group comprising at least one *cis* double bond, *e.g.*, 1, 2, 3, or 4 *cis* double bonds. In certain embodiments, R^{FA1} is an alkenyl group of formula (a):



wherein:

p is an integer between 2 and 8, inclusive;

q is an integer between 1 and 8, inclusive; and

R^{FA2} is an optionally substituted C_1 - C_{10} alkyl, or an optionally substituted C_2 - C_{10} alkenyl,

provided the sum of carbons of formula (a) does not exceed 20.

[00239] In certain embodiments, R^{FA2} is an optionally substituted C_1 - C_9 alkyl, C_1 - C_8 alkyl, C_1 - C_7 alkyl, C_1 - C_6 alkyl, C_1 - C_5 alkyl, C_1 - C_4 alkyl, C_1 - C_3 alkyl, C_1 - C_2 alkyl, C_2 - C_{10} alkyl, C_2 - C_9 alkyl, C_2 - C_8 alkyl, C_2 - C_7 alkyl, C_2 - C_6 alkyl, C_2 - C_5 alkyl, C_2 - C_4 alkyl, C_2 - C_3 alkyl, C_3 - C_{10} alkyl, C_3 - C_9 alkyl, C_3 - C_8 alkyl, C_3 - C_7 alkyl, C_3 - C_6 alkyl, C_3 - C_5 alkyl, C_3 - C_4 alkyl, C_4 - C_{10} alkyl, C_4 - C_9 alkyl, C_4 - C_8 alkyl, C_4 - C_7 alkyl, C_4 - C_6 alkyl, C_4 - C_5 alkyl, C_5 - C_{10} alkyl, C_5 - C_9 alkyl, C_5 - C_8 alkyl, C_5 - C_7 alkyl, C_5 - C_6 alkyl, C_6 - C_{10} alkyl, C_6 - C_9 alkyl, C_6 - C_8 alkyl, C_6 - C_7

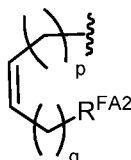
alkyl, C₇-C₁₀ alkyl, C₇-C₉ alkyl, C₇-C₈ alkyl, C₈-C₁₀ alkyl, C₈-C₉ alkyl, or C₉-C₁₀ alkyl. In certain embodiments, R^{FA2} is a straight chain (unbranched) alkyl group. In certain embodiments, R^{FA2} is an unsubstituted alkyl group, *i.e.*, comprising only carbon and hydrogen atoms. In certain embodiments, R^{FA2} is a substituted alkyl group, *e.g.*, substituted by halogen atoms.

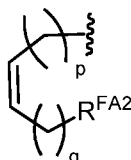
[00240] In certain embodiments, R^{FA2} is an optionally substituted C₂-C₉ alkenyl, C₂-C₈ alkenyl, C₂-C₇ alkenyl, C₂-C₆ alkenyl, C₂-C₅ alkenyl, C₂-C₄ alkenyl, C₂-C₃ alkenyl, C₃-C₁₀ alkenyl, C₃-C₉ alkenyl, C₃-C₈ alkenyl, C₃-C₇ alkenyl, C₃-C₆ alkenyl, C₃-C₅ alkenyl, C₃-C₄ alkenyl, C₄-C₁₀ alkenyl, C₄-C₉ alkenyl, C₄-C₈ alkenyl, C₄-C₇ alkenyl, C₄-C₆ alkenyl, C₄-C₅ alkenyl, C₅-C₁₀ alkenyl, C₅-C₉ alkenyl, C₅-C₈ alkenyl, C₅-C₇ alkenyl, C₅-C₆ alkenyl, C₆-C₁₀ alkenyl, C₆-C₉ alkenyl, C₆-C₈ alkenyl, C₆-C₇ alkenyl, C₇-C₁₀ alkenyl, C₇-C₉ alkenyl, C₇-C₈ alkenyl, C₈-C₁₀ alkenyl, C₈-C₉ alkenyl, or C₉-C₁₀ alkenyl. In certain embodiments, R^{FA2} is a straight chain (unbranched) alkenyl group. In certain embodiments, R^{FA2} is an unsubstituted alkenyl group, *i.e.*, comprising only carbon and hydrogen atoms. In certain embodiments, R^{FA2} is a substituted alkenyl group, *e.g.*, substituted by halogen atoms. In certain embodiments, R^{FA2} is a substituted alkenyl group, *e.g.*, substituted by halogen atoms. In certain embodiments, R^{FA2} is an alkenyl group comprising 1 or 2 double bonds, each independently *cis* or *trans*.

[00241] In certain embodiments, p is 2, 3, 4, 5, 6, 7, or 8. In certain embodiments, q is 1, 2, 3, 4, 5, 6, 7, or 8. In certain embodiments, p is 4, 5, 6, or 7. In certain embodiments, q is 1. In certain embodiments, q is 3, 4, or 5. In certain embodiments, q is 6, 7, or 8.

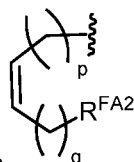
[00242] In certain embodiments, R^{FA1} is selected from any one of the following saturated or unsaturated fatty acyl moieties:

Lauric	-(CH ₂) ₁₀ CH ₃ (11 aliphatic carbons),
Myristic	-(CH ₂) ₁₂ CH ₃ (13 aliphatic carbons),
Palmitic	-(CH ₂) ₁₄ CH ₃ (15 aliphatic carbons),
Stearic	-(CH ₂) ₁₆ CH ₃ (17 aliphatic carbons),
Myristoleic	-(CH ₂) ₇ CH=CH(CH ₂) ₃ CH ₃ ,



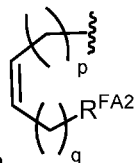
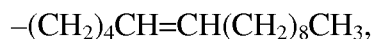
i.e., of formula , wherein p = 7, q = 3, R^{FA2} = -CH₃ (13 aliphatic carbons)

Palmitoleic	-(CH ₂) ₇ CH=CH(CH ₂) ₅ CH ₃ ,
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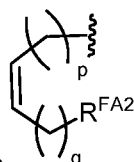
i.e., of formula $\text{---}(\text{CH}_2)_p\text{---CH=CH---}(\text{CH}_2)_q\text{---R}^{\text{FA2}}$, wherein $p = 7$, $q = 5$, $\text{R}^{\text{FA2}} = \text{---CH}_3$ (15 aliphatic carbons)

Sapenic



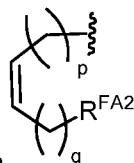
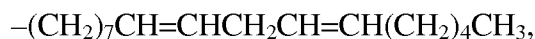
i.e., of formula $\text{---}(\text{CH}_2)_p\text{---CH=CH---}(\text{CH}_2)_q\text{---R}^{\text{FA2}}$, wherein $p = 4$, $q = 8$, $\text{R}^{\text{FA2}} = \text{---CH}_3$ (15 aliphatic carbons)

