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(54) Title: GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR MODULATORS AND USES THEREOF IN REGULATING BLOOD GLUCOSE LEVELS

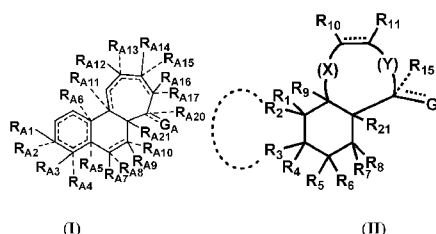
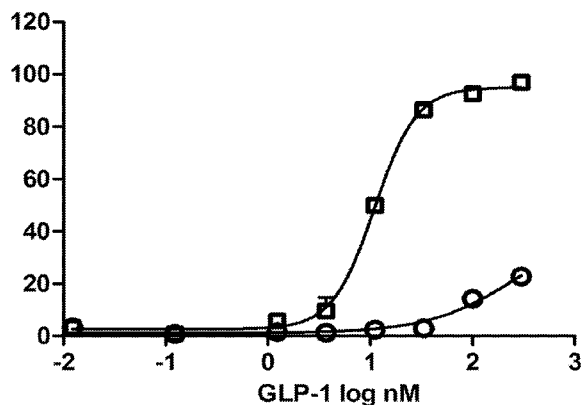


Fig. 1



(57) Abstract: The present disclosure provides novel glucagon-like peptide-1 (GLP-1) receptor modulators such as compounds of Formula (I) or (II), and pharmaceutically acceptable salts thereof. The present disclosure also provides pharmaceutical compositions, kits, and uses that involve the GLP-1 receptor modulators for regulating blood glucose levels and/or treating diabetes via, e.g., modulating the endogenous signaling pathways mediated by the GLP-1 receptor.



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GLUCAGON-LIKE PEPTIDE 1 (GLP-1) RECEPTOR MODULATORS AND USES THEREOF IN REGULATING BLOOD GLUCOSE LEVELS

RELATED APPLICATIONS

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent applications, 61/827,674, filed May 27, 2013 and 61/839,870, filed June 27, 2013, the entire content of each of which is incorporated by reference herein.

BACKGROUND

[0002] Type II diabetes is characterized by decrease in peripheral tissue response to insulin in association with impaired cell function, which results in increase in fasting glycemia (1,2). Currently antihyperglycemic drugs such as metformin, sulfonylureas, or thiazolidinediones have been prescribed to promote insulin secretion or enhance insulin sensitivity, these drugs do not target all of the symptoms of type II DM (3,4). Incretin hormones (*e.g.*, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide GIP) are intestinally derived hormones that stimulate cAMP production via their cognate receptors in pancreatic β cells and subsequently leads to glucose dependent insulin secretion in response to food intake, play an important role in glucose homeostasis (5). Apart from its insulinotropic effects, GLP-1 also preserves pancreatic cells, suppresses glucagon release, reduces hepatic gluconeogenesis, it delays gastric emptying, reduces food intake by promoting satiety and reveals a favorable cardiometabolic profile (6-9). GLP-1 also displays extra-pancreatic effects, notably targeting the brain, immune system and heart, where it plays a role in neuroprotection (10-13), regulating immune responses (14-16) and cardioprotection (17 - 19). All these physiological actions of GLP-1 are mediated via interaction with its cognate G-protein coupled receptor – GLP-1 receptor on the target tissues. However, the exact downstream signaling of these extra-pancreatic physiological actions of GLP-1 still needed further investigation.

[0003] GPCR (G protein-coupled receptor) signaling machinery was once considered as operating in an one-dimensional way, now has been proved to signal through several distinct mechanisms including those mediated by G proteins and by G-protein independent multifunctional adaptor proteins β -arrestins. In addition to heterotrimeric G proteins, two protein families specifically interact with the majority of GPCRs in their activated conformation: G protein-coupled receptor kinases (GRKs) and β -arrestins (20). GRKs and β -arrestins are considered to be G protein-independent signal transducers (20-22). In particular,

β -arrestins act as multifunctional scaffolds that interact with many protein partners (23) and protein kinases, thereby leading to the phosphorylation of numerous intracellular targets (24). Distinct selective coupling pathway will elicit quite distinct physiologic outcome and this finding has currently impacted further on the development of assay technology and search for pathway selective GPCR drug (25-28). Indeed, multi-pathway screening of against u-opioid receptor (29) and agonist for parathyroid hormone receptor (25) lead to discovery of compounds that provide therapeutic effect without the adverse side effects normally associated with these receptors, support the notion that pathway selective (biased) agonists may identify new classes of therapeutic agents that have fewer side effects. Though the insulinotropic effect of GLP-1 is mediated by stimulating cAMP generation in pancreatic cells via coupling to $G_{\alpha s}$, other effects of GLP-1 have been shown to be mediated via coupling to β -arrestin. GLP-1 anti-apoptotic effect on pancreatic β -cells has been shown to be mediated by phosphorylating the pro-apoptotic protein Bad through β -arrestin1 dependent ERK1/2 activation (30). β -Arrestin1-mediated recruitment of c-Src is involved in proliferative action of GLP-1 on pancreatic β -cells (31). It will be interesting to know other extrapancreatic function of GLP-1 will be also mediated by arrestin coupling and it will be more straightforward to use pathway selective compounds to correlate cellular responses to specific signaling pathway. However, pathway selective compound is rarely available for GLP-1 receptor signaling.

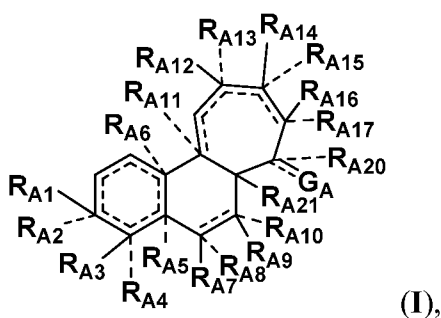
[0004] Current GLP-1 analogue therapeutics requires frequent subcutaneous administrations, and leads to reduced compliance and high prices in developing area. Typically, the plasma level of active GLP-1 is around 5 to 10 pM in the basal state, quickly rises to 20 to 50 pM after oral glucose or meal and will slowly declines to basal level over 2 hours (32 - 34). However, GLP-1 analogue therapeutics usually require to maintain constantly a supra-physiological level of GLP-1 analogues, thus lead to activating GLP-1 receptors constitutively and may cause severe complications upon chronic treatment (35-42).

[0005] Identification of novel compounds that modulate the endogenous GLP-1 receptor signaling pathways can lead to the development of new therapeutics useful in regulating blood glucose levels, thereby treating diabetes or disorders associated with the GLP-1 receptor.

SUMMARY

[0006] This present disclosure is based on the discovery of novel GLP-1 receptor modulators (*e.g.*, compounds of Formula (I) or (II), as being capable of modulating the endogenous glucagon-like peptide-1 (GLP-1) receptor signaling pathways and thus, may be useful in regulating blood glucose levels and/or treating diabetes and other disorders associated with the GLP-1 receptor. Accordingly, the present disclosure features GLP-1 receptor modulators such as compounds of Formula (I) or (II), or pharmaceutically acceptable salts thereof, and methods of using such compounds for regulating blood glucose levels and/or treating diabetes.

[0007] In one aspect, the GLP-1 receptor modulators described herein are compounds of Formula (I):



and pharmaceutically acceptable salts thereof, wherein:

GA is hydrogen, =O, =S, -OR'', -SR'', -N(R'')₂, alkenyl, alkynyl, an amide group, an ester group, a phosphate group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, wherein each instance of R'' is independently hydrogen, a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

RA1, RA2, RA3, RA4, RA5, RA6, RA7, RA8, RA9, and RA10 are each independently hydrogen, halogen, -OR'', -N(R'')₂, a carboxyl group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbons, or RA1 and RA2 are joined to form =O, or RA3 and RA4 are joined to form alkenyl;

RA11, RA13, RA15, and RA17 are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R_{A12} , R_{A14} , and R_{A16} are each independently halogen, $-N(R'')_2$, $-SR''$, $-OR''$, alkyl, alkenyl, alkynyl, an amide group, a carboxyl group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a urea group, a carbamate group, or a thiocarbamate group, or R_{A14} and R_{A15} are joined to form $=O$ or $=S$;

R_{A20} is hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms; and

R_{A21} is hydrogen, halogen, $-N(R'')_2$, $-SR''$, $-OR''$, $-CH_2OR''$, alkyl, alkenyl, alkynyl, an amide group, a carboxyl group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms.

[0008] All compounds described herein include the compounds themselves, as well as their salts and stereoisomers, if applicable. The salts, for example, can be formed between a positively charged substituent (*e.g.*, amino) on a compound and an anion. Suitable anions include, but are not limited to, chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, and acetate. Likewise, a negatively charged substituent (*e.g.*, carboxylate) on a compound can form a salt with a cation. Suitable cations include, but are not limited to, sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion.

[0009] In certain embodiments, a salt described herein is a pharmaceutically acceptable salt. The term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (*e.g.*, a human or non-human animal) without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds described herein include those derived from suitable inorganic and organic acids and bases. In certain embodiments, a pharmaceutically acceptable salt can be a salt described herein.

[0010] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or

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

[0011] In a formula, ===== is a single or double bond, and ----- is absent (and therefore any substituent attached thereto is also absent) or a single bond.

[0012] Unless otherwise specified, a moiety described herein may be unsubstituted or may be substituted (*e.g.*, at least one hydrogen atom of the moiety being replaced with a non-hydrogen atom or group). When a group described herein is substituted, the group may be substituted, as valency permits, with one or more substituents independently selected from the group consisting of C₁₋₆ alkyl (*e.g.*, unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, or butyl) or substituted C₁₋₆ alkyl (*e.g.*, -CF₃, -CH₂-CF₃, or -C₂F₅)), -OR^{al} (*e.g.*, -OH, -OMe, or -OEt), -N(R^{al})₂ (*e.g.*, -NH₂, -NHMe, or -NMe₂), -SR^{al} (*e.g.*, -SH or -SMe), =O, =S, -CHO, -C(=O)N(R^{al})₂ (*e.g.*, -C(=O)NH₂, -C(=O)NHMe, or -C(=O)NMe₂), -CN, -C(=O)OR^{al} (*e.g.*, -C(=O)OH, -C(=O)OMe, or -C(=O)OEt), -OC(=O)R^{bl} (*e.g.*, -OC(=O)Me, -OC(=O)Et, or -OC(=O)(CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃), -OC(=O)OR^{al} (*e.g.*, -OC(=O)OMe, -OC(=O)OEt, or -OC(=O)O(CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃), -C(R^{bl})₂OR^{al} (*e.g.*, -CH₂-OH or -CH₂-OMe), -C(R^{bl})₂SR^{al} (*e.g.*, -CH₂-SH or -CH₂-SMe), -C(R^{bl})₂N(R^{al})₂ (*e.g.*, -CH₂-NH₂, -CH₂-NHMe, or -CH₂-NMe₂), and -C(R^{bl})₂OC(=O)OR^{al} (*e.g.*, -CH₂-OC(=O)OMe, -CH₂-OC(=O)OEt, or -CH₂-OC(=O)O(CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃)), wherein each instance of R^{al} is independently H, C₁₋₆ alkyl (*e.g.*, unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, or butyl) or substituted C₁₋₆ alkyl (*e.g.*, -CF₃, -CH₂-CF₃, or -C₂F₅)), C₂₋₆ alkenyl (*e.g.*, unsubstituted C₂₋₆ alkenyl (*e.g.*, vinyl)), 3- to 10-membered cycloalkyl (*e.g.*, unsubstituted 3- to 10-membered cycloalkyl (*e.g.*, cyclopropyl)), or 6- to 10-membered aryl (*e.g.*, phenyl (*e.g.*, unsubstituted phenyl or substituted phenyl)), and each instance of R^{bl} is independently H,

halogen (*e.g.*, F, Cl, Br, or I (iodine)), C₁₋₆ alkyl (*e.g.*, unsubstituted C₁₋₆ alkyl (*e.g.*, methyl, ethyl, propyl, or butyl) or substituted C₁₋₆ alkyl (*e.g.*, –CF₃, –CH₂–CF₃, or –C₂F₅)), C₂₋₆ alkenyl (*e.g.*, unsubstituted C₂₋₆ alkenyl (*e.g.*, vinyl)), 3- to 10-membered cycloalkyl (*e.g.*, unsubstituted 3- to 10-membered cycloalkyl (*e.g.*, cyclopropyl)), or 6- to 10-membered aryl (*e.g.*, phenyl (*e.g.*, unsubstituted phenyl or substituted phenyl)).

[0013] 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.

[0014] The term “(hetero)aliphatic” refers to aliphatic or heteroaliphatic. The term “aliphatic” refers to alkyl, alkenyl, alkynyl, and carbocyclic groups. The term “heteroaliphatic” refers to heteroalkyl, heteroalkenyl, heteroalkynyl, and heterocyclic groups.

[0015] The term “alkyl” refers to a radical of a straight-chained (“unbranched”) or branched, saturated, hydrocarbon group. In some embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ 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).

[0016] The term “alkenyl” refers to a radical of a straight-chained or branched hydrocarbon group having one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 double bonds). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ 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 C₂₋₆ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), and hexenyl (C₆).

[0017] The term “alkynyl” refers to a radical of a straight-chained or branched hydrocarbon group having one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 triple bonds). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ 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 C₂₋₆ alkynyl groups include ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), and hexynyl (C₆).

[0018] “Heteroalkyl” refers to an alkyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal

position(s) of the parent chain. In some embodiments, a heteroalkyl group is a saturated group having 1 to 16 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₃ alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted or substituted with one or more substituents.

[0019] “Heteroalkenyl” refers to an alkenyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In some embodiments, a heteroalkenyl group has 2 to 16 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₆ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkenyl”). In some embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₃ alkenyl”). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted or substituted with one or more substituents.

[0020] “Heteroalkynyl” refers to an alkynyl group as defined herein which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In some embodiments, a heteroalkynyl group has 2 to 16 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₁₆ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₆ alkynyl”). In some embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 or more heteroatoms within the parent chain (“heteroC₂₋₃ alkynyl”). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted or substituted with one or more substituents.

[0021] “Carbocyclyl,” “carbocycle,” 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 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or contain a fused, bridged, or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”). Carbocyclyl can be saturated, and saturated carbocyclyl is referred to as “cycloalkyl.” In some embodiments, carbocyclyl is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₅). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃₋₁₀ cycloalkyl. Carbocyclyl can be partially unsaturated. Carbocyclyl including one or more C=C double bond in the carbocyclic ring is referred to as “cycloalkenyl.” Carbocyclyl including one or more C≡C triple bond in

the carbocyclic ring is referred to as “cycloalkynyl.” Carbocyclyl includes aryl.

“Carbocyclyl” also includes ring systems wherein the carbocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclic ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C₃₋₁₀ carbocyclyl.

[0022] “Heterocyclyl,” “heterocycle,” or “heterocyclic” refers to a radical of a 3– to 10–membered non–aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3–10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged, or spiro ring system, such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated (“heterocycloalkyl”) or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. Heterocyclyl includes heteroaryl. Heterocyclyl also includes ring systems wherein the heterocyclic ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclic ring, or ring systems wherein the heterocyclic ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclic ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclic ring system. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3–10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3–10 membered heterocyclyl.

[0023] In some embodiments, a heterocyclyl group is a 5–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“5–10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5–8 membered

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

[0024] Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, aziridinyl, oxiranyl, and thiiranyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0025] “Aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 pi electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C_{6–14} aryl. In certain embodiments, the aryl group is substituted C_{6–14} aryl.

[0026] “Aralkyl” is a subset of alkyl and aryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group. In certain embodiments, the aralkyl is optionally substituted benzyl. In certain embodiments, the aralkyl is benzyl. In certain embodiments, the aralkyl is optionally substituted phenethyl. In certain embodiments, the aralkyl is phenethyl.

[0027] “Aralkenyl” is a subset of alkenyl and aryl, as defined herein, and refers to an optionally substituted alkenyl group substituted by an optionally substituted aryl group. An example of aralkenyl is styrenyl (*i.e.*, $-\text{CH}=\text{CHPh}$).

[0028] “Aralkynyl” is a subset of alkynyl and aryl, as defined herein, and refers to an optionally substituted alkynyl group substituted by an optionally substituted aryl group.

[0029] “Heteroaryl” refers to a radical of a 5–10 membered monocyclic or bicyclic $4n+2$ aromatic ring system (*e.g.*, having 6 or 10 pi electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such

instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0030] In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–10 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–8 membered heteroaryl"). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5–6 membered heteroaryl"). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted heteroaryl") or substituted (a "substituted heteroaryl") with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

[0031] Exemplary 5–membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5–membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5–membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and

thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiopinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0032] The term “oxo” refers to the a moiety of the formula: =O.

[0033] The term “amide” or “amide group” refers to a moiety of the formula: –
 $N(R^{pp})C(=O)R^{qq}$, wherein R^{pp} is a nitrogen atom substituent described herein, and R^{qq} is a carbon atom substituent described herein.

[0034] The term “ester” or “ester group” refers to a moiety of the formula: – $C(=O)OR^{rr}$ or –
 $OC(=O)R^{rr}$, wherein R^{rr} is an oxygen atom substituent described herein.

[0035] The term “phosphate” or “phosphate group” refers to a moiety of the formula: –
 $OP(=O)(OR^{oo})_2$, wherein each instance of R^{oo} is independently an oxygen atom substituent described herein or a cationic counterion.

[0036] The term “carboxyl” or “carboxyl group” refers to a moiety of the formula: –
 $C(=O)OH$.

[0037] The term “aldehyde” or “aldehyde group” refers to a moiety of the formula: –
 $C(=O)H$.

[0038] The term “thialdehyde” or “thialdehyde group” refers to a moiety of the formula: –
 $C(=S)H$.

[0039] The term “nitrile” or “nitrile group” refers to a moiety of the formula: –CN or –L–CN, wherein L is substituted or unsubstituted, branched or unbranched, C_{1-16} alkylene; substituted or unsubstituted, branched or unbranched, C_{2-16} alkenylene; or substituted or unsubstituted, branched or unbranched, C_{2-16} alkynylene.