Oleic



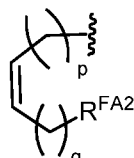
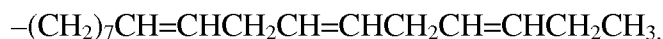
i.e., of formula $\text{---}(\text{CH}_2)_p\text{---CH=CH---}(\text{CH}_2)_q\text{---R}^{\text{FA2}}$, wherein $p = 7$, $q = 7$, $\text{R}^{\text{FA2}} = \text{---CH}_3$ (17 aliphatic carbons)

Linoleic



i.e., of formula $\text{---}(\text{CH}_2)_p\text{---CH=CH---}(\text{CH}_2)_q\text{---R}^{\text{FA2}}$, wherein $p = 7$, $q = 1$, $\text{R}^{\text{FA2}} = \text{C}_7\text{-alkenyl}$ (17 aliphatic carbons)

α -Linolenic



i.e., of formula $\text{---}(\text{CH}_2)_p\text{---CH=CH---}(\text{CH}_2)_q\text{---R}^{\text{FA2}}$, wherein $p = 7$, $q = 1$, $\text{R}^{\text{FA2}} = \text{C}_7\text{-alkenyl}$ (17 aliphatic carbons)

[00243] In certain embodiments, the total number of aliphatic carbons atoms in the fatty acid is between 11 and 19, inclusive, *i.e.*, 11, 12, 13, 14, 15, 16, 17, 18, or 19 aliphatic carbon atoms total. In certain embodiments, the total number of aliphatic carbons in the fatty acid is selected to approximate the aliphatic chain length of the PFPPRA compound (*e.g.*, latanoprost has 13 aliphatic carbons if the cyclizing carbons 9 through 11 of the cyclopentyl ring are not counted). For example, in certain embodiments, the total carbon atoms in the aliphatic chain

of the PFPPRA compound is between 11 and 19, inclusive, *i.e.*, 11, 12, 13, 14, 15, 16, 17, 18, or 19 aliphatic carbon atoms total.

[00244] In certain embodiments, the total number of carbons atoms in the fatty acid ester, which include the number of carbons of R^{FA1} and R^{FA3} is between 11 and 19, inclusive, *i.e.*, 11, 12, 13, 14, 15, 16, 17, 18, or 19 carbon atoms total. In some embodiments, the total number of carbons in the fatty acid ester is selected to approximate the total carbon atoms in the sum of the aliphatic chain and ester moiety of the PFPPRA compound. For example, in certain embodiments, the total carbon atoms in the sum of the aliphatic chain and ester moiety of the PFPPRA compound is between 11 and 19, inclusive, *i.e.*, 11, 12, 13, 14, 15, 16, 17, 18, or 19 carbon atoms total.

[00245] In some embodiments, fatty acid or fatty acid ester is selected such that its predicted length (*e.g.* by molecular modeling) is similar (*e.g.*, within ± 3 Å) to the predicted length of the PFPPRA compound. For example, the fatty acid oleic acid has a predicted length (between the two most distant heavy atoms) of about 19 Å, and the fatty acid ester isopropyl myristate has a predicted length (between the two most distant heavy atoms) of about 20 Å, each of which compares favorably with a length of about 17 Å for latanoprost free acid, tafluprost free acid, and bimatoprost free acid; 18 Å for latanoprost and tafluprost; about 19 Å for bimatoprost and travoprost free acid (*i.e.*, fluprostenol), and about 20 Å for travoprost. In some embodiments, the predicted length is in an energy-minimized conformation. In some embodiments, the predicted length is in an energy-minimized conformation. In some embodiments, the predicted length is of a conformation whereby freely rotating bonds are rotated as to provide a maximal length.

[00246] In some embodiments, the final concentration of the fatty acid is between about 1 percent to about 20 percent by weight, inclusive. In some embodiments, the final concentration of the fatty acid is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 1 and about 5 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, inclusive. In certain embodiments, the final concentration of the fatty acid is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 percent by weight.

[00247] In some embodiments, the final concentration of the fatty acid ester is between about 1 percent to about 20 percent by weight, inclusive. In some embodiments, the final

concentration of the fatty acid ester is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 1 and about 5 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, inclusive. In certain embodiments, the final concentration of the fatty acid ester is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 percent by weight

[00248] In some embodiments, fatty acid ester is isopropyl myristate. In some embodiments, the composition comprises isopropyl myristate and one or more additional different fatty acid esters. Alternatively, in some embodiments, isopropyl myristate cannot be replaced with a different fatty acid ester. In some embodiments, the composition comprises isopropyl myristate and does not comprise one or more additional different fatty acid esters.

[00249] In some embodiments, the composition further comprises an organic alcohol, *e.g.*, methanol, ethanol, propanol, isopropanol, 1,3-butanediol, ethylene glycol, or propylene glycol. In some embodiments, the final concentration of an organic alcohol is between about 5 percent and about 99 percent by weight.

[00250] In some embodiments, the composition comprises an organic alcohol which acts as a base excipient (*i.e.*, constituting the major component of the composition, such as for example, provided in greater than 50% by weight). In some embodiments, the final concentration of the organic alcohol base excipient is greater than 50 percent and about 99 percent by weight, inclusive. In some embodiments, the final concentration of the organic alcohol base excipient is between about 51 percent and 60 percent, 51 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. In certain embodiments, the organic alcohol which acts as a base excipient is ethanol.

[00251] In some embodiments, the composition comprises an organic alcohol which is not the base component of the composition (*e.g.*, provided as a component in 50% or less by weight). In certain embodiments, the final concentration of the organic alcohol is between about 5 percent and about 50 percent by weight, inclusive. In some embodiments, the final concentration of the organic alcohol is between about 5 percent and 10 percent, about 5

percent and about 15 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent, about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive. In certain embodiments, the composition comprises an organic alcohol in 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30% by weight. In certain embodiments, the organic alcohol is propylene glycol.

[00252] In certain embodiments, the composition further comprises an ointment base. As used herein, an ointment base is a homogeneous, viscous, semi-solid preparation, which comprises a greasy, ointment base having a medium-to-high viscosity, that is intended for topical application to the skin. Exemplary ointment bases include, but are not limited to, hydrocarbon bases/waxes (*e.g.*, plant and animal waxes (*e.g.*, beeswax, lanolin, carnauba wax), petroleum derived waxes (*e.g.*, hard paraffin wax or soft paraffin wax, *i.e.*, petroleum jelly), microcrystalline wax, ceresine wax, white wax, yellow wax, and cetyl esters wax). In certain embodiments, the ointment base is a hydrocarbon base, *e.g.*, petroleum jelly. Petroleum jelly (also known as petrolatum, white petrolatum, soft paraffin wax or multi-hydrocarbon wax) is a semi-solid preparation typically comprising (or consisting of) one or more saturated hydrocarbons with carbon numbers mainly higher than 25 (typically 25 to 50, such as 25 to 40, such as 25 to 35). It typically has a boiling point of from about 250°C to about 350°C, such as about 280°C to about 320°C, preferably about 300°C, and a melting point typically from about 36°C to about 60°C. In certain embodiments, the petroleum jelly is obtained in sterile form or is sterilized prior to manufacturing the composition. In certain embodiments, the petroleum jelly is pure ultra white petroleum jelly. In some embodiments, the final concentration of ointment base is between about 50 percent and about 99 percent by weight. In some embodiments, the final concentration of ointment base is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent.