[0040] The term “alcohol,” “alcohol group,” “hydroxyl,” or “hydroxy” refers to the group –OH. The term “substituted hydroxyl” or “substituted hydroxyl” refers to a hydroxyl group wherein the oxygen atom directly attached to the parent molecule is substituted with a group other than hydrogen, and includes groups selected from

–OR^{aa}, –ON(R^{bb})₂, –OC(=O)SR^{aa}, –OC(=O)R^{aa}, –OCO₂R^{aa}, –OC(=O)N(R^{bb})₂, –OC(=NR^{bb})R^{aa}, –OC(=NR^{bb})OR^{aa}, –OC(=NR^{bb})N(R^{bb})₂, –OS(=O)R^{aa}, –OSO₂R^{aa}, –OSi(R^{aa})₃, –OP(R^{cc})₂, –OP(R^{cc})₃, –OP(=O)₂R^{aa}, –OP(=O)(R^{aa})₂, –OP(=O)(OR^{cc})₂, –OP(=O)₂N(R^{bb})₂, and –OP(=O)(NR^{bb})₂, wherein R^{aa}, R^{bb}, and R^{cc} are as defined herein.

[0041] The term “amino” or “amino group” refers to a moiety of the formula: –N(Rⁱⁱ)₂, wherein each instance of Rⁱⁱ is independently a nitrogen atom substituent described herein, or two instances of Rⁱⁱ are connected to form substituted or unsubstituted heterocyclyl. In certain embodiments, the amino is unsubstituted amino (*i.e.*, –NH₂). In certain embodiments, the amino is a substituted amino group, wherein at least one instance of Rⁱⁱ is not hydrogen.

[0042] The term “imino” or “imino group” refers to a moiety of the formula: =NR^{ss}, wherein R^{ss} is a nitrogen atom substituent described herein.

[0043] The term “ketone” or “ketone group” refers to a moiety of the formula: –C(=O)R^{tt}, wherein R^{tt} is a carbon atom substituent described herein.

[0044] The term “thione” or “thione group” refers to a moiety of the formula: –C(=S)R^{uu}, wherein R^{uu} is a carbon atom substituent described herein.

[0045] The term “isonitrile” or “isonitrile group” refers to a moiety of the formula: –NC.

[0046] The term “isothiocyanide” or “isothiocyanide group” refers to a moiety of the formula: –SNC.

[0047] The term “thioate” or “thioate group” refers to a moiety of the formula: –C(=O)SR^{zz} or –C(=S)OR^{jj}, wherein R^{zz} is a sulfur atom substituent described herein, and R^{jj} is an oxygen atom substituent described herein.

[0048] The term “thioamide” or “thioamide group” refers to a moiety of the formula: –N(R^{mm})C(=S)Rⁿⁿ, wherein R^{mm} is a nitrogen atom substituent described herein, and Rⁿⁿ is a carbon atom substituent described herein.

[0049] The term “dithioate” or “dithioate group” refers to a moiety of the formula: –C(=S)SR^{kk}, wherein R^{kk} is a sulfur atom substituent described herein.

[0050] The term “isocyanato” or “isocyanato group” refers to a moiety of the formula: –NCO.

[0051] The term “isothiocyanato” or “isothiocyanato group” refers to a moiety of the formula: $-\text{NCS}$.

[0052] The term “carbamate” or “carbamate group” refers to a moiety of the formula: $-\text{N}(\text{R}^{\text{vv}})\text{C}(=\text{O})\text{OR}^{\text{ww}}$ or $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{vv}})_2$, wherein each instance of R^{vv} is independently a nitrogen atom substituent described herein, and R^{ww} is an oxygen atom substituent described herein.

[0053] The term “urea” or “urea group” refers to a moiety of the formula: $-\text{N}(\text{R}^{\text{zl}})\text{C}(=\text{O})\text{N}(\text{R}^{\text{zl}})_2$, wherein each instance of R^{zl} is independently a nitrogen atom substituent described herein.

[0054] The term “thiocarbamate” or “thiocarbamate group” refers to a moiety of the formula: $-\text{N}(\text{R}^{\text{vv}})\text{C}(=\text{S})\text{OR}^{\text{ww}}$ or $-\text{OC}(=\text{S})\text{N}(\text{R}^{\text{vv}})_2$, $-\text{N}(\text{R}^{\text{vv}})\text{C}(=\text{O})\text{SR}^{\text{yy}}$ or $-\text{SC}(=\text{O})\text{N}(\text{R}^{\text{vv}})_2$, wherein each instance of R^{vv} is independently a nitrogen atom substituent described herein, R^{ww} is an oxygen atom substituent described herein, and R^{yy} is a sulfur atom substituent described herein.

[0055] “Halo” or “halogen” refers to fluorine (fluoro, F), chlorine (chloro or Cl), bromine (bromo or Br), or iodine (iodo or I).

[0056] An atom, moiety, or group described herein may be unsubstituted or substituted, as valency permits, unless otherwise expressly provided. The term “substituted” refers to that at least one hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety. In certain embodiments, the substituent is a carbon atom substituent. In certain embodiments, the substituent is a nitrogen atom substituent. In certain embodiments, the substituent is an oxygen atom substituent. In

certain embodiments, the substituent is a sulfur atom substituent. In certain embodiments, a substituent may contribute to optical isomerism and/or stereo isomerism of a compound.

[0057] Exemplary carbon atom substituents include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; or two geminal hydrogens on a carbon atom are replaced with the group $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$,

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

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

heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{ee} is, independently, selected from hydrogen, 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^{ee} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups; each instance of R^{dd} is, independently, selected from halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OR^{ee}, -ON(R^{ff})₂, -N(R^{ff})₂, -N(R^{ff})₃⁺X⁻, -N(OR^{ee})R^{ff}, -SH, -SR^{ee}, -SSR^{ee}, -C(=O)R^{ee}, -CO₂H, -CO₂R^{ee}, -OC(=O)R^{ee}, -OCO₂R^{ee}, -C(=O)N(R^{ff})₂, -OC(=O)N(R^{ff})₂, -NR^{ff}C(=O)R^{ee}, -NR^{ff}CO₂R^{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, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form =O or =S;

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

each instance of R^{ff} is, independently, selected from hydrogen, C₁₋₆ alkyl, C₁₋₆ perhaloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3-10 membered heterocyclyl, C₆₋₁₀ aryl and 5-10 membered heteroaryl, or two R^{ff} groups are joined to form a 3-14 membered heterocyclyl or 5-14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, -CN, -NO₂, -N₃, -SO₂H, -SO₃H, -OH, -OC₁₋₆ alkyl, -ON(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₂, -N(C₁₋₆ alkyl)₃⁺X⁻, -NH(C₁₋₆ alkyl)₂⁺X⁻, -NH₂(C₁₋₆ alkyl)⁺X⁻, -NH₃⁺X⁻, -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), $-\text{OC}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{OCO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{OC}(=\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{N}(\text{C}_{1-6} \text{ alkyl})\text{C}(=\text{O})(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHCO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{NHC}(=\text{O})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{NHC}(=\text{O})\text{NH}_2$, $-\text{C}(=\text{NH})\text{O}(\text{C}_{1-6} \text{ alkyl})$, $-\text{OC}(=\text{NH})(\text{C}_{1-6} \text{ alkyl})$, $-\text{OC}(=\text{NH})\text{OC}_{1-6} \text{ alkyl}$, $-\text{C}(=\text{NH})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{C}(=\text{NH})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(=\text{NH})\text{NH}_2$, $-\text{OC}(=\text{NH})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{OC}(\text{NH})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{OC}(\text{NH})\text{NH}_2$, $-\text{NHC}(\text{NH})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{NHC}(=\text{NH})\text{NH}_2$, $-\text{NH}\text{SO}_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{SO}_2\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{SO}_2\text{NH}_2$, $-\text{SO}_2\text{C}_{1-6} \text{ alkyl}$, $-\text{SO}_2\text{OC}_{1-6} \text{ alkyl}$, $-\text{OSO}_2\text{C}_{1-6} \text{ alkyl}$, $-\text{SOC}_{1-6} \text{ alkyl}$, $-\text{Si}(\text{C}_{1-6} \text{ alkyl})_3$, $-\text{OSi}(\text{C}_{1-6} \text{ alkyl})_3$, $-\text{C}(=\text{S})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{C}(=\text{S})\text{NH}(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(=\text{S})\text{NH}_2$, $-\text{C}(=\text{O})\text{S}(\text{C}_{1-6} \text{ alkyl})$, $-\text{C}(=\text{S})\text{SC}_{1-6} \text{ alkyl}$, $-\text{SC}(=\text{S})\text{SC}_{1-6} \text{ alkyl}$, $-\text{P}(=\text{O})_2(\text{C}_{1-6} \text{ alkyl})$, $-\text{P}(=\text{O})(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{OP}(=\text{O})(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{OP}(=\text{O})(\text{OC}_{1-6} \text{ alkyl})_2$, $\text{C}_{1-6} \text{ alkyl}$, $\text{C}_{1-6} \text{ perhaloalkyl}$, $\text{C}_{2-6} \text{ alkenyl}$, $\text{C}_{2-6} \text{ alkynyl}$, $\text{C}_{3-10} \text{ carbocyclyl}$, $\text{C}_{6-10} \text{ aryl}$, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form $=\text{O}$ or $=\text{S}$; wherein X^- is a counterion.

[0058] A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, F^- , Cl^- , Br^- , I^-), NO_3^- , ClO_4^- , OH^- , H_2PO_4^- , HSO_4^- , sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, and glycolate).

[0059] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quaternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{cc}})_2$, $\text{C}_{1-10} \text{ alkyl}$, $\text{C}_{1-10} \text{ perhaloalkyl}$, $\text{C}_{2-10} \text{ alkenyl}$, $\text{C}_{2-10} \text{ alkynyl}$, $\text{C}_{3-10} \text{ carbocyclyl}$, 3–14 membered heterocyclyl, $\text{C}_{6-14} \text{ aryl}$, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are as defined herein.

[0060] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0061] For example, nitrogen protecting groups 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'*-dithiobenzyloxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine derivative, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0062] Nitrogen protecting groups also 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, alkyldithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacrylvinyl 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.

[0063] Nitrogen protecting groups further 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 phenacysulfonamide.

[0064] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethyleneamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethyleneamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethyleneamine, *N*-[(2-pyridyl)mesityl]methyleneamine, *N*-(*N'*,*N'*-dimethylaminomethylene)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[0065] Exemplary oxygen atom substituents include, but are not limited to, $-R^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc}

are as defined herein. In certain embodiments, the oxygen atom substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference. Exemplary oxygen protecting groups include, but are not limited to, methyl, *t*-butyloxycarbonyl (BOC or Boc), methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydriyl, 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-benzodisulfuran-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), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate, alkyl allyl carbonate, alkyl *p*-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl *o*-nitrobenzyl carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate, *o*-(methoxyacyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0066] Exemplary sulfur atom substituents include, but are not limited to, $-R^{aa}$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. In certain embodiments, the sulfur atom substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0067] In certain embodiments, G_A can be hydrogen, =O, =S, $-OR''$, $-SR''$, $-NR''H$, alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group,

a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, wherein each instance of R'' can be independently hydrogen, a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

R_{A1}, R_{A2}, R_{A3}, R_{A4}, R_{A5}, R_{A6}, R_{A7}, R_{A8}, R_{A9}, and R_{A10} can each independently be hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbons;

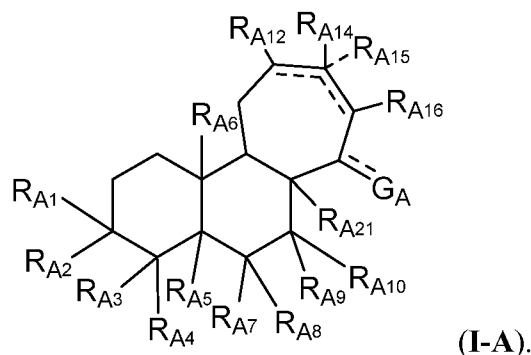
R_{A11}, R_{A12}, R_{A13}, R_{A15}, R_{A16}, and R_{A17} can each independently be hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R_{A14} can be halogen, -NR''H, -SR'', -OR'', alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, or a thiocarbamate group;

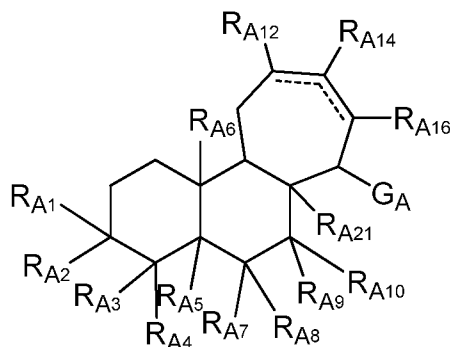
R_{A20} can be hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms; and

R_{A21} can be hydrogen, halogen, -NR''H, -SR'', -OR'', alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms.

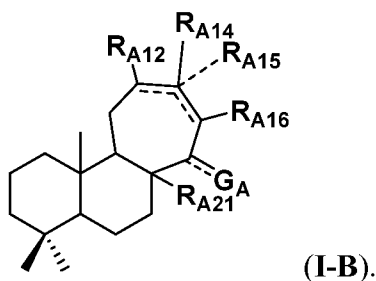
[0068] In certain embodiments, a compound of Formula (I) can be of Formula (I-A):



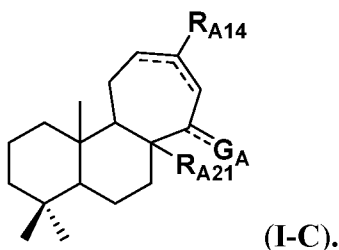
[0069] In certain embodiments, a compound of Formula (I) can be of the formula:



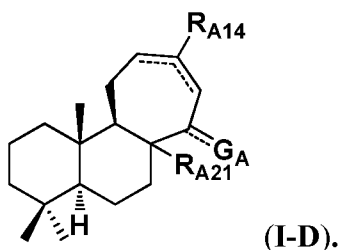
[0070] In certain embodiments, a compound of Formula (I) can be of Formula (I-B):



[0071] In certain embodiments, a compound of Formula (I) can be of Formula (I-C):



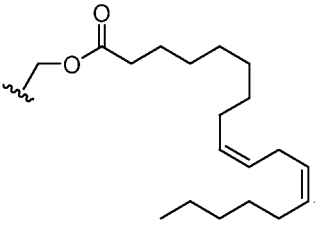
[0072] In certain embodiments, a compound of Formula (I) can be of Formula (I-D):



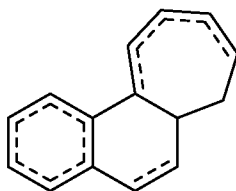
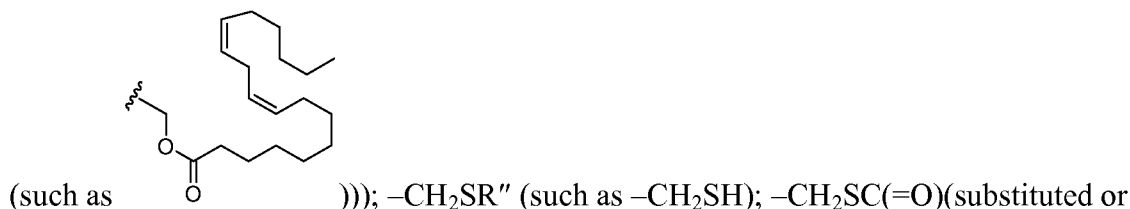
[0073] In certain embodiments, G_A can be hydrogen. In certain embodiments, G_A can be $=O$, $=S$, $-SR''$, $-OR''$, $-N(R'')_2$, $-OH$, $-SH$, or $-NH_2$. In certain embodiments, G_A can be $=O$. In certain embodiments, G_A can be $-OR''$ (e.g., $-OH$, $-O$ (substituted or unsubstituted C_{1-6} alkyl), or $-OC(=O)$ (substituted or unsubstituted C_{1-6} alkyl)). In certain embodiments, G_A can be $=S$. In certain embodiments, G_A can be $-SR''$ (e.g., $-SH$). In certain embodiments, G_A can be $-N(R'')_2$, $-NHR''$ (such as $-NH$ (substituted or unsubstituted C_{1-6}

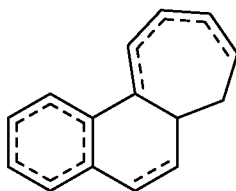
alkyl) or $\text{-NHC(=O)(substituted or unsubstituted } C_{1-6} \text{ alkyl))}$, or -NH_2 . In certain embodiments, G_A can be an alkenyl (e.g., acyclic, substituted or unsubstituted, C_{1-6} alkenyl, such as $\text{=CHC(=O)O(substituted or unsubstituted } C_{1-6} \text{ alkyl))}$. In certain embodiments, G_A can be a phosphate group (e.g., $\text{-OP(=O)(acyclic, substituted or unsubstituted, } C_{1-6} \text{ alkyl)}_2$). In certain embodiments, R_{A1} can be hydrogen. In certain embodiments, R_{A1} can be halogen. In certain embodiments, R_{A1} can be an acyclic, substituted or unsubstituted, branched or unbranched, aliphatic group having 1 to 6 carbons (e.g., acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (such as -CF_3)). In certain embodiments, R_{A1} can be -OR'' (e.g., -OH). In certain embodiments, R_{A1} can be -N(R'')_2 (e.g., -NMe_2). In certain embodiments, R_{A2} can be hydrogen. In certain embodiments, R_{A1} and R_{A2} can be joined to form =O . In certain embodiments, R_{A3} can be hydrogen. In certain embodiments, R_{A3} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl, -CF_3 , $\text{-CH}_2\text{Br}$, $\text{-CH}_2\text{OH}$, $\text{-CH}_2\text{OC(=O)(substituted or unsubstituted } C_{1-6} \text{ alkyl)}$, or ethyl). In certain embodiments, R_{A3} can be carboxyl. In certain embodiments, R_{A4} can be hydrogen. In certain embodiments, R_{A4} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl, -CF_3 , $\text{-CH}_2\text{OC(=O)(substituted or unsubstituted } C_{1-6} \text{ alkyl)}$, or ethyl). In certain embodiments, R_{A3} and R_{A4} can be joined to form alkenyl (e.g., =CH_2). In certain embodiments, R_{A5} can be hydrogen. In certain embodiments, R_{A5} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl or $\text{-CH}_2\text{OCF}_3$). In certain embodiments, R_{A5} cannot be hydrogen. In certain embodiments, R_{A6} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl, ethyl, $\text{-CH}_2\text{OH}$, $\text{-CH}_2\text{OC(=O)Me}$, or $\text{-CH}_2\text{OC(=S)Me}$). In certain embodiments, R_{A6} cannot be -CH_3 . In certain embodiments, R_{A7} can be hydrogen. In certain embodiments, R_{A7} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, R_{A7} can be -OR'' (e.g., -OH). In certain embodiments, R_{A8} can be hydrogen. In certain embodiments, R_{A8} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, at least one of R_{A7} and R_{A8} cannot be hydrogen. In certain embodiments, R_{A9} can be hydrogen. In certain embodiments, R_{A9} can be acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, R_{A10} can be hydrogen. In certain embodiments, at least one of R_{A9} and R_{A10} cannot be hydrogen. In certain embodiments, R_{A11} can be hydrogen. In certain embodiments, R_{A12} can be hydrogen. In certain embodiments, R_{A12} can be an amino group (e.g., -N(R'')_2 , -NHR'' , or -NH_2). In