[00253] Topical compositions as 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 PFPPRA compound into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a dosage form.

[00254] Compositions for topical administration of the PFPPRA compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, and/or patches. Generally, the PFPPRA compound is admixed under sterile conditions with a pharmaceutically acceptable excipient and/or any needed preservatives and/or buffers as can be required. Furthermore, a PFPPRA compound can be combined with, incorporated into, and/or delivered by means of a patch or dressing, which often have the added advantage of providing controlled delivery of the PFPPRA compound to the skin and/or subcutaneous fat. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the PFPPRA compound in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the PFPPRA compound in a polymer matrix and/or gel. In some embodiments, skin surface exposure can be controlled by applying or removing the patch or dressing.

[00255] As used herein, the term “dose” or “dosed” means the measured amount of a composition to be administered at one time. Relative amounts of the dose to be administered (*e.g.*, comprising the PFPPRA compound, the pharmaceutically acceptable excipient, and/or any additional ingredients) in the topical composition 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, a dose of the topical composition may comprise between about 0.0001% and about 10% (w/w) of the PFPPRA compound. In some embodiments, the concentration of the PFPPRA compound is between about 0.0001 percent and about 1 percent, about 0.0001 and about 0.0003 percent, about 0.0001 and about 0.001 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive, per dose of the topical composition.

[00256] In certain embodiments, the composition comprises a PFPPRA compound, fatty acid ester (*e.g.*, isopropyl myristate), and an ointment base. In some embodiments, the composition further comprises an organic alcohol, *e.g.*, methanol, ethanol, propanol, isopropanol, 1,3-butanediol, ethylene glycol, or propylene glycol. In certain embodiments,

the organic alcohol is propylene glycol. In certain embodiments, the composition comprises latanoprost, isopropyl myristate, and an ointment base. In certain embodiments, the composition comprises tafluoprost, isopropyl myristate, and an ointment base. In certain embodiments, the composition consists essentially of the above-recited components. In certain embodiments, the composition is not irritating to the skin. In certain embodiments, the composition is sterile, endotoxin-free or essentially endotoxin-free, ophthalmic, and/or ophthalmically compatible.

[00257] Kalayoglu (PCT/US2012/021692; WO2012/099942) teaches certain formulations for systemic (transdermal) delivery of a PFPPRA to the bloodstream. These include two emulsions (Lipoderm or pluronic lecithin organogel). Emulsions are challenging to manufacture and susceptible to phase separation; *e.g.*, for example, pluronic lecithin organogel is prone to phase separation at temperatures of about 5°C or below. Thus, in some embodiments, the composition is a non-emulsion, *i.e.*, is not an emulsion. In some embodiments, the composition is a non-emulsion comprising a PFPPRA compound, fatty acid ester (*e.g.*, isopropyl myristate), and an ointment base. In some embodiments, the composition is a non-emulsion comprising a PFPPRA compound, fatty acid ester (*e.g.*, isopropyl myristate), an organic alcohol, and an ointment base.

[00258] In some embodiments, the final concentration of the PFPPRA compound provided in the composition is between about 0.0001 percent and about 1 percent (by weight). In some embodiments, the final concentration is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive. These percentages are expressed by weight of the total weight of the composition.

[00259] In some embodiments, the PFPPRA compound is latanoprost and the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive.

[00260] In some embodiments, the PFPPRA compound is tafluprost and the final concentration of tafluprost is between about 0.001 percent and about 1 percent, 0.001 and

about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive. These percentages are expressed by weight of the total weight of the composition.

[00261] In some embodiments, the final concentration of the fatty acid ester (*e.g.*, isopropyl myristate) is between about 1 percent to about 20 percent by weight, inclusive. In some embodiments, the final concentration is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, inclusive. In certain embodiments, the final concentration of the fatty acid ester (*e.g.*, isopropyl myristate) is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 percent by weight. These percentages are expressed by weight of the total weight of the composition.

[00262] In some embodiments, the PFPPRA compound is latanoprost; the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00263] In some embodiments, the PFPPRA compound is tafluprost; the final concentration of tafluprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1

percent, or about 0.3 and about 1 percent (by weight) , inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00264] In some embodiments, the composition comprises an ointment base, *e.g.*, a hydrocarbon base. In some embodiments, the hydrocarbon base is selected from the group consisting of white wax, yellow wax, hard paraffin wax, petroleum jelly, and cetyl esters wax. In some embodiments, the final concentration of ointment base is between about 50 percent and about 99 percent by weight. In some embodiments, the final concentration of ointment base is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. In some embodiments, the ointment base is petroleum jelly, and the final concentration of petroleum jelly is between about 50 percent and about 99 percent by weight, inclusive. In some embodiments, the final concentration of petroleum jelly is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive.

[00265] In some embodiments, the PFPPRA compound is latanoprost; the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15

percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the ointment base (*e.g.*, petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00266] In some embodiments, the PFPPRA compound is tafluprost; the final concentration of tafluprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the ointment base (*e.g.*, petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00267] In some embodiments, the composition further comprises an organic alcohol (*e.g.*, propylene glycol). In some embodiments, the final concentration of propylene glycol is between about 5 percent and about 50 percent by weight, inclusive. In some embodiments,

the final concentration of the organic alcohol (*e.g.*, propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive.

[00268] In some embodiments, the PFPPRA compound is latanoprost; the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the organic alcohol (*e.g.*, propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00269] In some embodiments, the PFPPRA compound is tafluprost; the final concentration of tafluprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01

and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the organic alcohol (*e.g.*, propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent, about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00270] In some embodiments, the PFPPRA compound is latanoprost; the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; the final concentration of the organic alcohol (*e.g.*, propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about

20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive; and the final concentration of the ointment base (*e.g.*, petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00271] In some embodiments, the PFPPRA compound is tafluprost; the final concentration of tafluprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (*e.g.*, isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; the final concentration of the organic alcohol (*e.g.*, propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive; and the final concentration of the ointment base (*e.g.*, petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about

70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[00272] In some embodiments, the composition is sterile. Generally, methods of manufacturing a sterile composition include gamma irradiation, heat (*e.g.*, autoclave or dry heat), and microfiltration (*e.g.*, with a 0.2 micron filter); however, some of these methods can be unsuitable for certain compositions. For example, gamma irradiation or heat can cause degradation of the PFPPA compound; oleaginous bases such as petroleum jelly are not amenable to autoclave sterilization; and some excipients may be incompatible or poorly compatible with a 0.2 micron filter.

[00273] Although the descriptions of the topical compositions provided herein are principally directed to compositions that 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 the topical composition suitable for administration to humans in order to render the composition suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the composition and/or manufacture of compositions can be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005.

[00274] Still further encompassed by the invention are kits comprising a topical composition as described herein and instructions for use. Kits provided may comprise a provided composition and a container (*e.g.*, a tube, vial, ampoule, bottle, syringe, and/or dispenser package, or other suitable container).

Dosing Regimen for Reduction of Subcutaneous Fat

[00275] As generally described herein, the topical compositions as described herein are contemplated useful in the reduction of subcutaneous fat in a subject in need thereof.

[00276] In one aspect, provided is a prostaglandin FP receptor agonist compound for topical use in reducing body fat, whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hour and about 12 hours per dose of the

composition.

[00277] In another aspect, provided is a method for locally reducing body fat in a subject in need thereof, the method comprising administering a topical composition comprising a PFPPRA compound to the skin surface, and removing the topical composition or residue thereof from the skin surface between about 4 hour and about 12 hours after said administering. In certain embodiments, at the dermis has taken up at least 80% of maximal load by the PFPPRA compound (or active metabolite thereof) within about 4 to about 12 hours of administration (with maximal load as defined herein). In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after the dermis has taken up at least 80% of maximal load. In certain embodiments, more than about 60 percent of the 24-hour transcutaneous flux occurs within 4 to 12 hours after administration. In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60 percent of the 24-hour transcutaneous flux has occurred.

[00278] In another aspect, provided is a kit comprising a topical fat-reducing composition and instructions for use, wherein the composition comprises a PFPPRA compound, and wherein the instructions provide for a duration of skin surface exposure to the composition or residue thereof of between about 4 hours and about 12 hours per dose of the composition.

[00279] In certain specific embodiments, provided is latanoprost for use in reducing body fat, wherein the latanoprost is provided in a topical composition, and whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the composition is administered about once every 24 hours.

[00280] In certain specific embodiments, further provided is a method for locally reducing body fat in a subject in need thereof, the method comprising the steps of administering a composition comprising latanoprost to the skin surface; and removing the composition or residue thereof from the skin surface between about 4 hours and about 12 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 10 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 8 hours, inclusive, after said administering. In certain

embodiments, the removing is between about 6 hours and about 10 hours, inclusive, after said administering. In certain embodiments, more than about 60 percent of the 24-hour flux of latanoprost or an active metabolite thereof occurs within 4 to 12 hours, inclusive, after the step of administering, and wherein the step of removing is after more than about 60 percent of the 24-hour flux has occurred. In certain embodiments, the dermis is fully loaded with latanoprost, an active metabolite thereof, or a combination thereof, within 4 to 12 hours, inclusive, after the administering, and wherein the step of removing is after the dermis is fully loaded.

[00281] In certain specific embodiments, provided is tafluprost for use in reducing body fat, wherein the tafluprost is provided in a topical composition, and whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the composition is administered about once every 24 hours.

[00282] In certain specific embodiments, further provided is a method for locally reducing body fat in a subject in need thereof, the method comprising the steps of administering a composition comprising tafluprost to the skin surface; and removing the composition or residue thereof from the skin surface between about 4 hours and about 12 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 10 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 8 hours, inclusive, after said administering. In certain embodiments, the removing is between about 6 hours and about 10 hours, inclusive, after said administering. In certain embodiments, more than about 60 percent of the 24-hour flux of tafluprost or an active metabolite thereof occurs within 4 to 12 hours, inclusive, after the step of administering, and wherein the step of removing is after more than about 60 percent of the 24-hour flux has occurred. In certain embodiments, the dermis is fully loaded with tafluprost, an active metabolite thereof, or a combination thereof, within 4 to 12 hours, inclusive, after the administering, and wherein the step of removing is after the dermis is fully loaded.

[00283] In certain specific embodiments, provided is travoprost for use in reducing body fat, wherein the travoprost is provided in a topical composition, and whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and

about 12 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the composition is administered about once every 24 hours.

[00284] In certain specific embodiments, further provided is a method for locally reducing body fat in a subject in need thereof, the method comprising the steps of administering a composition comprising travoprost to the skin surface; and removing the composition or residue thereof from the skin surface between about 4 hours and about 12 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 10 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 8 hours, inclusive, after said administering. In certain embodiments, the removing is between about 6 hours and about 10 hours, inclusive, after said administering. In certain embodiments, more than about 60 percent of the 24-hour flux of travoprost or an active metabolite thereof occurs within 4 to 12 hours, inclusive, after the step of administering, and wherein the step of removing is after more than about 60 percent of the 24-hour flux has occurred. In certain embodiments, the dermis is fully loaded with travoprost, an active metabolite thereof, or a combination thereof, within 4 to 12 hours, inclusive, after the administering, and wherein the step of removing is after the dermis is fully loaded.

[00285] In certain specific embodiments, provided is bimatoprost for use in reducing body fat, wherein the bimatoprost is provided in a topical composition, and whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the composition is administered about once every 24 hours.

[00286] In certain specific embodiments, further provided is a method for locally reducing body fat in a subject in need thereof, the method comprising the steps of administering a composition comprising bimatoprost to the skin surface; and removing the composition or residue thereof from the skin surface between about 4 hours and about 12 hours, inclusive,

after said administering. In certain embodiments, the removing is between about 4 hours and about 10 hours, inclusive, after said administering. In certain embodiments, the removing is between about 4 hours and about 8 hours, inclusive, after said administering. In certain embodiments, the removing is between about 6 hours and about 10 hours, inclusive, after said administering. In certain embodiments, more than about 60 percent of the 24-hour flux of bimatoprost or an active metabolite thereof occurs within 4 to 12 hours, inclusive, after the step of administering, and wherein the step of removing is after more than about 60 percent of the 24-hour flux has occurred. In certain embodiments, the dermis is fully loaded with bimatoprost, an active metabolite thereof, or a combination thereof, within 4 to 12 hours, inclusive, after the administering, and wherein the step of removing is after the dermis is fully loaded.

[00287] In certain specific embodiments, further provided is a kit comprising a topical fat-reducing composition and instructions for use, wherein the composition comprises a prostaglandin FP receptor agonist compound, and wherein the instructions provide for a duration of skin surface exposure to the composition or residue thereof of between about 4 hours and about 12 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition. In certain embodiments, the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition. In certain embodiments, the dose frequency is about once every 24 hours.