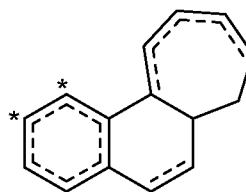
certain embodiments, -----R_{A13} is absent. In certain embodiments, at least one of R_{A12} and R_{A13} cannot be hydrogen. In certain embodiments, R_{A14} can be halogen, -NR''H, -SR'', -OR'', alkenyl, alkynyl, an amide group, a carboxyl group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, or a thiocarbamate group. In certain embodiments, R_{A14} can be hydrogen. In certain embodiments, R_{A14} can be alkyl (*e.g.*, acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl (*e.g.*, -CH₂CF₃, -CH₂OR'' (such as -CH₂OH), -CH₂SR'' (such as -CH₂SH), -CH₂N(R'')₂ (such as -CH₂NHMe or -CH₂NH₂), -CH₂OC(=O)(acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₂₀ aliphatic

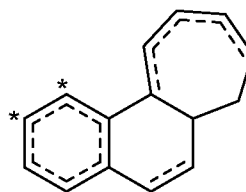
(such as , or -CH₂C(=O)N(R'')₂ (such as -CH₂C(=O)NH(substituted or unsubstituted C₁₋₆ alkyl))). In certain embodiments, R_{A14} cannot be -CH₂OH. In certain

embodiments, R_{A14} can be a carboxyl group. In certain embodiments, R_{A14} can be an ester group (*e.g.*, -C(=O)O(acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl), such as -C(=O)OMe). In certain embodiments, R_{A14} can be an aldehyde group. In certain embodiments, R_{A14} can be a ketone group (*e.g.*, -C(=O)-(acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl), such as -C(=O)Me). In certain embodiments, R_{A14} can be a urea group (*e.g.*, -NHC(=O)-NH(substituted or unsubstituted phenyl), such as -NHC(=O)-NHPh). In certain embodiments, -----R_{A15} can be absent. In certain embodiments, R_{A14} and R_{A15} can be joined to form =O or =S. In certain embodiments, R_{A16} can be hydrogen. In certain embodiments, R_{A16} can be a carbamate group (*e.g.*, -NHC(=O)O(acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl), such as -NHC(=O)OEt). In certain embodiments, R_{A17} can be hydrogen. In certain embodiments, at least one of R_{A16} and R_{A17} cannot be hydrogen. In certain embodiments, R_{A20} can be hydrogen. In certain embodiments, -----R_{A20} can be absent. In certain embodiments, R_{A21} can be hydrogen. In certain embodiments, R_{A21} can be a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms. In certain embodiments, R_{A21} can be acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl (*e.g.*, -CH₂OR'' (such as -CH₂OH, -CH₂OC(=O)OMe, or -CH₂OC(=O)(acyclic, substituted or unsubstituted, branched or unbranched, C₁₋₂₀ aliphatic



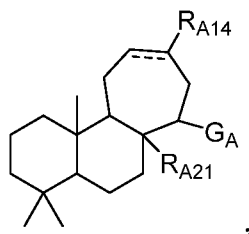
[0074] The tricyclic ring system (e.g., ) of Formula (I) may include substituents in addition to one or more of $\text{R}_{\text{A}1}$ to $\text{R}_{\text{A}17}$, $\text{R}_{\text{A}20}$ to $\text{R}_{\text{A}21}$, and G_{A} , as valency permits. In certain embodiments, the tricyclic ring system of Formula (I) can further be



substituted at one or two of the positions marked with “*”: . In certain embodiments, the tricyclic ring system of Formula (I) can further be substituted with one or more substituents independently selected from the group consisting of halogen; substituted and unsubstituted C_{1-6} aliphatic (e.g., unsubstituted C_{1-6} alkyl, such as $-\text{CH}_3$); and $-\text{OR}''$ (e.g., $-\text{OH}$).

[0075] In certain embodiments, at least one of $\text{R}_{\text{A}1}$, $\text{R}_{\text{A}2}$, $\text{R}_{\text{A}5}$, $\text{R}_{\text{A}7}$, $\text{R}_{\text{A}8}$, $\text{R}_{\text{A}9}$, $\text{R}_{\text{A}10}$, $\text{R}_{\text{A}11}$, $\text{R}_{\text{A}12}$, $\text{R}_{\text{A}13}$, $\text{R}_{\text{A}15}$, $\text{R}_{\text{A}16}$, and $\text{R}_{\text{A}17}$ cannot be hydrogen. In certain embodiments, at least one of $\text{R}_{\text{A}3}$, $\text{R}_{\text{A}4}$, and $\text{R}_{\text{A}6}$ cannot be $-\text{CH}_3$. In certain embodiments, when $\text{R}_{\text{A}21}$ is $-\text{CHO}$ and G_{A} is $-\text{OH}$ or $=\text{O}$, each of $\text{R}_{\text{A}14}$ and $\text{R}_{\text{A}15}$ cannot be $-\text{CHO}$.

[0076] In certain embodiments, the compound of Formula (I) cannot be of the formula:



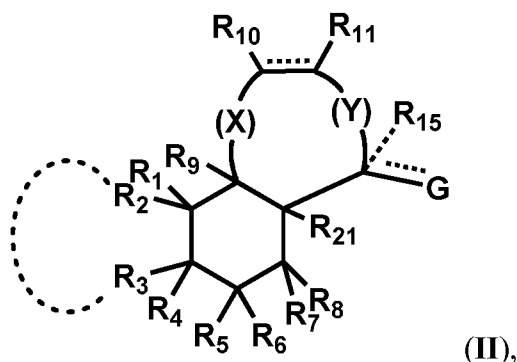
wherein:

GA is $-OR''$ or $-N(R'')_2$;

RA14 is an amide group, a nitrile group, an ester group, or substituted methyl; and

RA21 is an aldehyde group, $-CH_2OR''$, or an ester group.

[0077] In another aspect, the GLP-1 receptor modulators described herein are compounds of Formula (II):



and pharmaceutically acceptable salts thereof, wherein:

G is hydrogen, $=O$, $=S$, $-NR'H$, $-SR'$, or $-OR'$, wherein R' is hydrogen, an ester group, a ketone group, a thione group, or a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

W is $-O-$, $-S-$ or $-NR'-$;

X and Y are each independently a single bond or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 3 carbon atoms;

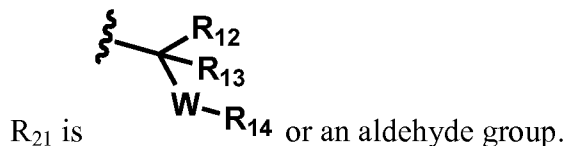
R1, R2, R3, R4, R5, R6, R7, R8, R9, R12 and R13 are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, or R2 and R3 may join to form cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R10 and R11 are each independently hydrogen, halogen, an amino group, an amide group, an ester group, an aldehyde group, a nitrile, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate

group, or a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R_{14} is hydrogen or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1-16 carbon atoms;

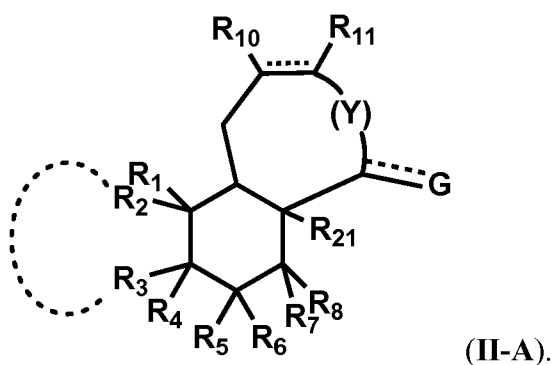
R_{15} is hydrogen or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1-6 carbon atoms; and



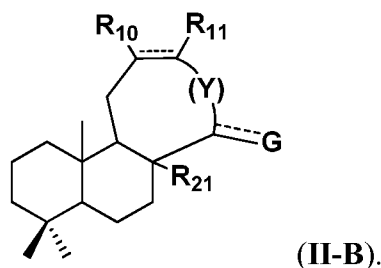
[0078] In certain embodiments, X and Y can each be methylene; R_1 can be methyl; R_2 , R_3 and the two carbon atoms directly bonded therewith can form a 3,3-dimethyl cyclohexane ring; R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{12} , and R_{13} can each be hydrogen; R_{11} can be an amide group, an acid group, an ester group, an aldehyde group, an alcohol group, a carbamate group, a thiocarbamate, a carbonate, a nitrile group, an amino group, or an imino group; and the bond between the two carbon atoms directly bonded with R_{10} and R_{11} can be a double bond.

[0079] In certain embodiments, X and Y can each be methylene; R_1 can be methyl; R_2 , R_3 and the two carbon atoms directly bonded therewith can form a 3,3-dimethyl cyclohexane ring; R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{12} , and R_{13} can each be hydrogen; R_{11} can be an amide group, an acid group, an ester group, an aldehyde group, an alcohol group, a carbamate group, a thiocarbamate, a carbonate, a nitrile group, an amino group, or an imino group; W can be $-O-$; R_{12} , R_{13} , R_{14} , and R_{15} can each be hydrogen; G can be $=O$; and the bond between the two carbon atoms directly bonded with R_{10} and R_{11} can be a double bond.

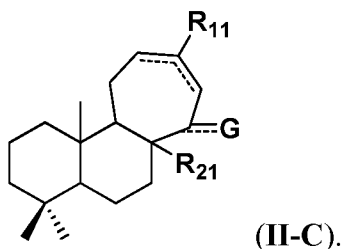
[0080] In certain embodiments, a compound of Formula (II) can be of Formula (II-A):



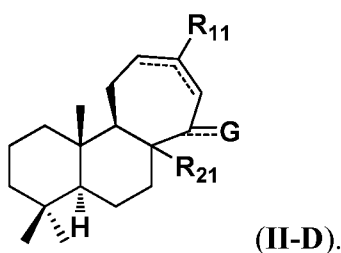
[0081] In certain embodiments, a compound of Formula (II) can be of Formula (II-B):



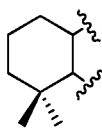
[0082] In certain embodiments, a compound of Formula (II) can be of Formula (II-C):

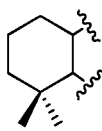


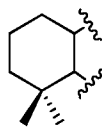
[0083] In certain embodiments, a compound of Formula (II) can be of Formula (II-D):

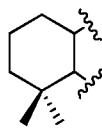


[0084] In certain embodiments, G can be =O. In certain embodiments, G can be –OR' (e.g., –OH, –O(substituted or unsubstituted C₁₋₆ alkyl), or –OC(=O)(substituted or unsubstituted C₁₋₆ alkyl)). In certain embodiments, G can be =S. In certain embodiments, G can be –SR' (e.g., –SH or –S(substituted or unsubstituted C₁₋₆ alkyl)). In certain embodiments, G can be –NHR' (such as –NH(substituted or unsubstituted C₁₋₆ alkyl) or –NHC(=O)(substituted or unsubstituted C₁₋₆ alkyl)) or –NH₂. In certain embodiments, W can be –O–. In certain embodiments, W can be –S–. In certain embodiments, W can be –NR'– (e.g., –N(substituted or unsubstituted C₁₋₆ alkyl)– or –NH–). In certain embodiments, X can be methylene. In certain embodiments, X can be ethanediyl, vinylene bridge, or propanediyl. In certain embodiments, Y can be methylene. In certain embodiments, Y can be ethanediyl, vinylene bridge, or propanediyl. In certain embodiments, R₁ can be substituted or unsubstituted, branched or unbranched, C₁₋₆ alkyl (e.g., methyl, –CH₂OH, –CH₂OC(=O)Me, or –CH₂OC(=S)Me). In certain embodiments, R₁ cannot be –CH₃. In certain embodiments, R₂, R₃, and the two carbon atoms directly bonded therewith form cycloalkyl (e.g., a 3,3-

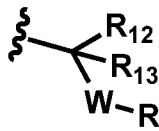


dimethyl cyclohexane ring (e.g., ) that is unsubstituted or substituted (e.g., substituted with $-\text{OH}$)). In certain embodiments, R_2 , R_3 , and the two carbon atoms directly



bonded therewith cannot form  that is unsubstituted. In certain embodiments, R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{12} , and R_{13} can each be hydrogen. In certain embodiments, R_4 can be hydrogen. In certain embodiments, R_4 can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl or $-\text{CH}_2\text{OCF}_3$). In certain embodiments, R_4 cannot be hydrogen. In certain embodiments, R_5 can be hydrogen. In certain embodiments, R_5 can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, R_5 can be $-\text{OR}'$ (e.g., $-\text{OH}$). In certain embodiments, R_6 can be hydrogen. In certain embodiments, R_6 can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, at least one of R_5 and R_6 cannot be hydrogen. In certain embodiments, R_7 can be hydrogen. In certain embodiments, R_7 can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl). In certain embodiments, R_8 can be hydrogen. In certain embodiments, at least one of R_7 and R_8 cannot be hydrogen. In certain embodiments, R_9 can be hydrogen. In certain embodiments, R_{10} can be hydrogen. In certain embodiments, R_{10} can be an amino group (e.g., $-\text{N}(\text{R}')_2$, $-\text{NHR}'$, or $-\text{NH}_2$). In certain embodiments, R_{11} can be hydrogen. In certain embodiments, R_{11} can be an amide group, an ester group, an aldehyde group, a carbamate group, a thiocarbamate, a nitrile group, an amino group, an imino group, or substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl. In certain embodiments, R_{11} can be an ester group, an aldehyde group, a ketone group, or substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl. In certain embodiments, R_{11} can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{OR}'$ (such as $-\text{CH}_2\text{OH}$), $-\text{CH}_2\text{SR}'$ (such as $-\text{CH}_2\text{SH}$), $-\text{CH}_2\text{N}(\text{R}')_2$ (such as $-\text{CH}_2\text{NHMe}$ or $-\text{CH}_2\text{NH}_2$), or $-\text{CH}_2\text{C}(=\text{O})\text{N}(\text{R}')_2$ (such as $-\text{CH}_2\text{C}(=\text{O})\text{NH}$ (substituted or unsubstituted C_{1-6} alkyl))). In certain embodiments, R_{11} cannot be $-\text{CH}_2\text{OH}$. In certain embodiments, R_{11} can be an ester group (e.g., $-\text{C}(=\text{O})\text{O}$ (substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl), such as $-\text{C}(=\text{O})\text{OMe}$). In certain embodiments, R_{11} can be an aldehyde group. In certain embodiments, R_{11} can be a ketone group (e.g., $-\text{C}(=\text{O})-$ (substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl), such as $-\text{C}(=\text{O})\text{Me}$). In certain embodiments, R_{12} can be

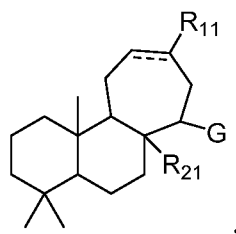
hydrogen. In certain embodiments, R_{13} can be hydrogen. In certain embodiments, R_{14} can be hydrogen. In certain embodiments, R_{14} can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., $-C(=O)OMe$ or $-C(=O)$ (substituted or unsubstituted, C_{2-20}



alkenyl). In certain embodiments, R_{21} can be $-CH_2OH$. In certain embodiments, R_{21} can be an aldehyde group. In certain embodiments, R_{15} can be hydrogen. In certain embodiments, ----- R_{15} can be absent. In certain embodiments, the bond between the two carbon atoms directly bonded with R_{10} and R_{11} can be a double bond. In certain embodiments, the bond between the two carbon atoms directly bonded with R_{10} and R_{11} can be a single bond. In certain embodiments, R' can be hydrogen. In certain embodiments, R' can be substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl (e.g., methyl, ethyl, propyl, or butyl).

[0085] In certain embodiments, at least one of R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , and R_{10} cannot be hydrogen. In certain embodiments, R_1 cannot be $-CH_3$. In certain embodiments, when R_{21} is $-CHO$ and G is $-OH$ or $=O$, R_{11} cannot be $-CHO$.