[00288] As used herein, the term “skin surface exposure” means the duration in which the PFPPRA compound is in contact with the surface of the skin, prior to removal of the composition or residue thereof. For example, skin surface exposure begins when the topical composition comprising the PFPPRA compound is applied to the skin and ends when the topical composition or residue thereof (which may or may not comprise unabsorbed PFPPRA compound) is removed from the skin. Removal of the topical composition, in this instance, means gross removal (*e.g.*, removal of 90%, 95%, 99%, or 100%) of the remaining topical composition, including any remaining PFPPRA compound and any remaining excipients, from the skin surface, *e.g.*, by washing, scrubbing, scraping, removing patches and the like, and/or stripping the skin. It should be understood that some ingredients of the topical composition can be volatile and can evaporate following application to the skin. Other ingredients do not necessarily evaporate. For example, PFPPRA compounds are not generally considered to be volatile compounds.

[00289] As used herein, the “residue” of a composition refers to the portion(s) of a composition that remain on the skin surface after a period of time, taking into account losses due to absorption into the skin, evaporation, perspiration, chemical reaction, incidental physical losses, and the like.

[00290] As used herein in reference to a tissue, “maximal load,” or “maximum load,” or “maximally loaded” refer to the maximal concentration of a compound in a tissue (*e.g.*, dermis or fat) during the dosing interval (*e.g.*, 24 hours). The concentration can be expressed in terms of mass of compound per mass of tissue, for example, ng of compound per mg of tissue. Alternatively, the concentration can be expressed in terms of mass of compound per cm^2 of skin surface area. The maximal concentration can be the maximum value observed in the course of *an vitro* or *in vivo* pharmacokinetic experiment, or can be the calculated maximum based on any generally accepted method of regression or pharmacokinetic modeling (*e.g.*, a nonlinear model).

[00291] In some embodiments, the maximal load is between about 0.01 nanograms (ng) and about 1000 nanograms (ng) of PFPPRA compound per milligram of tissue. In some embodiments, the maximal load is between about 0.01 ng and about 0.1 ng, about 0.01 ng and about 1 ng, about 0.01 ng and about 10 ng, about 0.01 ng and about 100 ng, about 0.1 ng and about 1 ng, about 0.1 ng and about 10 ng, about 0.1 ng and about 100 ng, about 1 ng and about 10 ng, about 1 ng and about 100 ng, about 10 ng and about 100 ng, about 10 ng and about 1000 ng, and about 100 ng and about 1000 ng of PFPPRA compound per milligram of tissue.

[00292] In some embodiments, the maximal load is between about 1 ng and about 100,000 ng of PFPPRA compound per cm^2 square of skin. In some embodiments, the maximal load is between about 1 ng and about 10 ng, about 1 ng and about 100 ng, about 1 ng and about 1000 ng, about 1 ng and about 10,000 ng, about 10 ng and about 100 ng, about 10 ng and about 1000 ng, about 1 ng and about 10,000 ng, about 100 ng and about 1000 ng, about 100 ng and about 10,000 ng, about 1000 ng and about 10,000 ng, about 1000 ng and about 100,000 ng, and about 10,000 ng and about 100,000 ng of PFPPRA per cm^2 of skin.

[00293] As used herein, the term “24-hour flux” (or interchangeably, “24-hour transcutaneous flux”) means the cumulative amount of a PFPPRA compound that crosses the skin and/or is detected in subcutaneous fat over the 24-hour period that commences upon application to the skin. In some cases, 24-hour flux can be determined or estimated by the amount of a PFPPRA compound (or metabolite thereof) that has crossed the skin (*e.g.*, into a serosal receptor compartment) in an *in vitro* or *ex vivo* skin permeation experiment (*e.g.*,

Franz cell); in subcutaneous fat in an *in vivo* experiment; or in blood (*e.g.*, plasma or serum) in an *in vivo* experiment. In some cases, 24-hour flux is determined or estimated by the area under a time-concentration curve. In some cases, 24-hour flux can be determined by use of chromatography, spectroscopy, immunoassay, or autoradiography. In some cases, 24-hour flux is normalized for the surface area of treated skin. In some cases, 24-hour flux is normalized for the dose, volume, and/or dose concentration of the composition. The skilled artisan will further appreciate that as the concept of 24-hour flux is particularly suitable for a 24-hour dose interval, the concept can be generalized for other dose intervals, *e.g.*, a 72-hour flux for a 72-hour dose interval.

[00294] In some embodiments, 24-hour flux is between about 0.01 micrograms (μg) and about 1000 micrograms (μg) of PFPPRA compound per cm^2 square of skin. In some embodiments, 24-hour flux is between about 0.01 μg and about 0.1 μg , about 0.01 μg and about 1 μg , about 0.01 μg and about 10 μg , about 0.01 μg and about 100 μg , about 0.1 μg to about 1 μg , about 0.1 μg and about 10 μg , about 0.1 μg and about 100 μg , about 1 μg and about 10 μg , about 1 μg and about 100 μg , about 10 μg and about 100 μg , about 10 μg and about 1000 μg , and about 100 μg and about 1000 μg of PFPPRA compound per cm^2 of skin.

[00295] In some embodiments wherein the area of treated skin is about 10 cm^2 and about 100 cm^2 , 24-hour flux is between about 0.1 μg and about 100,000 μg of PFPPRA compound. In some embodiments wherein the area of treated skin is about 10 and about 100 cm^2 , 24-hour flux is between about 0.1 μg and about 1 μg , about 0.1 μg and about 10 μg , about 0.1 μg and about 100 μg , about 0.1 μg and about 1,000 μg , about 0.1 μg and about 10,000 μg , about 1 μg and about 10 μg , about 1 μg and about 100 μg , about 1 μg and about 1000 μg , about 1 μg and about 10,000 μg , about 10 μg and about 100 μg , about 10 μg and about 1000 μg , about 10 μg and about 10,000 μg , about 10 μg and about 100,000 μg , about 100 μg and about 1000 μg , about 100 μg and about 10,000 μg , about 100 μg and about 100,000 μg , about 1000 μg and about 10,000 μg , about 1000 μg and about 100,000 μg , and about 10,000 μg and about 100,000 μg of PFPPRA compound.

[00296] In some embodiments, the composition is washed with water, and optionally with soap. In some embodiments, the composition is removed with the aid of a solvent. In some embodiments, the solvent comprises water, ethanol, and/or isopropanol. In some embodiments, the composition is removed mechanically. In some embodiments, composition is removed with the aid of an adhesive, tape (*e.g.*, by epidermal stripping), or scraper. In some embodiments, wherein the composition is delivered by use of a patch or dressing, the composition is removed by removing the patch or dressing.

[00297] Fat reduction can include reducing fat as measured by at least one of volume, size, mass, bulk, density, amount, and/or quantity. The present invention is expected to reduce fat by greater than or equal to 75%, greater than or equal to 70%, greater than or equal to 60%, greater than or equal to 50%, greater than or equal to 40%, greater than or equal to 30%, greater than or equal to 25%, greater than or equal to 20%, greater than or equal to 15%, greater than or equal to 10%, or greater than or equal to 5%. For example, fat reduction can also include reducing fat cell amount (for example, fat cell number), reducing fat cell volume, reducing fat cell maturation, and/or dedifferentiating a fat cell.

[00298] In certain embodiments, the body fat is local, *e.g.*, concentrated on the face, periorbital area, cheeks, chin, neck, chest, breast, abdomen, buttocks, hips, thighs, legs, and/or arms.

[00299] In some embodiments of any of the above aspects of the invention, the duration of skin surface exposure to the composition is between about 4 hours and about 12 hours per dose of the composition, or about 6 hours and about 10 hours per dose of the composition. For example, in certain embodiments, the composition is administered to the skin surface, and then the remainder of the composition is removed after 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, or 12 hours, after this application to the skin.

[00300] In any embodiment where the duration of skin surface exposure is described by an approximate range, *e.g.*, between about 4 hours and about 12 hours, a corresponding exact range can be used, *e.g.*, between 4 hours and 12 hours. Therefore, in some embodiments, the duration of skin surface exposure can be between 4 hours and 12 hours, between 4 hours and 8 hours, between 4 hours and 10 hours, or between 6 hours and 10 hours.

[00301] In certain embodiments of any of the above aspects of the invention, optionally wherein the dosing interval is about once per 24 hours, the dermis has more than 80% of maximal load within 4 to 12 hours after administration, *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration. In certain embodiments, this dermis has more than about more than about 75 percent, more than about 80 percent, more than about 85 percent, more than about 90 percent, or more than about 95 percent of the maximal load within 4 to 12 hours after administration, *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration. In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 70 percent of the maximal load has occurred, or is considered to have occurred based on prior experimental evidence.

[00302] In some embodiments wherein 24-hour flux is about 100 nanograms per cm² of skin, the step of removing comprises removing the composition or residue thereof from the

skin surface after more than about 60 to about 95 nanograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 100 nanograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 nanograms per cm^2 of flux have occurred.

[00303] In some embodiments wherein 24-hour flux is about 1 microgram per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 0.6 to about 0.95 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 1 microgram per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95 micrograms per cm^2 of flux have occurred.

[00304] In some embodiments wherein 24-hour flux is about 10 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6 to about 9.5 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 10 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, or about 9.5 micrograms per cm^2 of flux have occurred.

[00305] In some embodiments wherein 24-hour flux is about 100 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60 to about 95 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 100 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 micrograms per cm^2 of flux have occurred.

[00306] In certain embodiments of any of the above aspects of the invention, more than about 60 percent of the 24-hour flux occurs within 4 to 12 hours after administration, *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration. In certain embodiments, more than about 65 percent, more than about 70 percent, more than about 75 percent, more than about 80 percent, more than about 85 percent, more than about 90 percent, or more than about 95 percent of the 24-hour flux occurs within 1 to 12 hours after administration, *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration. In certain embodiments, the step of removing comprises removing the composition or residue thereof from the skin

surface after more than 60 percent of the 24-hour flux has occurred, or is likely to have occurred based on prior experimental evidence.

[00307] In some embodiments wherein 24-hour flux is about 10 nanograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6 to about 9.5 nanograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 10 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, or about 9.5 nanograms per cm^2 of flux have occurred.

[00308] In some embodiments wherein 24-hour flux is about 100 nanograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60 to about 95 nanograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 100 nanograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 nanograms per cm^2 of flux have occurred.

[00309] In some embodiments wherein 24-hour flux is about 1 microgram per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 0.6 to about 0.95 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 1 microgram per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95 micrograms per cm^2 of flux have occurred.

[00310] In some embodiments wherein 24-hour flux is about 10 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6 to about 9.5 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 10 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, or about 9.5 micrograms per cm^2 of flux have occurred.

[00311] In some embodiments wherein 24-hour flux is about 100 micrograms per cm^2 of skin, the step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60 to about 95 micrograms per cm^2 of flux have occurred. In some embodiments wherein 24-hour flux is about 100 micrograms per cm^2 of skin, the

step of removing comprises removing the composition or residue thereof from the skin surface after more than about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 micrograms per cm² of flux have occurred.

[00312] As used herein, unless otherwise defined by the context, the term “steady state” or “steady-state” means a condition in which the overall (*e.g.*, daily) penetration of a PFPPRA compound into subcutaneous fat is roughly in dynamic equilibrium with its removal from subcutaneous fat. Removal can occur, for example, by systemic absorption, (re)distribution into another compartment, and/or local metabolism to an inactive metabolite.

[00313] In certain embodiments, more than about 60 percent of steady-state exposure in subcutaneous fat is attributable to delivery of a PFPPRA within 4 to 12 hours after administration *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration. This is measured, for example, as the ratio of steady-state exposure in subcutaneous fat for 12 hours vs. 24 hours of skin surface exposure. In certain embodiments, more than about 65 percent, more than about 70 percent, more than about 75 percent, more than about 80 percent, more than about 85 percent, more than about 90 percent, or more than about 95 percent of steady-state exposure in subcutaneous fat is attributable to delivery of a PFPPRA within 4 to 12 hours after administration, *e.g.*, within 4, 5, 6, 7, 8, 9, 10, 11, or 12 hours after administration.

[00314] In some embodiments of any of the above aspects of the invention, the dose frequency is about once every 24 hours, about once every day, about once every 48 hours, about once every two days, about once every three days, about once every week, about once every two weeks, or about once every four weeks, or about once every month.

[00315] In some embodiments, steady-state in subcutaneous fat occurs after about 4 doses, about 5 doses, about 6 doses, about 7 doses, about 8 doses, about 9 doses, about 10 doses, about 15 doses, about 4 days, about 5 days, about 6 days, about 7 days, about 10 days, about 2 weeks, about 3 weeks, or about 1 month.

[00316] In some embodiments, treatment period is for about 1 weeks, about 2 weeks, about 3 weeks, about 4 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 18 months, about 2 years, or about 3 years. In some embodiments, treatment period continues indefinitely.

[00317] In some embodiments, a higher dose (“loading dose”) is administered at or around the beginning of a treatment period, compared to subsequent doses in the treatment period. In some embodiments, the loading dose is achieved by use of higher dose concentration,

higher dose volume, or higher dose frequency. In some embodiments, the loading dose is 1.5 times or greater than the subsequent dose(s), *e.g.*, between about 1.5 times to about 5 times the subsequent dose(s), *e.g.*, about 1.5 times, about 2 times, about 3 times, about 4 times, or about 5 times the subsequent dose(s).