[0086] In certain embodiments, the compound of Formula (II) cannot be of the formula:



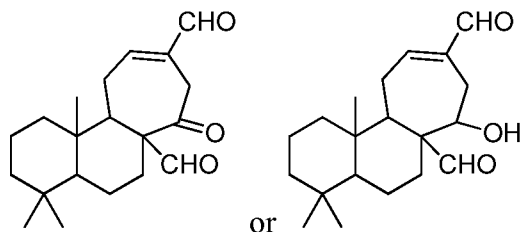
wherein:

G is $-OR'$ or $-NR'H$;

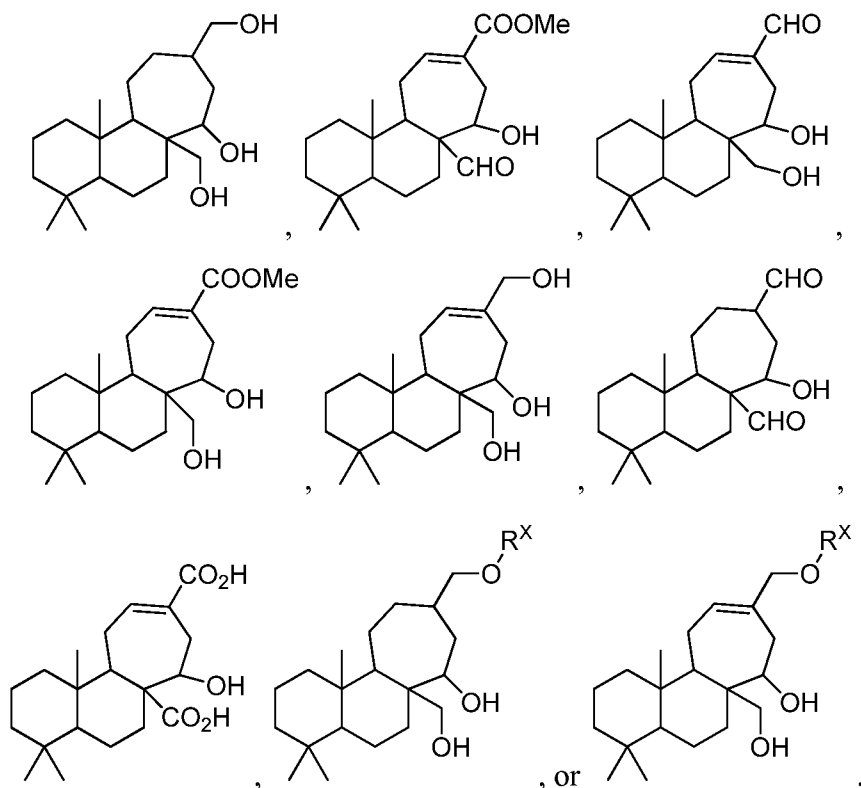
R_{11} is an amide group, a nitrile, an ester group, or substituted methyl; and

R_{21} is an aldehyde group or $-CH_2OR_{14}$.

[0087] In certain embodiments, a compound described herein cannot be of the formula:

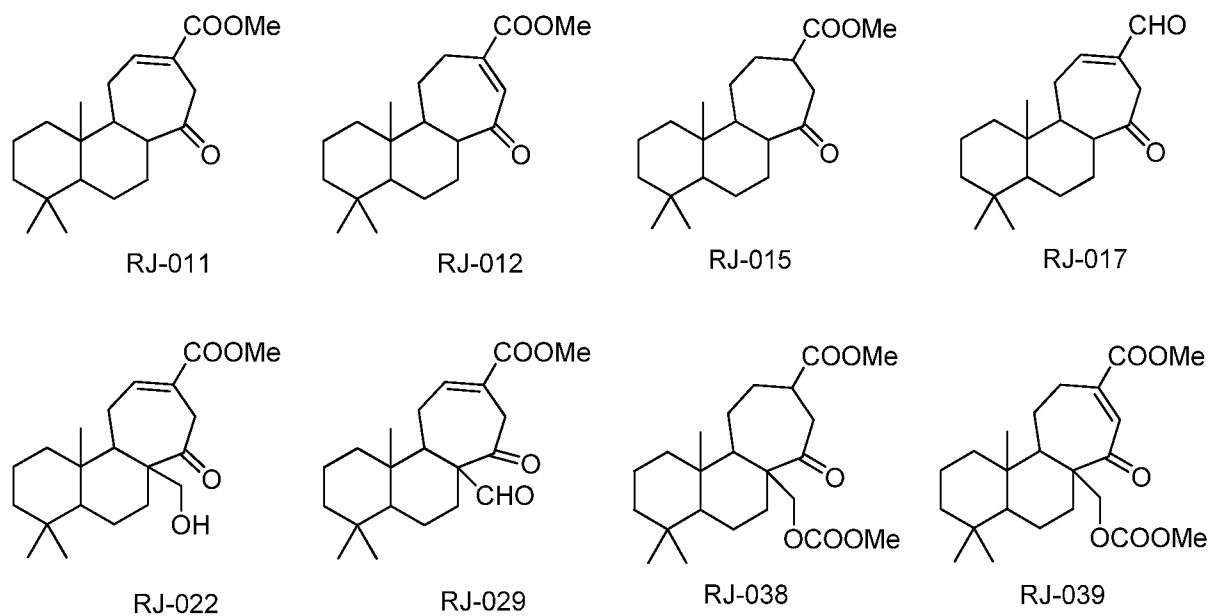


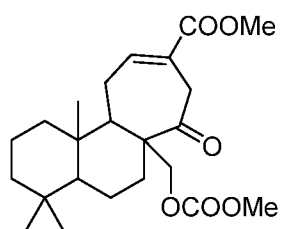
[0088] In certain embodiments, a compound described herein cannot be of the formula:



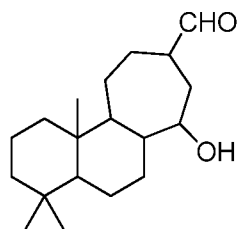
wherein R^x is a phosphorous-containing group.

[0089] Exemplary compounds described herein include, but are not limited to:

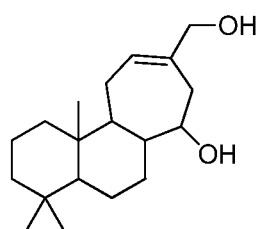
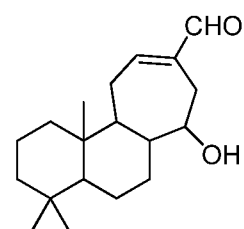
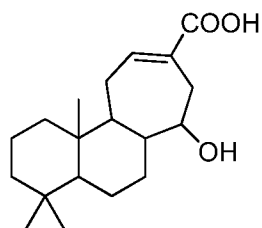




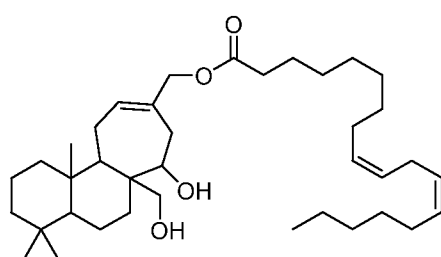
RJ-040



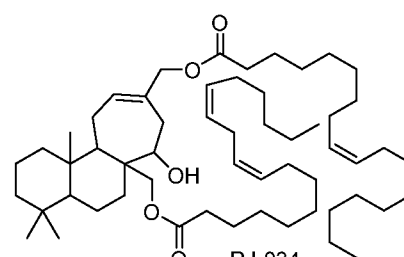
RJ-002

RJ-013
RJ-014RJ-018
RJ-019

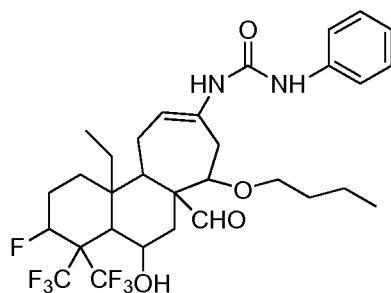
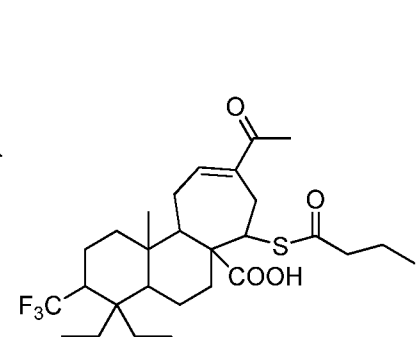
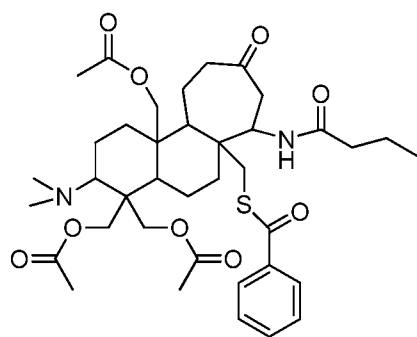
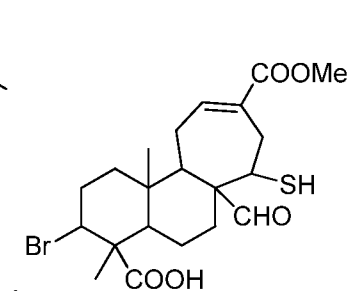
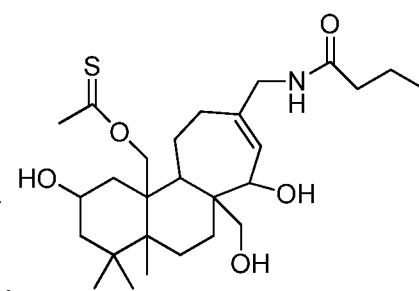
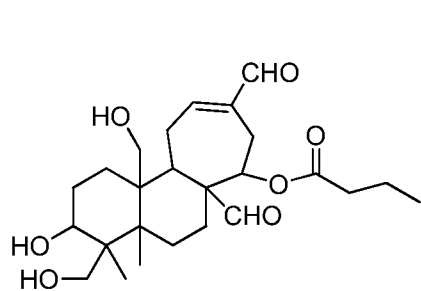
RJ-026