Examples

[00318] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that these compositions may also consist essentially of, or consist of, the recited components. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously.

[00319] In light of the foregoing description, the specific non-limiting examples presented below are for illustrative purposes and not intended to limit the scope of the invention in any way.

Example 1

[00320] The following example describes a single-dose tissue pharmacokinetic experiment of topical latanoprost in minipigs. A composition comprising 0.8% latanoprost by weight was applied at different time points, each time to a separate but comparable application area on the back of an adult minipig. Twenty-four hours after the first dose, the animal was sacrificed and the skin was washed. Samples of skin, subcutaneous fat, and muscle were dissected *en bloc* from each application area and flash-frozen. Resulting fat samples were surface-washed with methanol, weighed, pulverized, resuspended, and homogenized. The content of latanoprost free acid (LFA, the active metabolite of latanoprost) in each sample was determined by an LC/MS/MS assay. The results are shown in Table 1.

Table 1.		
Composition	Time since dose (h)	LFA concentration in subcutaneous fat (nanomolar)
Latanoprost 0.8% in DMSO	1	15
	2	7
	3	8
	8	23
	24	7

[00321] Thus, in an animal model with skin and subcutaneous fat similar to those of a human, a biphasic LFA concentration curve was seen in subcutaneous fat, with peak

concentrations at about 8 hours after a single topical dose of latanoprost. Thus, most of the latanoprost to be delivered over a 24-hour period is delivered in the first 8 hours.

Example 2

[00322] Skin permeation studies were conducted with compositions of latanoprost, *ex vivo*, on fresh human skin. Skin was obtained from live donors undergoing abdominoplasty and mounted on a standard (Franz-type) diffusion cell apparatus. All test articles contained 0.8% latanoprost (by weight) and were applied uniformly to a skin surface of 0.8 cm². Each study was replicated on skin from at least two different donors. Treated skin was left open to the atmosphere to simulate clinical conditions. Receptor fluid flowed continuously over 24 hours and was collected in fractions. The amount of active drug metabolite (LFA) in these fractions was determined by Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS). Table 2 shows the relative amounts of LFA delivered at different time intervals for each formulation, *i.e.* the percentage of 24-hour flux that occurred in each time interval. [Ethanol formulation 1 consisted essentially of 27% propylene glycol and 3% oleic acid in a base of about 69% ethanol.

Table 2.			
Composition	0-4 hours	4-12 hours	12-24 hours
DMSO (experiment 1)	14%	69%	17%
DMSO (experiment 2)	4%	57%	39%
Ethanol formulation 1	6%	57%	36%

[00323] Thus, when DMSO- or ethanol-based compositions of latanoprost were applied to human skin *in vitro*, proportionately more permeation of latanoprost (and/or its active metabolite) occurred at initial application (0 hours) to about 12 hours compared to 12-24 hours after latanoprost administration. For DMSO-based formulations, about 61% to about 84% of the 24-hour flux occurred within 12 hours of application. For an ethanol-based formulation, about 63% of the 24-hour flux occurred within 12 hours of application.

Example 3

[00324] Skin permeation studies were conducted with a petroleum jelly composition of latanoprost, *ex vivo*, on fresh pig skin. The composition consisted essentially of 0.3% latanoprost, 5% isopropyl myristate, and 95% petroleum jelly. Skin was mounted on a standard (Franz-type) diffusion cell apparatus. All test articles were applied uniformly to a

skin surface of 0.8 cm². Each study was replicated on skin from at least two different donors. Treated skin was left open to the atmosphere to simulate clinical conditions. After 1, 2, 4 or 8 hours, the test articles were removed by wiping with a swab soaked in a soap-and-water solution, followed by wiping with a dry swab. After 24 hours, samples were removed from the diffusion cells, and the dermis was isolated. The amount of active drug metabolite (LFA) in each dermis samples was determined by Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS). Table 3 shows the results of this experiment.

Table 3.		
Time product removed (h)	Total drug (latanoprost plus LFA) (ng) in dermis	% maximal load
1	125	35%
2	253	71%
4	357	100%
8	344	96%

[00325] Thus, when a petroleum jelly-based composition of latanoprost was applied to skin *in vitro*, the dermis became fully loaded with drug (latanoprost or LFA) within 4 hours of skin contact.

Example 4

[00326] A randomized, placebo-controlled trial of topical latanoprost was conducted on male and female minipigs. Animals were randomized to no treatment, placebo (vehicle only), latanoprost 0.16%, or latanoprost 0.8% in an emulsion consisting essentially of water, poloxamer, lecithin, and isopropyl palmitate. The treatment was applied once daily to a 400 cm² area on the dorsum, with a semi-occlusive dressing. Treatment continued for 42 days. Animals received a full panel of local and systemic safety assessments over the course of the study. Plasma toxicokinetics (TK) were assessed at various timepoints. After 42 days of treatment, animals were sacrificed. Samples of skin and subcutaneous fat were dissected from the treatment area in a controlled fashion and submitted for microscopic examination by a veterinary pathologist who was not informed of the compound tested or its therapeutic purpose.

[00327] At steady state, TK showed a peak LFA plasma concentration at about 2 to 3 hours after latanoprost application. There was evidence of accumulation of latanoprost and/or LFA in subcutaneous fat, with a plasma exposure accumulation ratio (steady state vs. first dose) of about 5 to 6 at the 0.8% dose. Such accumulation does not occur in plasma (half-life in humans is about 17 minutes) and can only be explained by redistribution from

another tissue compartment. The methods of Example 1 were used to verify that substantial levels of LFA had in fact remained in subcutaneous fat after the 24-hours dose interval. The result was a mean concentration of 9600 nM at the 0.8% dose.

[00328] Dose-dependent depletion of subcutaneous fat was noted on microscopic examination of treated subcutaneous fat. Reduction of subcutaneous fat thickness was quantified using ImageJ software. In the high-dose group the mean reduction was 2.2 cubic centimeters of fat per 100 cm² of treated skin.

[00329] Thus, in a controlled trial of daily topical latanoprost in minipigs, there was evidence of peak latanoprost/LFA penetration at about 2-3 hours, accumulation and persistence of LFA in subcutaneous fat beyond 24 hours, and dose-dependent reduction of subcutaneous fat.

Example 5

[00330] A pharmacokinetic (PK) experiment was conducted on male and female minipigs (n = 6 per sex). Ointment comprising latanoprost 0.5% w/w in a vehicle comprising petroleum jelly and isopropyl myristate was applied once daily for 91 days to skin over 10% of body surface area. After the last topical application, plasma PK was assessed by sampling all animals through 24 hours, and in 2 animals per sex over for an additional 48 hours. Table 4 shows the results.

Table 4.	
Time after last dose (h)	Mean LFA concentration (pg/mL)
0	1260
24	932
48	255
72	186

[00331] The results at 24, 48, and 72 hours, which correspond to the elimination (beta) phase of the time-concentration curve, were fit to a first-order kinetic model, which indicated a surprisingly long terminal elimination half-life of about 18-24 hours. This result can be attributed to redistribution from subcutaneous fat and/or dermis. The result is in contrast to a half-life of about 9-17 minutes or about 17-85 minutes, respectively, for LFA after intravenous or ocular administration. (See Sjöquist B *et al.*, The pharmacokinetics of a new antiglaucoma drug, latanoprost, in the rabbit, *Drug Metabol Distribution* 1998;26:745-754; and Sjöquist B and Stjernschantz J, Ocular and systemic pharmacokinetics of latanoprost in humans, *Surv Ophthalmol* 2002;47:S6-S12).

Example 6

[00332] A randomized, double-blind, placebo-controlled trial of topical latanoprost applied to the submental area was conducted with adult men and women with excess submental fat. In one cohort, participants were randomized to receive latanoprost in an ethanol-based composition, or a matching placebo composition. In another cohort, participants were randomized to receive latanoprost in a petroleum jelly-based composition, or a matching placebo composition. The composition was applied at bedtime to a controlled 50 cm² area of submental skin. Participants were instructed to wash the 50 cm² area after 8-10 hours, so as to remove the composition. Treatment continued for 42 days. Topical latanoprost was well tolerated.

Example 7

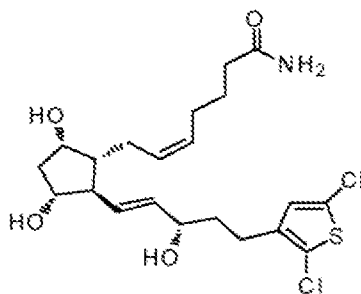
[00333] A kit is provided comprising a tube of a topical composition comprising a PFPFRA compound, *e.g.*, latanoprost, tafluprost, travoprost, or bimatoprost, for reducing subcutaneous fat, and instructions for use. The instructions for use comprise instructions to apply the composition in a thin film to a particular area of the body once nightly, *e.g.*, at bedtime, and to remove the gel, *e.g.*, by washing with soap and water, 6 to 10 hours after application.

Example 8

[00334] A randomized, double-masked, placebo-controlled trial of latanoprost ointment applied to lower eyelids was conducted with adult men and women with lower lid steatoblepharon, *i.e.*, eye bags. Participants received a kit comprising a tube of latanoprost ointment and instructions to apply the topical composition to the lower eyelids once nightly at bedtime. Participants were instructed to wash the lower eyelids 8-10 hours after ointment application, so as to remove the ointment or residue thereof. Treatment continued for 10 weeks. Latanoprost ointment was associated with statistically significant improvements in patient- and clinician-reported measures of eyelid fat volume, patient appearance, and patient satisfaction over the course of the study. The topical latanoprost composition was well tolerated.

Example 9

[00335] A topical composition comprising a compound of the formula:



(at a concentration between about 0.03% and about 3% w/w) and one or more pharmaceutically acceptable excipients (*e.g.*, water, ethanol, propylene glycol, petrolatum, mineral oil, white wax, isopropyl myristate, and/or diethylene glycol monoethyl ether), is administered once daily to an area of skin (*e.g.*, eyelid, face and/or submental region) on a patient for a period between about 1 to 6 months. After each administration the composition is removed after about 6 to 12 hours. It is contemplated that after 1 to 6 months of repeated administration, subcutaneous fat will be reduced at the site of administration.

Other Embodiments

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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. Latanoprost for use in reducing body fat, wherein the latanoprost is provided in a topical composition, and whereby the duration of skin surface exposure to the composition or residue thereof is between about 4 hours and about 12 hours, inclusive, per dose of the composition.
2. The use of claim 1, wherein the duration is between about 4 hours and about 10 hours, inclusive, per dose of the composition.
3. The use of claim 2, wherein the duration is between about 4 hours and about 8 hours, inclusive, per dose of the composition.
4. The use of claim 2, wherein the duration is between about 6 hours and about 10 hours, inclusive, per dose of the composition.
5. The use of claim 1 wherein the dose frequency is once every 24 hours.
6. The use of claim 1, wherein the body fat is eyelid fat.
7. The use of claim 1, wherein the topical composition is an ointment.
8. The use of claim 1, wherein the topical composition comprises petroleum jelly.
9. The use of claim 8, wherein the topical composition further comprises isopropyl myristate.
10. A method for locally reducing body fat in a subject in need thereof, the method comprising the steps of: administering a composition comprising latanoprost to the skin surface; and removing the composition or residue thereof from the skin surface between about 4 hours and about 12 hours, inclusive, after said administering.

11. The method of claim 10, wherein the removing is between about 4 hours and about 10 hours, inclusive, after said administering.
12. The method of claim 11, wherein the removing is between about 4 hours and about 8 hours, inclusive, after said administering.
13. The method of claim 11, wherein the removing is between about 6 hours and about 10 hours, inclusive, after said administering.
14. The method of claim 10, wherein more than about 60 percent of the 24-hour flux of latanoprost or an active metabolite thereof occurs within 4 to 12 hours, inclusive, after the step of administering, and wherein the step of removing is after more than about 60 percent of the 24-hour flux has occurred.
15. The method of claim 10, wherein the dermis is fully loaded with latanoprost, an active metabolite thereof, or a combination thereof, within 4 to 12 hours, inclusive, after the administering, and wherein the step of removing is after the dermis is fully loaded.
16. The method of claim 10, wherein the dose frequency is once every 24 hours.
17. The method of claim 10, wherein the body fat is eyelid fat.
18. The method of claim 10, wherein the composition is an ointment.
19. The method of claim 10, wherein the composition comprises petroleum jelly.
20. The use of claim 19, wherein the topical composition further comprises isopropyl myristate.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/037323

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/5575 A61K9/00 A61K9/06 A61K47/06 A61K47/14 A61P27/00 A61P43/00 ADD.		
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) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/099942 A2 (TERAKINE THERAPEUTICS INC) 26 July 2012 (2012-07-26) cited in the application paragraphs [0294], [0354] - [0360]; examples 2, 3, 7 examples 5-6	1-20
X	WO 2007/111806 A2 (MASSACHUSETTS EYE & EAR INFIRM [US]; GROSSKREUTZ CYNTHIA L [US]; PASQU) 4 October 2007 (2007-10-04) cited in the application claims 1, 5, 34, 41-44; examples 3, 8	1-20
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 4 August 2015		Date of mailing of the international search report 12/08/2015
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Madalinska, K

INTERNATIONAL SEARCH REPORT

Information on patent family members

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