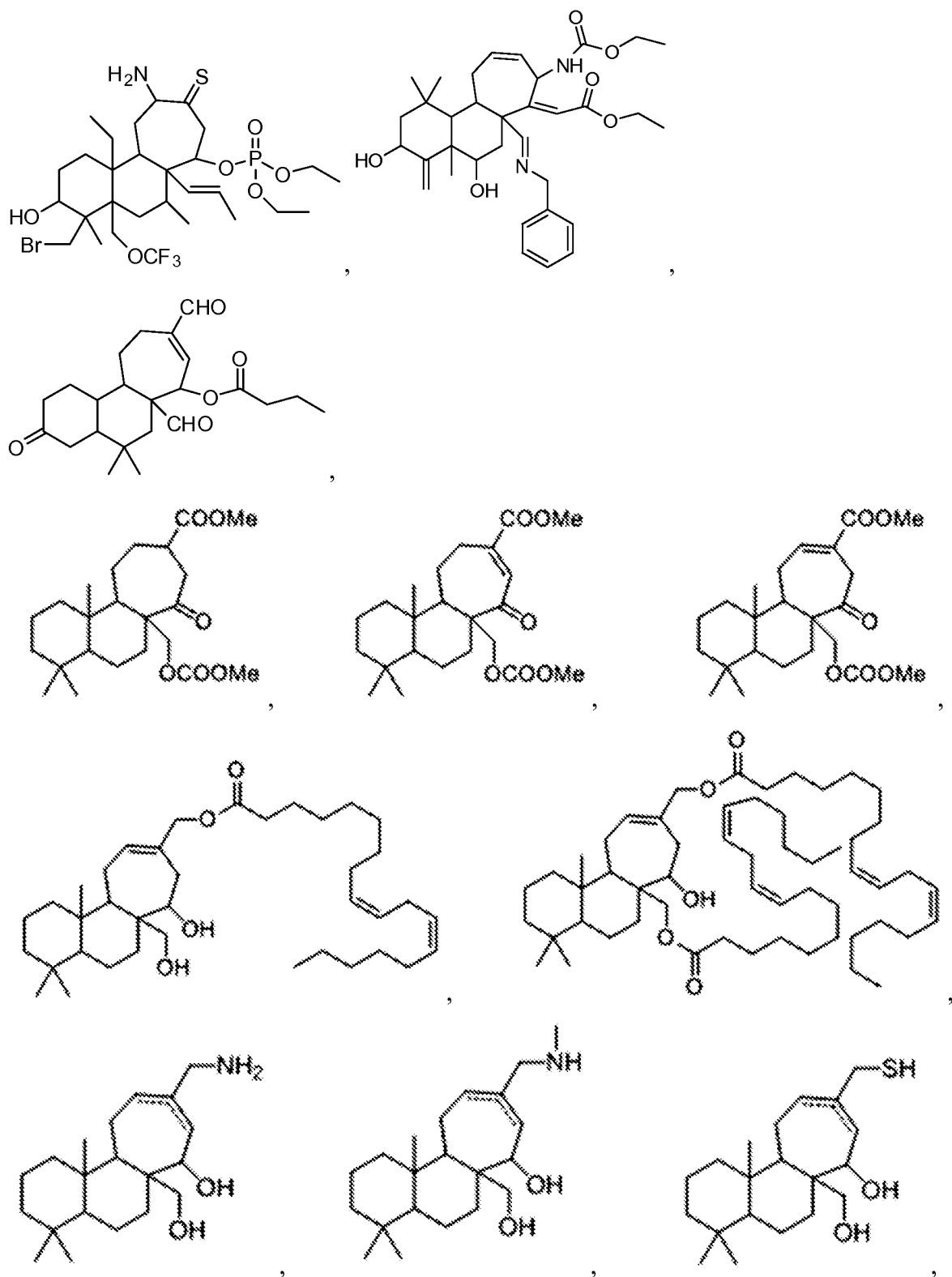


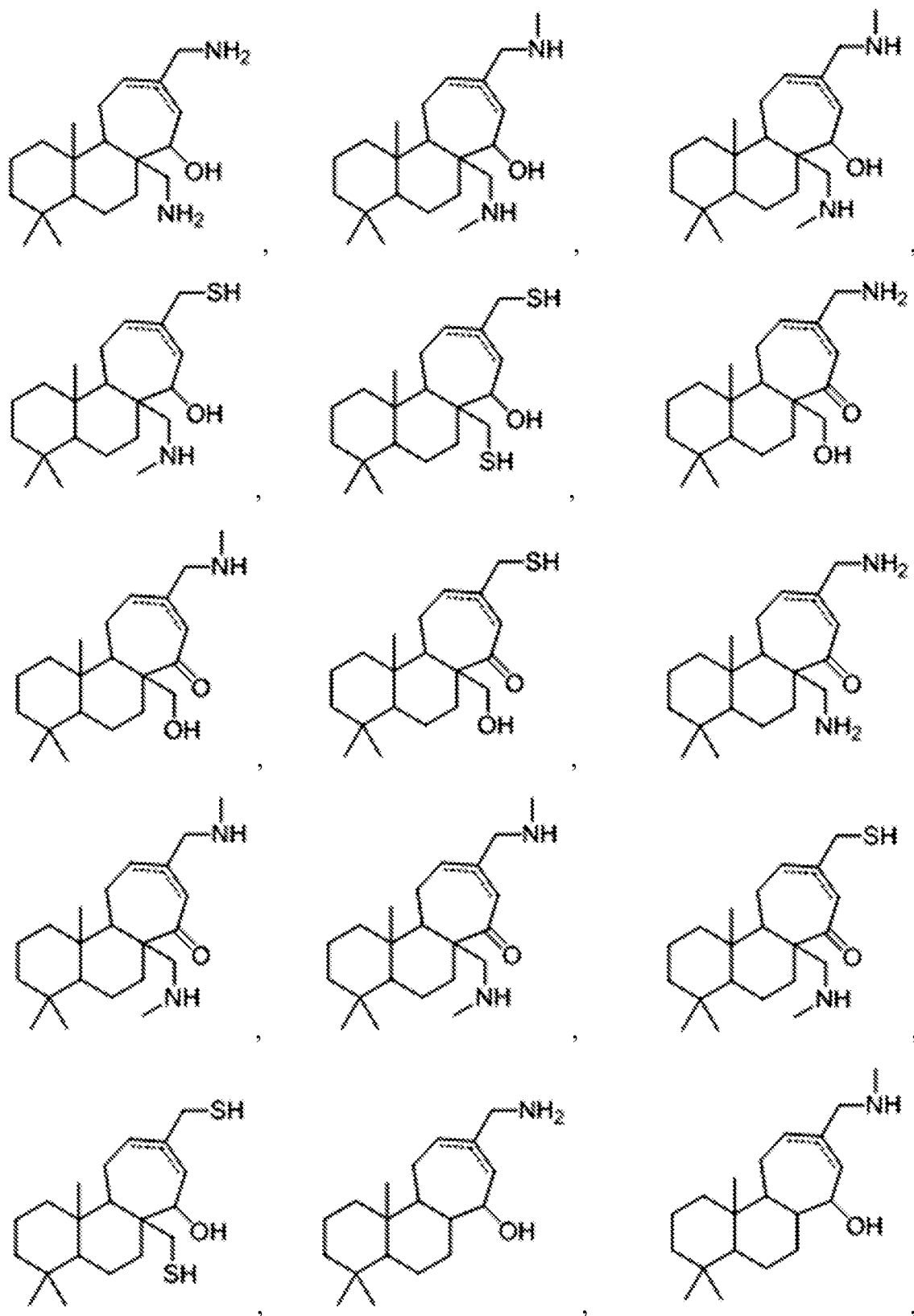
RJ-033

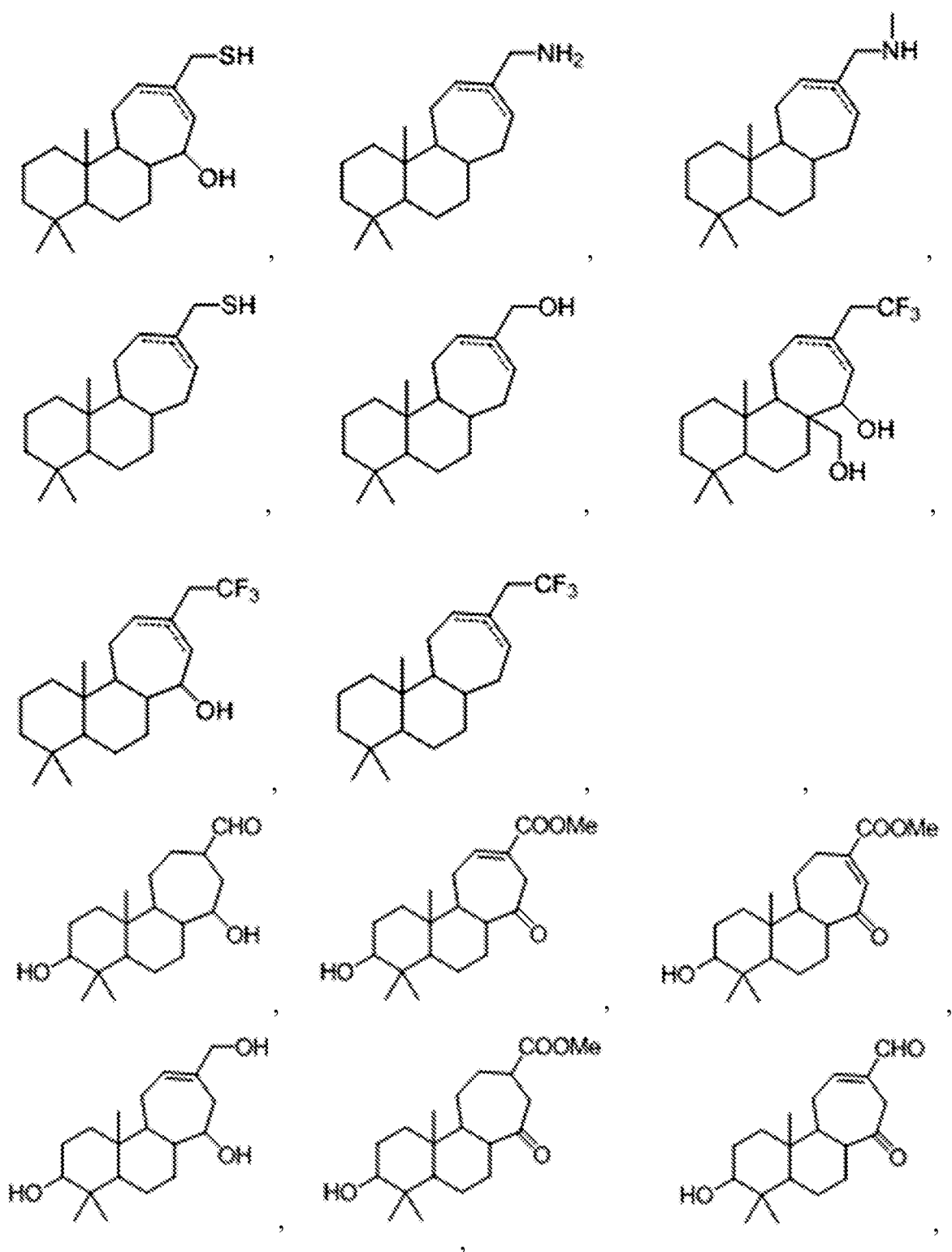


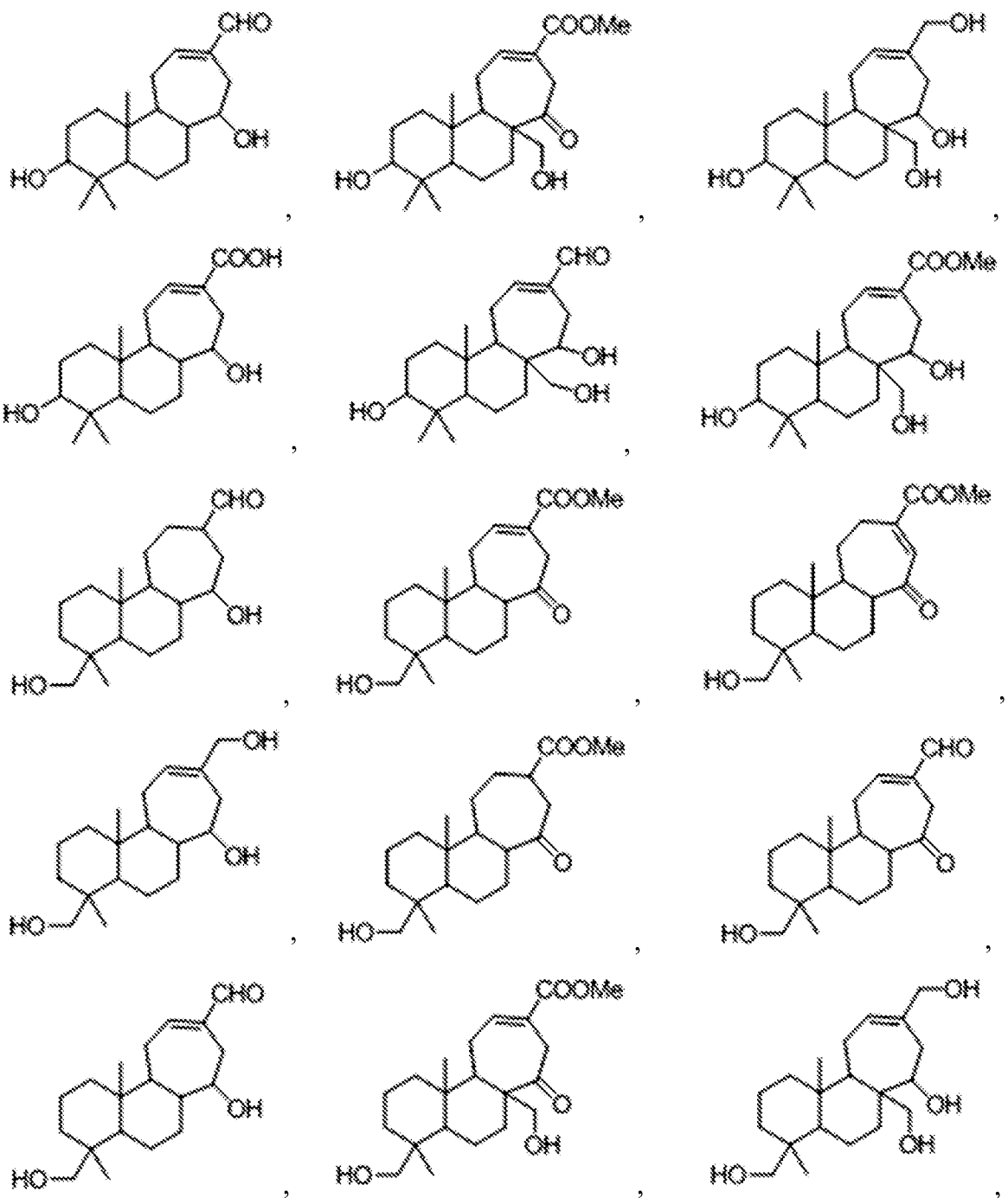
RJ-034

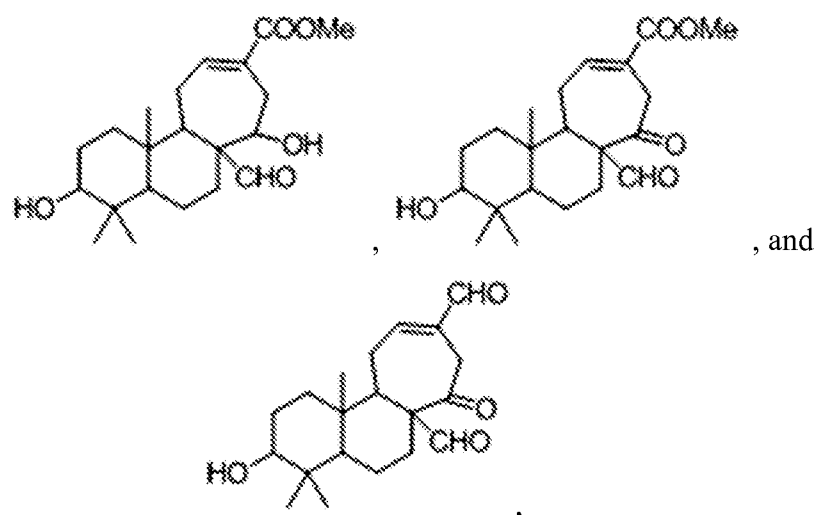




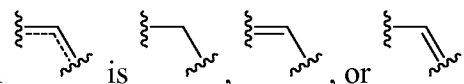








and pharmaceutically acceptable salts thereof, wherein



[0090] In still another aspect, this present disclosure features pharmaceutical compositions including one or more of the GLP-1 receptor modulators described herein and a pharmaceutically acceptable carrier.

[0091] In yet another aspect, this present disclosure features methods for regulating blood glucose level and/or treating diabetes in a subject. The method comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition described herein. In certain embodiments, the subject is a human (e.g., a human patient having, at risk for, or suspected of having diabetes, e.g., type I or type II diabetes).

[0092] In still another aspect, this present disclosure features methods of treating diabetes in a subject, the method including administering to a subject in need thereof an effective amount (e.g., a therapeutically effective amount) of a pharmaceutical composition described herein.

[0093] The methods described above can also include the step of identifying a subject in need of the treatment, e.g., a human patient having or at risk for developing abnormal blood glucose levels or any disorder associated therewith.

[0094] In further another aspect, the present disclosure features kits comprising a pharmaceutical composition described herein and optionally, instructions for using the kits.

[0095] Also within the scope of this present disclosure are a pharmaceutical composition as described herein for use in regulating blood glucose level and/or treating diabetes in a subject, and the use of such a pharmaceutical composition for the manufacture of a medicament for regulating blood glucose level and/or treating diabetes in a subject.

[0096] Other features or advantages of the present disclosure will be apparent from the following detailed description of several embodiments, and also from the appending claims.

BRIEF DESCRIPTION OF DRAWINGS

[0097] *Fig. 1* is a chart showing the effect of GLP-1 (7-36) on endocytosis mediated by GLP-1 receptor. The GLP-1R/ β -arrestin2 GFP double stable expression U2OS cells were plated in 384-well plastic plates at a density of 3000 cell/well and cultured overnight. Wells were treated with vehicle or various concentrations of GLP-1(7-36) for 60 min at room temperature in the presence (●) or absence (■) of 1 μ M of exendin 9.

[0098] *Fig. 2* shows the activity of an ethanol extract of *Hedychium coronarium* (HC) in potentiating the GLP-1 activity. (*Panel A*) Cell images of GLP-1 receptor endocytosis elicited by 0 or 4 nM of GLP-1 in the presence or absence of 0.06 mg/ml ethanol extract of HC. (*Panel B*) Dose response data of GLP-1 from 0.15 nM to 324 nM on GLP-1 receptor activation in the presence (▼) or absence (■) of 0.06 mg/ml of ethanol extract of HC. (*Panel C*) Dose response data of ethanol extract of HC from 0.0025 mg/ml to 0.2 mg/ml on GLP-1 receptor activation by 4 nM of GLP-1.

[0099] *Fig. 3* includes charts showing normal phase silica gel chromatograms of HC ethyl acetate partition fraction. 7 g of EtOAc partition material was subjected to normal phase silica gel chromatography and resolved into 37 fractions. The activity was assayed for each fraction (the ability of 0.002 mg/ml partially purified compounds to potentiate the receptor endocytosis elicited by 4 nM of GLP-1) and expressed as % of the maximal activity elicited by 1 μ M of GLP-1. ♦ represents weight of each fraction. ■ indicates the activity of each fraction. I is the pooled fraction 5 to fraction 12.

[0100] *Fig. 4* shows an exemplary fractionation of I (the pooled fraction 5 to fraction 12) on a KROMASIL C₁₈ column. 1.7 gram of I was injected into a KROMASIL C₁₈ column (250 × 50 mm, 10 μ m) eluted at flow rate of 109 ml/min with a gradient started with 57% acetonitrile in water and finally with 100 % acetonitrile. Weight of each fraction (♦) and (■) indicates activity of each fraction.

[0101] *Fig. 5* shows exemplary results of a dose response analysis of galanin B on GLP-1 (*Panel A*) or PTH (*Panel B*) induced receptor endocytosis. The GLP-1R/ β -arrestin2 GFP (*Panel A*) or PTHR/ β -arrestin 2 GFP (*Panel B*) double stable expression U2OS cells were plated in 384-well plastic plates at a density of 3000 cell/well and cultured overnight. Dose titration of galanin B on cell stimulated with 4 nM of GLP-1 7-36 (*Fig. 5A*) or stimulated

with 15 nM of PTH (*Panel B*). *Panel C* shows exemplary results of a dose response data of GLP-1 from 0.15 nM to 324 nM on GLP-1 receptor activation in the presence (▼) or absence (■) of 0.001 mg/ml of galanin B.

[0102] *Fig. 6* shows that galanin B potentiated GLP-1 elicited GLP-1 receptor endocytosis. Dose response data of GLP-1 from 0.15 nM to 324 nM on GLP-1 receptor activation in the presence (▼) of 0.001 mg/ml of galanin B (*Panel A*) or in the absence (■) of 0.001 mg/ml of galanin B (*Panel B*).

[0103] *Fig. 7* shows that galanin B, compound 1, and compound 2 increased the potency of GLP-1 dependent receptor endocytosis. Dose response titration of GLP-1 from 0.15 nM to 324 nM on GLP-1 receptor endocytosis in the presence (○), (▽), (□) of 0.0001 mg/ml of galanin B, 0.001 mg/ml of compound 1, 0.001 mg/ml of compound 2, respectively, or GLP-1 alone (▲).

[0104] *Fig. 8* shows that exendin 9 diminished positive modulation effect compound 1, compound 2, and galanin B on GLP-1 elicited GLP-1 receptor endocytosis. (*Panel A*) Titration of GLP-1 on GLP-1 receptor endocytosis in the presence of 0.0001 mg/ml of galanin B (●), absence of galanin B (▲), and in the presence of 0.0001 mg/ml of galanin B plus 1.8 mM of Exendin 9 (■). (*Panel B*) Titration of GLP-1 on GLP-1 receptor endocytosis in the presence of 0.001 mg/ml of compound 2 (●), absence of compound 2 (▲) and in the presence of 0.001 mg/ml of compound 2 plus 1.8 mM of Exendin 9 (■). (*Panel C*) Titration of GLP-1 on GLP-1 receptor endocytosis in the presence of 0.001 mg/ml of compound 1 (●), absence of compound 1 (▲) and in the presence of 0.001 mg/ml of compound 1 and 1.8 mM of Exendin 9 (■).

[0105] *Fig. 9* shows that compound 1 suppressed, and compound 2 potentiated, GLP-1 dependent cAMP production in RINm5F cells (*Panel A*) Dose response titration of GLP-1 in the presence of 0.003 mg/ml of galanin B (○), compound 2 (◇), compound 1 (▽), or GLP-1 alone (●). (*Panel B*) Dose response of galanin (○) or compound 2 (△) on cAMP production in RINm5F cells stimulated by 3 nM of GLP-1. (*Panel C*) Dose response of compound 1 (●) on cAMP production in RINm5F cells elicited by 60 nM of GLP-1.

[0106] *Fig. 10* shows that potentiation effect of compound 2 on GLP-1 elicited cAMP generation is blocked by exendin 9 and MDL 12330A. (*Panel A*) Titration of exendin 9 on cAMP production in RINm5F cells stimulated by 2 nM of GLP-1 in the presence (△) and absence (●) of 0.0025 mg/ml of compound 2. (*Panel B*) Titration of GLP-1 on cAMP

production in RIMm5F cells (○) or in the presence of 0.0025 mg/ml of compound 2 (a) or in the presence of 0.0025 mg/ml of compound 2 plus 250 mM of MDL 12330A (b).

[0107] *Fig. 11* shows the effect of compound 1 and compound 2 on cAMP production in RINm5F cells elicited by GIP and Glucagon. (*Panel A*) Titration of GIP on the production of cAMP from RINm5F cells (△) or in the presence of 0.025 mg/ml of compound 2 (▣) or compound 1 (○). (*Panel B*) Titration of glucagon on the production of cAMP from RINm5F cells (▲) or in the presence of 0.025 mg/ml of compound 2 (■) or compound 1 (●).

DETAILED DESCRIPTION

[0108] In an attempt to identify orally active and physiologically more compliant GLP-1 therapeutics for diabetes (*e.g.*, type II diabetes) and compounds that selectively regulates the GLP-1 pathway, edible plants were screened for activities that modulate the GLP-1 receptor signaling. In particular, plant extracts were screened to identify components that positively modulate GLP-1 receptor signaling in a GLP-1 dependent manner. The compounds identified in the screening process do not act merely in an on-and-off manner, as those GLP-1 therapies known in the art. Rather, the positive modulators identified from plants act more like a dimmer switch, providing control over the intensity of activation according to the secreting level of endogenous GLP-1 and allowing the body to retain its physiological control over initiating receptor activation.

[0109] Accordingly, described herein are novel GLP-1 receptor modulators (*e.g.*, activators) such as compounds having Formula (I) or Formula (II) as described herein, or pharmaceutically acceptable salts thereof, and uses thereof in regulating blood glucose levels and treating diabetes such as type I or type II diabetes. The GLP-1 receptor modulators described herein activates GLP-1 receptor only in the presence of GLP-1, which is different from the GLP-1 independent GLP-1 receptor activators known in the art. See, *e.g.*, US Patent No. 8,501,982.

[0110] Preparation of GLP-1 Receptor Modulators

[0111] The compounds described herein can be prepared by methods well known in the art. In some examples, the compounds can be isolated from a native source, such as a plant. In other examples, the compounds are chemically synthesized following routine synthetic routes, *e.g.*, by *Scheme 1* and *Scheme 2* shown below.

[0112] The chemicals used in the above-described synthetic routes may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds described herein. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds described herein are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[0113] A compound thus obtained can be further purified by methods known in the art (e.g., flash column chromatography, high performance liquid chromatography, or crystallization). The bioactivity of any of the compounds described herein can be verified via in vitro or in vivo assay systems known in the art, e.g., those described in the Examples below.

[0114] Pharmaceutical Compositions Comprising GLP-1 Receptor Modulators and Therapeutic Uses Thereof

[0115] Any of the compounds described herein may be useful in regulating blood glucose levels or treating diabetes in a subject via, e.g., modulating the GLP-1 receptor signaling pathways.

[0116] A pharmaceutical composition that includes one or more compound described herein and a pharmaceutically acceptable carrier. . In certain embodiments, a pharmaceutical composition described herein includes a compound described herein in an amount sufficient to regulate blood glucose level in a subject. The carrier in the pharmaceutical composition must be "acceptable" in the sense that it is compatible with the active ingredient of the composition, and preferably, capable of stabilizing the active ingredient and not deleterious to the subject to be treated. For example, solubilizing agents such as cyclodextrins, which form specific, more soluble complexes with the compounds described herein, or one or more solubilizing agents, can be utilized as pharmaceutical excipients for delivery of the

compounds described herein. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow # 10.

[0117] To practice the methods described herein, an effective amount of a pharmaceutical composition as described herein can be administered to a subject in need of the treatment via a suitable route.

[0118] An “effective amount” is that amount of the one or more GLP-1 receptor modulator that alone, or together with further doses, produces the desired response, e.g. reduce the blood glucose levels in the subject. In the case of treating a particular disease or condition such as Type I or Type II diabetes, characterized by dysregulated GLP-1 receptor signaling, the desired response is inhibiting the progression of the disease or condition. This may involve only slowing the progression of the disease temporarily, although more preferably, it involves halting the progression of the disease permanently. This can be monitored by routine methods or can be monitored according to routine medical practices. The desired response to treatment of the disease or condition also can be delaying the onset or even preventing the onset of the disease or condition.

[0119] Effective amounts will depend, of course, on the particular condition being treated, the severity of the condition, the individual patient parameters including age, physical condition, size, gender and weight, the duration of the treatment, the nature of concurrent therapy (if any), the specific route of administration and like factors within the knowledge and expertise of the health practitioner. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is generally preferred that a maximum dose of the individual components or combinations thereof be used, that is, the highest safe dose according to sound medical judgment. It will be understood by those of ordinary skill in the art, however, that a patient may insist upon a lower dose or tolerable dose for medical reasons, psychological reasons or for virtually any other reasons.

[0120] The subject to be treated by any of the methods described herein can be a human patient, e.g., a human patient having, at risk for, or suspected of having an elevated blood glucose level or any disease/condition associated therewith, such as Type I or Type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, and a metabolic disorder. Such a human patient can be identified by routine medical practices. Alternatively, the subject can be a non-human mammal, e.g., dog, cat, cow, pig, horse, sheep, or goat.

[0121] The GLP-1 receptor modulator activates GLP-1 receptor only in the presence of GLP-1. Thus, when a subject's endogenous level of GLP-1 is too low, any of the modulators described herein can be co-administered with GLP-1 or a functional variant thereof.

[0122] The terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of diabetes. In some embodiments, treatment may be administered after one or more signs or symptoms have developed or have been observed. In other embodiments, treatment may be administered in the absence of signs or symptoms of diabetes. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example, to delay or prevent recurrence.

[0123] The pharmaceutical composition described herein can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0124] A sterile injectable composition, *e.g.*, a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as TWEEN 80) and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (*e.g.*, synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

[0125] A pharmaceutical composition for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. A pharmaceutical composition described herein can also be administered in the form of suppositories for rectal administration.

[0126] Also within the scope of the present disclosure are kits (*e.g.*, pharmaceutical packs) comprising one or more compound or pharmaceutical compositions described herein. Such a kit can further comprise a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container) for placing the compounds/compositions. In some embodiments, a kit described herein may include a second container comprising a pharmaceutically acceptable excipient for dilution or suspension of a compound or pharmaceutical composition described herein. In some embodiments, the compound or pharmaceutical composition provided in the first container and the second container are combined to form one unit dosage form.

[0127] A kit described herein may include instructions for using the kit (*e.g.*, for administering a compound or pharmaceutical composition contained therein to a subject). A kit described herein may also include information as required by a regulatory agency such as the FDA. In certain embodiments, the information included in the kit is prescribing information. A kit described herein may include one or more additional pharmaceutical agents described herein as a separate composition.

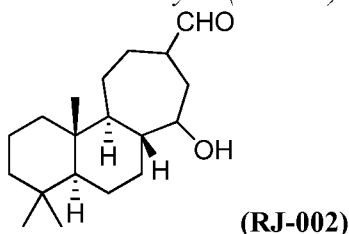
[0128] A compound or pharmaceutical composition described herein may be administered concurrently with, prior to, or subsequent to one or more additional pharmaceutical agents, which may be useful as, *e.g.*, combination therapies. The additional pharmaceutical agents may be therapeutically active agents or prophylactically active agents.

EXAMPLES

[0129] Without intent to limit the scope of the present disclosure, exemplary compounds and methods of using or making such, as well as their related results according to the embodiments of the present disclosure are given below. Note that titles or subtitles may be used in the examples for convenience of a reader, which in no way should limit the scope of the present disclosure. Moreover, certain theories are proposed and disclosed herein; however, in no way they, should limit the scope of the present disclosure so long as the present disclosure is practiced according to the present disclosure without regard for any particular theory or scheme of action.

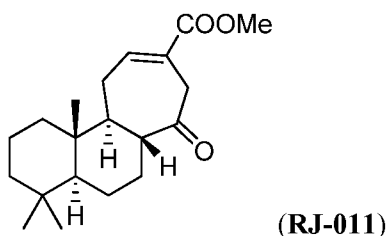
[0130] **Example 1: Synthesis of Exemplary GLP-1 Receptor Modulators**

[0131] (1) $(\pm)$ -(4a*S*,6a*R*,11a*S*,11b*R*)-7-hydroxy-4,4,11b-trimethyltetradecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-002)



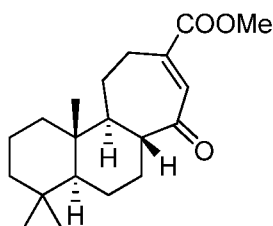
[0132] A solution of $(\pm)$ -(4a*S*,6a*R*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b-trimethyltetradecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol, TEMPO, and TBACl in DCM and aqueous solution of NaHCO₃ (0.5M) and K₂CO₃ (0.05M) were vigorously stirred at room temperature. NCS was then added. Stirring was maintained and the reaction monitored by TLC. The reaction was quenched with sat. NH₄Cl, the organic layer was separated, and the aqueous layer was extracted with DCM (three times). The DCM extracts were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was coated on silica gel and purified by flash column chromatography to give $(\pm)$ -(4a*S*,6a*R*,11a*S*,11b*R*)-7-hydroxy-4,4,11b-trimethyltetradecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-002) as a white solid.

(2) $(\pm)$ -(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a, 11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-011)



[0133] A solution of (±)-(6a*S*,11a*S*,11b*R*)-methy 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-012) (757 mg, 2.38 mmol) and DBU (0.71 mL, 4.75 mmol) in benzene (48.0 mL) was refluxed for 5 h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography (EtOAc:hexanes, 1:19) to afford (±)-(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-011) (691 mg, 91%) as a white solid. Data for RJ-011: Mp 93–94 °C; IR (film) 2944, 2867, 2845, 1711, 1643, 1436, 1388, 1366, 1259, 1199, 1161, 1122, 1088, 1059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.13–7.10 (m, 1H), 3.74 (s, 3H), 3.51–3.41 (m, 2H), 2.63 (td, *J* = 12.0 Hz, *J* = 3.6 Hz, 1H), 2.46–2.37 (m, 1H), 2.16–2.12 (m, 1H), 1.82–1.67 (m, 3H), 1.65–1.52 (m, 2H), 1.52–1.36 (m, 3H), 1.36–1.23 (m, 1H), 1.15 (td, *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 0.95–0.88 (m, 2H), 0.85 (s, 6H), 0.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 211.0, 166.9, 162.7, 126.8, 54.6, 52.6, 52.2, 52.1, 41.8, 40.2, 38.4, 37.5, 33.3, 33.2, 29.0, 27.1, 21.4, 20.9, 18.6, 14.3; HRMS (APCI) calcd for C₂₀H₃₀O₃ [M+Na]⁺: 341.2093, found: 341.2092.

(3) (±)-(6a*S*,11a*S*,11b*R*)-methy 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-012)

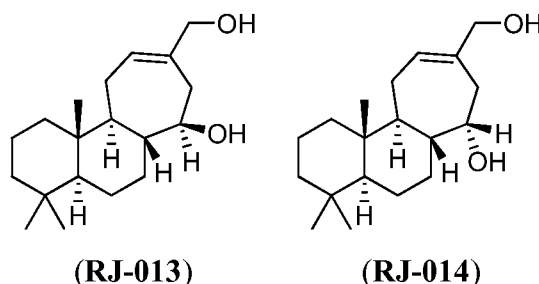


(RJ-012)

[0134] To a solution of (±)-(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxo-tetradecahydro-1*H*-cyclo-hepta-*a*]naphthalene-9-carboxylate (RJ-015) (872 mg, 2.72 mmol) and NEt₃ (1.5 mL, 10.89 mmol) in CH₂Cl₂ (27.0 mL) was added TMSOTf (1.0 mL, 5.4 mmol) at 0 °C, and stirring was continued for 2 h. The reaction contents were quenched with sat. NaHCO_{3(aq)} (60 mL) at 0 °C, and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The organic extracts were combined, washed with brine (60 mL), dried with Na₂SO₄, and concentrated by rotary evaporator. To a solution of the dried residue in THF (27.0 mL) was added PhSeCl (626 mg, 3.27 mmol) at –78 °C. The mixture was stirred at –78 °C for 30 min before the addition of pyridine (0.44 mL, 5.45 mmol) and 30% H₂O₂ (0.48 mL, 5.45 mmol). The mixture was allowed to warm to 0 °C and stirred for 1 h. The reaction was quenched by sat. NaHCO_{3(aq)} (60 mL), and the aqueous layer was extracted with ether (3 × 30 mL). The organic extracts were combined, washed with brine (60 mL), dried over Na₂SO₄,

and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc:hexanes, 4:96) to afford (±)-(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (**RJ-012**) (815 mg, 95%) as a colorless oil. Data for **RJ-012**: IR (film) 2925, 2866, 1722, 1667, 1436, 1388, 1366, 1228, 1135, 1022 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.85 (s, 1H), 3.77 (s, 3H), 2.71–2.57 (m, 3H), 1.91–1.78 (m, 3H), 1.73–1.63 (m, 1H), 1.63–1.52 (m, 1H), 1.50–1.28 (m, 5H), 1.28–1.21 (m, 1H), 1.14 (td, *J* = 13.0 Hz, *J* = 4.0 Hz, 1H), 0.96–0.86 (m, 2H), 0.86 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 208.0, 167.9, 143.2, 135.6, 55.0, 54.8, 52.4, 51.2, 42.0, 38.2, 37.7, 33.3, 33.2, 31.4, 30.8, 25.7, 21.5, 21.4, 18.5, 13.9; HRMS (ESI) calcd for C₂₀H₃₀O₃ [M+H]⁺: 319.2273, found: 319.2270.

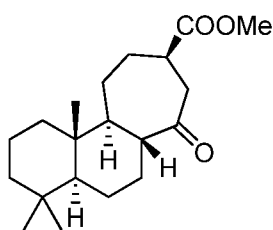
[0135] (4) (±)-(6a*S*,7*R*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (**RJ-013**) & (±)-(6a*S*,7*S*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (**RJ-014**)



[0136] To a solution of (±)-(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (**RJ-011**) (600 mg, 1.88 mmol) in DCM (19 mL) at -78°C was added DIBAL solution (1.0 M in toluene, 7.5 mL, 7.54 mmol), and the stirring was continued for 3h. The reaction was quenched by 1N HCl_(aq) (40 mL) and allowed to warm to room temperature. The phases were separated, and the aqueous layer was extracted with DCM (3 × 20 mL). The organic extracts were combined, washed with brine (40 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient from 1:9 → 1:4 → 2:3 EtOAc:hexanes) to afford (±)-(6a*S*,7*R*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (**RJ-013**) (296 mg, 54%) and (±)-(6a*S*,7*S*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (**RJ-014**) (200 mg,

36%). Both RJ-013 and RJ-014 are white solids. Data for RJ-013: Mp 134–135 °C; IR (film): 3350, 2918, 2865, 2840, 1652, 1452, 1384, 1123, 1088, 1035, 999 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.88–5.84 (m, 1H), 3.99 (s, 2H), 3.38–3.33 (m, 1H), 2.53 (dd, $J = 15.0$ Hz, $J = 8.4$ Hz, 1H), 2.38–2.30 (m, 1H), 2.20 (dd, $J = 15.0$ Hz, $J = 8.4$ Hz, 1H), 2.09–2.01 (m, 1H), 1.95–1.80 (m, 2H), 1.72–1.60 (m, 4H), 1.60–1.50 (m, 1H), 1.49–1.41 (m, 1H), 1.41–1.34 (m, 1H), 1.34–1.24 (m, 1H), 1.12 (td, $J = 13.0$ Hz, $J = 4.0$ Hz, 1H), 1.05–0.91 (m, 2H), 0.90–0.77 (m, 2H), 0.84 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.6, 128.8, 75.0, 68.1, 54.8, 53.5, 48.5, 42.0, 38.8, 37.8, 34.9, 33.4, 33.3, 32.7, 26.3, 21.7, 21.6, 18.9, 14.0; HRMS (MALDI) calcd for $\text{C}_{19}\text{H}_{32}\text{O}_2$ $[\text{M}+\text{Na}]^+$: 315.2300, found: 315.2314. Data for RJ-014: Mp 89–91 °C; IR (film): 3354, 2921, 2865, 1449, 1386, 1365, 1062, 1045, 1000, 738 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 5.89 (t, $J = 7.3$ Hz, 1H), 3.95–3.89 (m, 2H), 3.71 (d, $J = 5.7$ Hz, 1H), 2.60–2.54 (m, 1H), 2.44 (dd, $J = 14.5$ Hz, $J = 7.0$ Hz, 1H), 2.16 (dd, $J = 14.0$ Hz, $J = 8.5$ Hz, 1H), 1.90–1.83 (m, 1H), 1.80–1.71 (m, 1H), 1.67–1.56 (m, 3H), 1.56–1.46 (m, 2H), 1.46–1.39 (m, 1H), 1.39–1.26 (m, 1H), 1.16–1.08 (m, 1H), 0.95 (t, $J = 10.8$ Hz, 1H), 0.91–0.77 (m, 2H), 0.84 (s, 3H), 0.81 (s, 3H), 0.81 (s, 3H), 0.80–0.77 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.5, 130.1, 70.0, 67.8, 54.5, 47.3, 47.3, 42.0, 39.2, 37.5, 35.4, 33.5, 33.4, 32.1, 27.4, 22.0, 21.5, 18.9, 13.9; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{32}\text{O}_2$ $[\text{M}+\text{Na}]^+$: 315.2300, found: 315.2294.

[0137] (5) ($\pm$)-(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxotetradecahydro-1*H*-cyclohepta-[a]naphthalene-9-carboxylate (RJ-015)



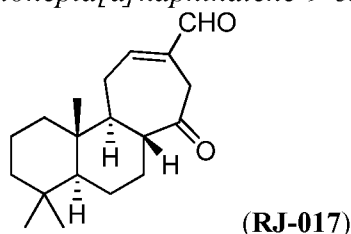
(RJ-015)

[0138] To a solution of ($\pm$)-(4a*S*,4b*R*,10a*S*)-4b,8,8-trimethyldodecahydro-phenanthren-1(4b*H*)-one (890 mg, 3.59 mmol) in THF (18 mL) was added LHMDs (1.0 M in THF, 5.4 mL, 5.38 mmol) at -78 °C. The mixture was allowed to warm slowly to 0 °C over the course of 2h. Then, cooled down to -78 °C, and NCCOOMe (0.43 mL, 5.38 mmol) and TMEDA (0.73 mL, 5.38 mmol) were added dropwise to the reaction mixture. Let it slowly warmed to room temperature and the stirring was continued overnight. The reaction contents were quenched with 1N $\text{HCl}_{(\text{aq})}$ (40 mL) and extracted with DCM (3×20 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4 , and concentrated *in*

vacuo. To a solution of Et₂Zn (1.0 M in hexane, 5.4 mL, 5.38 mmol) in DCM (30 mL) under ice-bath was added neat CH₂I₂. The mixture was stirred at 0°C for 1h, and then the aforementioned crude in DCM (30 mL) was added. After 5 minutes, removed the ice-bath, and the stirring was continued for 3h at room temperature. The reaction contents were quenched with sat. NH₄Cl_(aq) at 0°C and allowed to warm to room temperature. The phases were separated, and the aqueous layer was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed with sat. NaHCO_{3(aq)} (80 mL) and brine (80 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient from 1:48 → 1:24 EtOAc:hexanes) to afford (±)-

(6a*S*,11a*S*,11b*R*)-methyl 4,4,11b-trimethyl-7-oxotetradecahydro-1*H*-cyclo- hepta-[a]naphthalene-9-carboxylate (RJ-015) (918 mg, 80%) as a white solid. Data for **RJ-015**: Mp 67–68 °C; IR (film) 2924, 2852, 1739, 1707, 1461, 1365, 1277, 1199, 1174 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 3H), 2.85–2.70 (m, 3H), 2.47 (td, *J* = 12.0Hz, *J* = 4.0 Hz, 1H), 2.18–2.08 (m, 1H), 1.82–1.71 (m, 3H), 1.70–1.63 (m, 1H), 1.60–1.21 (m, 7H), 1.13 (td, *J* = 13.0Hz, *J* = 4.0 Hz, 1H), 1.04–0.96 (m, 1H), 0.93–0.85 (m, 2H), 0.84 (s, 3H), 0.81 (s, 3H), 0.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 213.9, 174.8, 54.9, 53.9, 53.5, 51.8, 42.1, 42.0, 39.5, 38.6, 37.9, 33.4, 33.3, 29.6, 29.6, 23.8, 21.6, 21.0, 18.8, 14.0; HRMS (EI) calcd for C₂₀H₃₂O₃ [M]⁺: 320.2351, found: 320.2352.

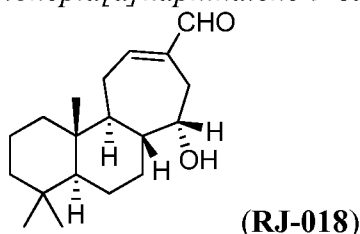
[0139] (6) (±)-(6a*S*,11a*S*,11b*R*)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[a]naphthalene-9-carbaldehyde (RJ-017)



[0140] To a solution of (±)-(6a*S*,7*S*,11a*S*,11b*R*)-9-(hydroxymethyl)-4,4,11b- trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[a]naphthalen-7-ol (RJ-014) (6.8 mg, 0.023 mmol) in DCM (0.27 mL) at room temperature was added Dess-Martin periodinane (29.3 mg, 0.069 mmol), and the stirring was continued for 6h. The reaction was quenched by 1M Na₂SO_{3(aq)} (0.5 mL) and sat. NaHCO_{3(aq)} (0.5 mL) and stirred for another 30 minutes. The phases were separated, and the aqueous layer was extracted with DCM (3 × 4 mL). The organic extracts were combined, washed with brine (10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash chromatography (1:19 EtOAc:hexanes) to afford (±)-(6a*S*,11a*S*,11b*R*)-4,4,11b-trimethyl-7-oxo-

2,3,4,4a,5,6,6a,7,8,11,11a,11b- dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-017) (4.4 mg, 65%). Data for RJ-017: Mp 87–88 °C; IR (film): 2927, 2867, 2837, 1707, 1686, 1639, 1461, 1444, 1388, 1366, 1251, 1152, 1139, 1114 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 6.85–6.82 (m, 1H), 3.45–3.35 (m, 2H), 2.72–2.62 (m, 1H), 2.56 (td, *J* = 12.0 Hz, *J* = 4.0 Hz, 1H), 2.24–2.13 (m, 1H), 1.88–1.79 (m, 2H), 1.79–1.72 (m, 1H), 1.71–1.66 (m, 1H), 1.66–1.58 (m, 1H), 1.54–1.30 (m, 4H), 1.18 (td, *J* = 13.4 Hz, *J* = 4.0 Hz, 1H), 1.00–0.90 (m, 2H), 0.88 (s, 6H), 0.84 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 210.6, 192.3, 153.8, 137.3, 54.7, 53.9, 51.0, 41.8, 38.6, 37.4, 36.4, 33.3, 33.3, 29.8, 28.6, 21.5, 21.0, 18.7, 14.2; HRMS (EI) calcd for C₁₉H₂₈O₂ [M]⁺: 288.2089, found: 288.2084.

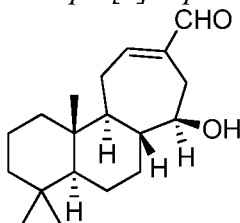
[0141] (7) (±)-(7*S*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-018)



[0142] A solution of (±)-(6*aS*,7*S*,11*aS*,11*bR*)-9-(hydroxymethyl)-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (RJ-014) (58 mg, 0.20 mmol), TEMPO (3.1 mg, 0.02 mmol), and TBACl (5.5 mg, 0.02 mmol) in DCM (2 mL) and aqueous solution of NaHCO₃ (0.5M, 1 mL) and K₂CO₃ (0.05M, 1 mL) were vigorously stirred at room temperature. NCS (53 mg, 0.40 mmol) was then added. Stirring was maintained and the reaction monitored by TLC. After 8h, the reaction was quenched with sat. NH₄Cl (4 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The DCM extracts were washed with brine (15 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The residue was coated on silica gel and purified by flash column chromatography (gradient from 1:19 → 1:4 EtOAc:hexanes) to give (±)-(7*S*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-018) (43 mg, 75%) as a white solid. Data for RJ-018: Mp 148–150 °C; IR (film) 3470, 2934, 2918, 2859, 2846, 1671, 1645, 1444, 1387, 1109, 1082, 1046, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 6.96–6.92 (m, 1H), 3.82 (d, *J* = 6.8 Hz, 1H), 2.97 (dd, *J* = 15.2 Hz, *J* = 8.0 Hz, 1H), 2.53 (dd, *J* = 14.6 Hz, *J* = 9.0 Hz, 1H), 2.30 (d, *J* = 15.6 Hz, 1H), 2.11–2.00 (m, 1H), 1.90–1.59 (m, 6H), 1.59–1.49 (m, 1H), 1.49–1.34 (m, 3H), 1.34–1.21 (m, 1H), 1.18–1.07 (m, 2H), 0.90 (dd, *J* = 12.9 Hz, *J* = 3.5 Hz, 1H), 0.85 (s, 3H), 0.84 (s, 3H), 0.81 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 193.8, 156.3,

142.3, 69.8, 54.6, 47.2, 46.1, 41.8, 39.1, 37.7, 33.4, 33.4, 30.8, 29.2, 28.8, 21.8, 21.4, 18.8, 14.0; HRMS (ESI) calcd for $C_{19}H_{30}O_2$ $[M+Na]^+$: 313.2143, found: 313.2151.

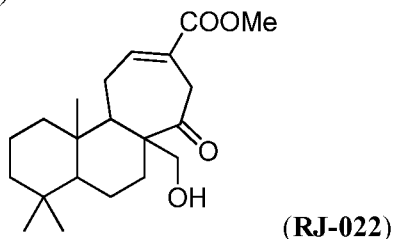
[0143] (8) ($\pm$)-(7*R*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-019)



(RJ-019)

A solution of ($\pm$)-(6*aS*,7*R*,11*aS*,11*bR*)-9-(hydroxymethyl)-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalen-7-ol (RJ-013) (30 mg, 0.10 mmol), TEMPO (1.6 mg, 0.01 mmol), and TBACl (2.8 mg, 0.01 mmol) in DCM (1 mL) and aqueous solution of $NaHCO_3$ (0.5M, 0.5 mL) and K_2CO_3 (0.05M, 0.5 mL) were vigorously stirred at room temperature. NCS (27.5 mg, 0.21 mmol) was then added. Stirring was maintained and the reaction monitored by TLC. After 24h, the reaction was quenched with sat. NH_4Cl (4 mL), the organic layer was separated, and the aqueous layer was extracted with DCM (3×5 mL). The DCM extracts were washed with brine (15 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was coated on silica gel and purified by flash column chromatography (gradient from 1:9 $\rightarrow$ 1:4 EtOAc:hexanes) to give ($\pm$)-(7*R*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-019) (19 mg, 64%) as a white solid. Data for RJ-019: Mp 142–144 °C; IR (film): 3507, 2963, 2917, 2863, 2844, 1678, 1648, 1436, 1384, 1345, 1302, 1212, 1041, 1007 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 6.96–6.93 (m, 1H), 3.49–3.43 (m, 1H), 2.70 (dd, $J = 16.0$ Hz, $J = 8.5$ Hz, 1H), 2.63–2.49 (m, 2H), 2.30–2.20 (m, 1H), 2.07–2.00 (m, 1H), 1.89–1.82 (m, 1H), 1.79–1.70 (m, 1H), 1.70–1.52 (m, 4H), 1.52–1.43 (m, 1H), 1.43–1.29 (m, 2H), 1.14 (td, $J = 13.5$ Hz, $J = 3.0$ Hz, 1H), 1.09–0.93 (m, 2H), 0.87 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H), 0.82–0.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.9, 157.6, 140.5, 74.4, 54.8, 53.1, 48.1, 42.0, 38.8, 38.0, 33.4, 33.4, 32.6, 28.8, 28.1, 21.7, 21.6, 18.9, 14.0; HRMS (ESI) calcd for $C_{19}H_{30}O_2$ $[M+Na]^+$: 313.2143, found: 313.2137.

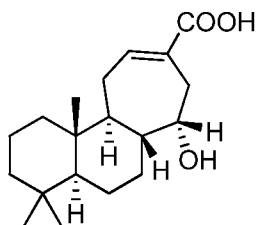
[0144] (9) (6aR,11aR,11bS) -methyl6a-(hydroxymethyl) -4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-carboxylate (RJ-022)



[0145] A mixture of Cp_2TiCl_2 (794 mg, 2.20 equiv.) and Zinc powder (625 mg, 6.60 equiv) in deoxygenated THF (14 mL) was stirred at room temperature (30 min) until the red solution turned green. The green Ti(III) solution was slowly added via cannula to the stirred solution of (*E*)-methyl 2-(cyanomethyl) -4-((1*R*,2*R*,8*aS*) -5,5,8*a*-trimethyl octahydro-1*H*-spiro[naphthalene-2,2'-oxiran]-1-yl)but-2-enoate (500 mg, 1.45 mmol) in THF (15 mL) and stirred for 12 h. After this, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 30 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into ether (3 x 30 mL), and the combined organic layers were washed with saturated NaHCO_3 (20 mL) and brine, dried over Na_2SO_4 , concentrated and the crude product was column chromatographed (EtOAc-hexanes, 1:9) to afford (6*aR*,11*aR*,11*bS*) -methyl6*a*-(hydroxymethyl) -4,4,11*b*-trimethyl-7-oxo-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[a]naphthalene-9-carboxylate (**RJ-022**) as colorless needles (302 mg, 60%).

[0146] Characteristic data of **RJ-022**: $[\alpha]_D^{25}$ -21.1 (*c* 0.93, CHCl_3); mp 179-180 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.07 (dt, *J* = 6.2, 3.1 Hz, 1H), 4.14 – 3.98 (m, 2H), 3.93 (ddd, *J* = 13.9, 6.7, 2.8 Hz, 1H), 3.74 (s, 3H), 3.49 (d, *J* = 13.9 Hz, 1H), 2.80 (dd, *J* = 8.0, 5.8 Hz, 1H), 2.65 – 2.44 (m, 2H), 2.18 (dd, *J* = 11.8, 2.1 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.81 (d, *J* = 12.4 Hz, 1H), 1.66 (ddd, *J* = 14.0, 8.7, 3.8 Hz, 2H), 1.53 – 1.34 (m, 5H), 1.18 (td, *J* = 13.5, 4.1 Hz, 2H), 0.95 (s, 3H), 0.88 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 214.6, 167.0, 143.7, 124.3, 63.3, 56.8, 56.5, 52.2, 50.6, 41.6, 39.8, 37.9, 37.7, 33.4, 33.1, 32.4, 26.3, 21.3, 18.4, 18.1, 16.1. IR (film) 3542, 2935, 1708, 1702, 1640, 1440, 1386, 1263, 1165, 1115, 1060, 753 cm^{-1} . HRMS (FAB+) calcd for $\text{C}_{21}\text{H}_{33}\text{O}_4$ $[(\text{M} + \text{H})^+]$ 349.2379, found 349.2380.

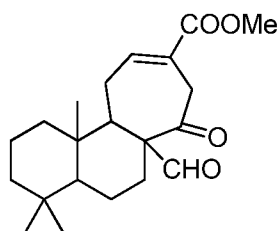
[0147] (12) (7*S*,11*aS*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[a]naphthalene-9-carboxylic acid (RJ-026)



(RJ-026)

[0148] A solution of sodium chlorite (12 mg, 0.13 mmol) and NaH_2PO_4 (41 mg, 0.34 mmol) in H_2O (0.2 mL) was added dropwise to a rapidly stirred solution of $(\pm)$ -(7*S*, 11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carbaldehyde (RJ-018) (10 mg, 0.034 mmol) and 2-methyl-2-butene (36 μL , 0.34 mmol) in *tert*-butyl alcohol (0.34 mL) at room temperature and the stirring was continued for 30h. The reaction mixture was made basic with 3N $\text{NaOH}_{(\text{aq})}$ and the *tert*-butyl alcohol was removed *in vacuo*. The residue was dissolved in water and extracted twice with hexanes. The water layer was acidified with 3N $\text{HCl}_{(\text{aq})}$ and extracted twice with ether. The organic layer was washed with water and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was coated on silica gel and purified by flash column chromatography (1:9 EtOAc:MeOH) to give (7*S*,11*aS*,11*bR*)-7-hydroxy-4,4,11*b*-trimethyl-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylic acid (RJ-026) (7.8 mg, 74%) as a white solid. Data for RJ-026: Mp 229–231 °C; IR (film): 3448, 2938, 2865, 2837, 1701, 1458, 1440, 1385, 1363, 1121, 1104, 1039, 1016, 969 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 7.16–7.13 (m, 1H), 3.83–3.80 (m, 1H), 2.93–2.85 (m, 1H), 2.48 (d, $J = 15.5$ Hz, 1H), 2.37 (dd, $J = 15.0$ Hz, $J = 9.0$ Hz, 1H), 2.00–1.87 (m, 2H), 1.84–1.76 (m, 1H), 1.76–1.65 (m, 2H), 1.65–1.57 (m, 1H), 1.50–1.44 (m, 1H), 1.44–1.27 (m, 4H), 1.19 (td, $J = 13.5$ Hz, $J = 4.0$ Hz, 1H), 1.11 (t, $J = 10.8$ Hz, 1H), 0.94–0.89 (m, 1H), 0.88 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 171.7, 145.1, 133.3, 71.3, 56.3, 49.6, 47.0, 43.2, 40.2, 38.8, 34.4, 34.0, 33.2, 31.1, 28.7, 22.7, 22.3, 20.0, 14.5; HRMS (EI) calcd for $\text{C}_{19}\text{H}_{30}\text{O}_3$ $[\text{M}]^+$: 306.2195, found: 313.2196.

[0149] (15) (6*aR*,11*aR*,11*bS*)-methyl6*a*-formyl-4,4,11*b*-trimethyl-7-oxo-2,3,4,4*a*,5,6,6*a*,7,8,11,11*a*,11*b*-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-029)

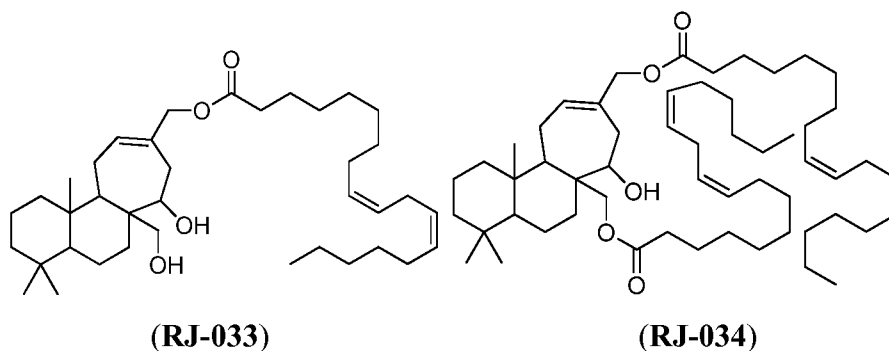


(RJ-029)

[0150] A solution of (6aR,11aR,11bS) –methyl 6a-(hydroxymethyl) -4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-carboxylate (40 mg, 0.11 mmol) in DCM (1 mL) was treated with Dess Martin periodinane (70 mg, 0.16 mmol), which was added in portions at room temperature. After being stirred for 1 h, the mixture was diluted with saturated aqueous Na₂S₂O₃ (1 mL) and NaHCO₃ (1 mL) were added. The resulting mixture was stirred vigorously for 30 min and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ and the combined organic extracts were washed with brine and concentrated under vacuum. The residue was column chromatographed (EtOAc-hexanes, 1:11) to obtain (6aR,11aR,11bS) -methyl 6a-formyl-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-carboxylate (**RJ-029**) as white solid (80%).

[0151] Characteristic data of **RJ-029**: mp 86-88 °C. IR (film) 2948, 1727, 1693, 1645, 1437, 1389, 1366, 1258, 1115, 1064, 733 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 9.84 (d, *J* = 1.0 Hz, 1H), 7.16 (dt, *J* = 6.3, 3.1 Hz, 1H), 3.92 – 3.80 (m, 1H), 3.75 (d, *J* = 6.6 Hz, 3H), 3.54 (d, *J* = 14.2 Hz, 1H), 2.89 – 2.65 (m, 2H), 2.40 – 2.26 (m, 2H), 1.84 – 1.70 (m, 2H), 1.68 – 1.58 (m, 1H), 1.53 – 1.39 (m, 4H), 1.18 (td, *J* = 13.4, 4.3 Hz, 1H), 1.01 – 0.92 (m, 2H), 0.89 (s, 3H), 0.79 (s, 3H), 0.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 206.2, 199.6, 166.6, 142.6, 125.0, 66.5, 55.4, 52.4, 51.4, 41.6, 38.8, 38.2, 37.6, 33.3, 33.2, 31.2, 25.5, 21.3, 18.8, 18.5, 15.2. HRMS (ES-) calcd for C₂₁H₂₉O₄ [(M - H)⁺] 345.2066, found 345.2059.

[0152] (18) (9Z,12Z)-(7-hydroxy -6a-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-yl)methyl octadeca-9,12,dienoate (**RJ-033**)/ (9Z,9'Z,12Z,12'Z)-((6aR,7R,11bS)-(7-hydroxy-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-6a,9-diyl)bis(methylene)bis(octadeca-9,12-dienoate (**RJ-034**))

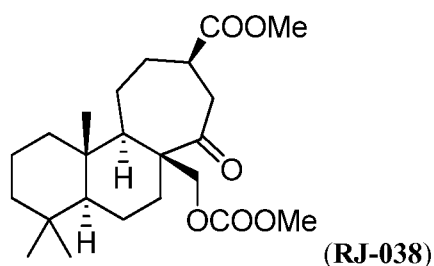


[0153] To the linoleic acid (LA) (10.4 mg, 0.037 mmol), DMAP (5.5 mg, 0.44 mmol) was added at room temperature, to this, ((6aR,7R,11aR,11bS) -7-hydroxy-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-6a,9-diyl)dimethanol (12 mg, 0.037 mmol) in CH_2Cl_2 (0.5 mL) was added, stirred and cooled to 0 °C and DCC (9 mg, 0.044 mmol) was directly added to the above mixture. The reaction mixture was stirred at room temperature for overnight and then the mixture was filtered, washed with CH_2Cl_2 (2 mL). The filtrate was successively washed with aq. HCl, sat. NaHCO_3 solution and then brine. The CH_2Cl_2 layer was dried over Na_2SO_4 , concentrated and the resulting residue was column chromatographed to give (9Z,12Z)-(7-hydroxy -6a-(hydroxymethyl)-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-9-yl)methyl octadeca-9,12,dienoate (**RJ-033**) as colorless oil (40%) and (9Z,9'Z,12Z,12'Z)-((6aR,7R,11bS)- (7-hydroxy-4,4,11b-trimethyl-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1H-cyclohepta[a]naphthalene-6a,9-diyl)bis(methylene)bis(octadeca-9,12-dienoate (**RJ-034**) as colorless oil (20%).

[0154] Characteristic data of **RJ-033**: IR (film) 3346, 3009, 2925, 2854, 1737, 1660, 1646, 1463, 1385, 1169, 1055, 967 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 5.93 (dd, $J = 8.2, 3.3$ Hz, 1H), 5.50 – 5.24 (m, 4H), 4.44 (s, 2H), 4.21 (d, $J = 11.4$ Hz, 1H), 3.95 (d, $J = 11.4$ Hz, 1H), 3.52 (d, $J = 8.1$ Hz, 1H), 2.77 (t, $J = 6.5$ Hz, 2H), 2.66 (dd, $J = 16.3, 8.7$ Hz, 2H), 2.44 (d, $J = 16.4$ Hz, 1H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.27 (dt, $J = 13.2, 3.1$ Hz, 1H), 2.16 (dd, $J = 16.1, 10.2$ Hz, 1H), 2.09 – 1.98 (m, 4H), 1.75 (d, $J = 12.5$ Hz, 1H), 1.66 – 1.54 (m, 8H), 1.47 – 1.25 (m, 14H), 1.13 (td, $J = 13.5, 4.3$ Hz, 1H), 1.04 (tdd, $J = 13.3, 4.1, 1.5$ Hz, 1H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 3.6$ Hz, 3H), 0.85 – 0.81 (m, 2H), 0.80 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 132.6, 132.2, 130.2, 130.0, 128.1, 127.9, 79.4, 69.5, 62.7, 56.3, 55.8, 46.4, 41.9, 39.7, 38.4, 34.3, 33.7, 33.5, 33.4, 33.2, 31.5, 29.6, 29.3, 29.1, 27.2, 25.6, 25.0, 22.9, 22.6, 21.3, 18.6, 18.4, 16.2, 14.1. HRMS (ES⁺) calcd for $\text{C}_{38}\text{H}_{64}\text{O}_4\text{Na}$ [(M + Na)⁺] 607.4702, found 607.4695.

[0155] Characteristic data of **RJ-034**: IR (film) 3457, 3007, 2924, 2854, 1737, 1659, 1650, 1454, 1385, 1243, 1163, 1087, 1054, 723 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 5.91 (d, $J = 4.7$ Hz, 1H), 5.48 – 5.20 (m, 8H), 4.70 (d, $J = 11.5$ Hz, 1H), 4.45 (d, $J = 12.8$ Hz, 1H), 4.43 (s, 2H), 3.43 (t, $J = 8.1$ Hz, 1H), 2.77 (t, $J = 6.5$ Hz, 4H), 2.57 (dd, $J = 16.3, 8.8$ Hz, 1H), 2.39 (d, $J = 16.2$ Hz, 1H), 2.33 (dd, $J = 15.3, 7.7$ Hz, 4H), 2.10 – 2.00 (m, 8H), 1.77 (d, $J = 12.1$ Hz, 1H), 1.69 – 1.57 (m, 4H), 1.44 (d, $J = 13.9$ Hz, 2H), 1.40 – 1.24 (m, 28H), 1.13 (td, $J = 13.4, 3.9$ Hz, 2H), 0.89 (t, $J = 6.8$ Hz, 6H), 0.86 (s, 3H), 0.83 (s, 3H), 0.80 (s, 3H).

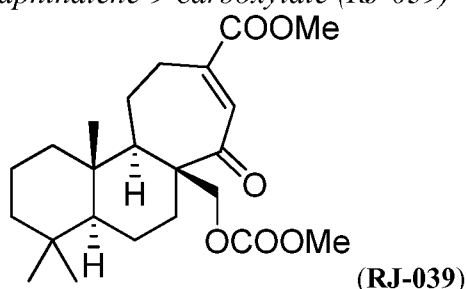
[0156] (22) ($\pm$)-(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxotetradecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (**RJ-038**)



[0157] To a solution of ($\pm$)-(4a*R*,4b*S*,10a*R*)-methyl 10a-((methoxycarbonyloxy) methyl)-4b,8,8-trimethyl-1-oxotetradecahydrophenanthrene-2-carboxylate (**RJ-037**) (23 mg, 0.058 mmol) in DCE (0.6 mL) was added Et_2Zn (1.0 M in hexane, 93 μL , 0.093 mmol) at 0 °C. After 10 minutes, CH_2I_2 (8 μL , 0.093 mmol) was added and the mixture was stirred at 0 °C for 2h. Then the reaction mixture was allowed to warm to room temperature and stirred for another 14h. The reaction contents were quenched with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (2 mL) at 0 °C and allowed to warm to room temperature. The phases were separated, and the aqueous layer was extracted with ether (3 $\times$ 2 mL). The organic extracts were combined, washed with sat. $\text{NaHCO}_{3(\text{aq})}$ (10 mL) and brine (10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient from 0:1 $\rightarrow$ 1:1 $\text{EtOAc}:\text{DCM}$) to afford ($\pm$)-(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyl oxy)methyl)-4,4,11b-trimethyl-7-oxotetradecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (**RJ-038**) (16 mg, 61%) as colorless liquid. Data for **RJ-038**: IR (film) 2951, 2868, 2843, 1750, 1704, 1441, 1389, 1367, 1264, 1201, 1175, 1158, 1116, 961, 791 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.72 (d, $J = 11.2$ Hz, 1H), 4.55 (d, $J = 11.2$ Hz, 1H), 3.76 (s, 3H), 3.69 (s, 3H), 2.99 (dd, $J = 11.6$ Hz, $J = 6.8$ Hz, 1H), 2.87–2.73 (m, 2H), 2.14–2.04 (m, 1H), 1.84–1.72 (m, 3H), 1.72–1.61 (m, 5H), 1.61–1.57 (m, 1H), 1.52–1.42 (m, 1H), 1.42–1.28 (m, 2H), 1.28–1.21 (m, 1H), 1.15 (td, $J = 13.4$ Hz, $J = 4.0$ Hz, 1H), 0.94–0.89 (m, 1H), 0.87 (s, 3H), 0.87 (s, 3H), 0.81 (s,

3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.2, 175.5, 155.6, 68.5, 56.4, 56.2, 54.8, 54.6, 52.1, 41.7, 39.6, 38.7, 38.5, 38.5, 33.4, 33.2, 31.5, 29.4, 21.4, 21.3, 18.6, 18.1, 16.0; HRMS (MALDI) calcd for $\text{C}_{23}\text{H}_{36}\text{O}_6$ $[\text{M}+\text{Na}]^+$: 431.2410, found: 431.2422.

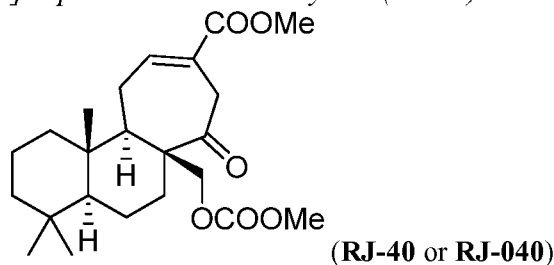
[0158] (23) ($\pm$)-(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,10,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-039)



[0159] To a solution of ($\pm$)-(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyloxy) methyl)-4,4,11b-trimethyl-7-oxotetradecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-038) (8.0 mg, 0.020 mmol) in THF (0.2 mL) was added LHMDs (0.5M in THF, 59 μL , 0.029 mmol) at -78°C . The mixture was allowed to warm slowly to -20°C over the course of 2h. Then, cooled down to -78°C , a solution of PhSeCl (5.6 mg, 0.029 mmol) in THF (0.05 mL) was added at -78°C . After 3h, the reaction was quenched by sat. $\text{NaHCO}_3(\text{aq})$ (2 mL), and the aqueous layer was extracted with ether (3×2 mL). The organic extracts were combined, washed with brine (6 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. To a solution of the residue mentioned above in THF (0.4 mL) was added $\text{H}_2\text{O}_2(\text{aq})$ (4 μL , 0.050 mmol) and pyrene (4 μL , 0.050 mmol) at room temperature. After 2h, the reaction was quenched by sat. $\text{NaHCO}_3(\text{aq})$ (2 mL), and the aqueous layer was extracted with ether (3×2 mL). The organic extracts were combined, washed with brine (6 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient from 1:49 $\rightarrow$ 1:9 EtOAc:hexanes) to give ($\pm$)-(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,10,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-039) (5.0 mg, 63%) as colorless oil. Data for 37: IR (film) 2952, 2865, 2845, 1752, 1721, 1693, 1440, 1389, 1363, 1264, 1210, 1134, 965, 948 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.94 (d, $J = 2.0$ Hz, 1H), 4.70 (d, $J = 11.0$ Hz, 1H), 4.59 (d, $J = 11.0$ Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.88–2.79 (m, 1H), 2.32–2.21 (m, 1H), 1.96–1.85 (m, 1H), 1.85–1.77 (m, 2H), 1.72–1.65 (m, 1H), 1.65–1.42 (m, 4H), 1.42–1.23 (m, 3H), 1.14 (td, $J = 13.4$ Hz, $J = 4.0$ Hz, 1H), 0.97–0.87 (m, 2H), 0.92 (s, 3H), 0.86 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 207.2, 167.5, 155.5, 138.1, 137.0, 69.0, 56.2, 55.5, 54.9,

54.9, 52.5, 41.7, 39.3, 38.9, 33.4, 33.2, 32.4, 29.5, 21.8, 21.4, 18.5, 18.2, 16.2; HRMS (ESI) calcd for $C_{23}H_{34}O_6$ $[M+Na]^+$: 429.2253, found: 429.2254.

[0160] (24) $(\pm)$ -(6a*R*,11a*R*)-methyl 6a-((methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-40)



[0161] A solution of $(\pm)$ -(6a*R*,11a*R*,11b*S*)-methyl 6a-((methoxycarbonyloxy) methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,10,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-039) (25 mg, 0.062 mmol) and DBU (19 μ L, 0.124 mmol) in benzene (1.24 mL) was refluxed for 3 h. The reaction was cooled down to room temperature and then quenched by sat. $NH_4Cl_{(aq)}$ (2 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3×2 mL). The combined organic layers were washed with sat. $NaHCO_{3(aq)}$ (5 mL) and brine (5 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The residue was purified by flash column chromatography (gradient from 1:49 $\rightarrow$ 1:9 EtOAc:hexanes) to give $(\pm)$ -(6a*R*,11a*R*)-methyl 6a-((methoxycarbonyloxy)methyl)-4,4,11b-trimethyl-7-oxo-2,3,4,4a,5,6,6a,7,8,11,11a,11b-dodecahydro-1*H*-cyclohepta[*a*]naphthalene-9-carboxylate (RJ-40) (20 mg, 80%) as colorless oil. Data for RJ-40: IR (film) 2950, 2868, 2843, 1751, 1711, 1645, 1440, 1388, 1367, 1260, 1116, 1069, 963, 790 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13–7.09 (m, 1H), 4.75 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 3.81 (dd, J = 13.8 Hz, J = 2.2 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.58 (d, J = 14.0 Hz, 1H), 2.78–2.66 (m, 1H), 2.60–2.50 (m, 1H), 2.08–2.01 (m, 1H), 1.86–1.78 (m, 1H), 1.73–1.54 (m, 3H), 1.54–1.44 (m, 1H), 1.44–1.23 (m, 3H), 1.16 (td, J = 13.4 Hz, J = 4.0 Hz, 1H), 0.95 (s, 3H), 0.94–0.88 (m, 2H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2, 167.0, 155.4, 144.0, 124.4, 69.3, 56.3, 55.8, 54.8, 52.2, 52.1, 41.6, 39.8, 38.3, 37.5, 33.7, 33.4, 33.1, 26.6, 21.3, 18.5, 18.5, 15.6; HRMS (EI) calcd for $C_{23}H_{34}O_6$ $[M+Na]^+$: 429.2253, found: 429.2260.

Example 2: Characterization of Bioactivities of Exemplary GLP-1 Receptor Modulators

[0162] Receptor endocytosis following arrestin recruitment and cAMP production subsequent to *G* α s coupling are two major immediate downstream cellular pathways upon

GLP-1 receptor activation. Arrestin recruitment will lead to proliferation and anti-apoptosis of pancreatic b-cells (30, 31), while production of cAMP will lead to insulin secretion (Doyle et al., Pharmacology & Therapeutics, 2007, 113, 546). In this example, the β -arrestin2-GFP biosensor technology (45) was employed in screening for a plant extract library to identify those that can potentiate GLP-1 to elicit receptor endocytosis. Upon agonist binding to GPCR, the cytoplasmic arrestin rapidly translocate to and bind to the activated GPCR. Arrestin also mediates receptor internalization by targeting the receptor to clathrin-coated pits (46) which is a convergent step of GPCR activation. β -arrestin2-GFP biosensor technology involved less steps of enzymatic cascade and yielded more information on the compound (45), thus was used in the initial screening of plant crude extracts and also used as an assay for purifying active compounds from plant crude extracts there would found to be active in eliciting receptor endocytosis. Following the activity of this assay, a *Hedychium coronarium* (HC) extract was identified to potentiate GLP-1 in arrestin mediated GLP-1 receptor endocytosis. Furthermore, compounds were isolated and purified from HC extract to homogeneity by activity directed fractionation, one of the active compounds was identified to be galanal B. Abilities of synthetic galanal B and its analogs to modulate GLP-1 dependent cAMP production in RINm5F cells and to modulate GLP-1 dependent receptor endocytosis were compared. This analysis revealed that by modifying structure of galanal B, novel compounds can be generated that selectively potentiate or suppress GLP-1 in G α s coupling pathway. Since it is well documented that type II diabetes still retain their ability to secrete GLP-1 (43,44), it is expected that compound positively modulates GLP-1 by increasing the potency of GLP-1 should be potential drug of choice in anti-diabetics.

Materials and Methods

[0163] *Extraction of HC leaves*

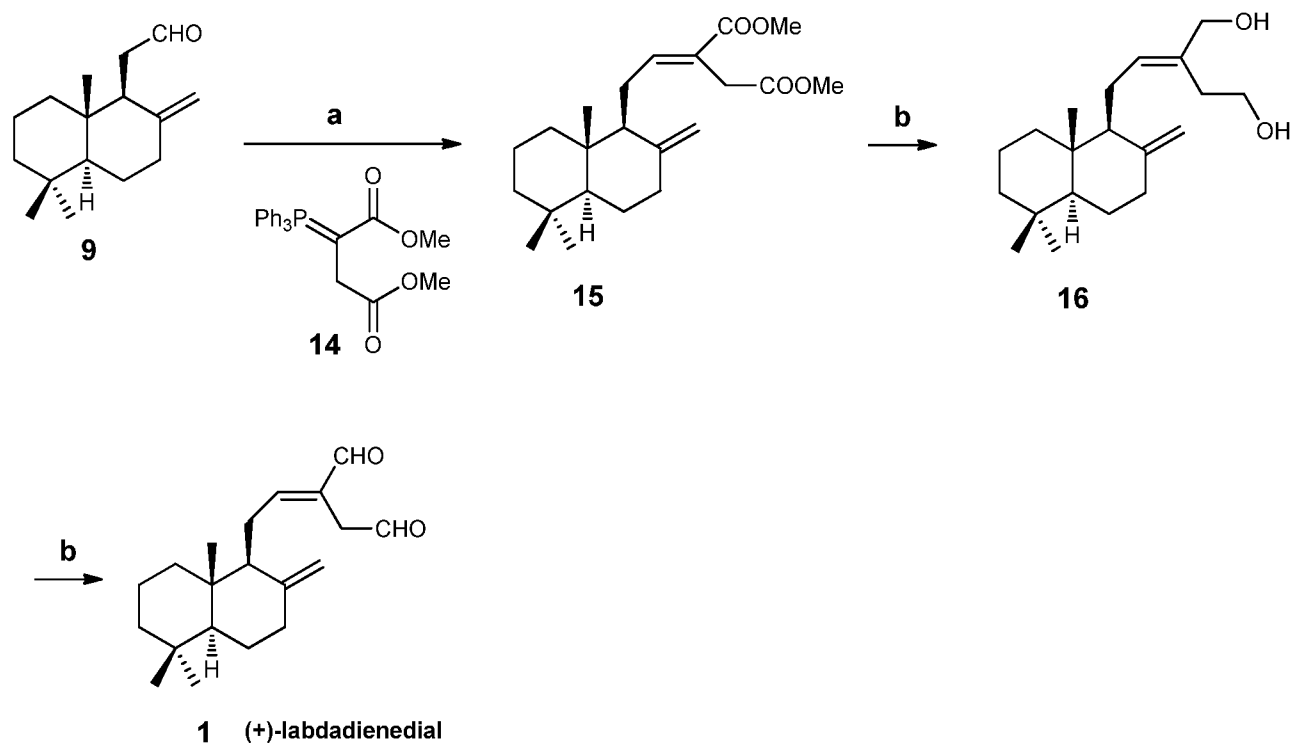
[0164] Dried leaves of HC (2 kg) was minced and extracted with ethanol (20 L) at room temperature with constant stirring for 2 days. The extract was filtered off and concentrated to give a residue that was suspended in 500 ml of 80% ethanol and partitioned with 500 ml of n-hexane for three times. The remaining was concentrated, suspended in 500 ml of water and partitioned with 500 ml ethyl acetate three times followed by 500 ml *n*-BuOH three times. 7 g of ethyl acetate fraction was chromatographed on a silica-gel column (4.5 cm $\times$ 21 cm, 180 g MERCK 200-400 mesh silica gel) eluted with 1200 ml of 20% and 1200 ml of 30% hexane-EtOAc each, followed by 1600 ml of 50%, 800 ml of 80% hexane-EtOAc and 800 ml of

100% EtOAc, the column was further eluted with 800 ml each of 20% and 50% methanol: EtOAc; 200 ml was collected for each fraction.

[0165] *Chemical synthesis of galanal B and its analogues*

[0166] Commercially available (+)-sclareolide (**3**) was selected as the starting material and readily converted, as shown in *Scheme 1*, to olefin **5** in 68% yield through a two-step protocol (**1**, **2**) and subsequently reduced by LiAlH_4 to afford aldehyde **6** in 90% yield. With considerable optimization, the subjection of **6** into a solution of ylide **7** in hot toluene efficiently furnished Wittig adduct **8** as a single isomer in 85% yield. The terminal double bond of compound **8** was then epoxidized selectively by *m*-CPBA, giving an inseparable mixture of **9** and **10** in a ratio of 10:1. When the mixture of epoxides **9** and **10** was subjected to Cp_2TiCl_2 and Zn metal (**3-7**), the Ti(III) species generated *in situ* would react with oxirane to afford the homolytic cleavage of the more substituted C–O bond, giving the more stable tertiary radical intermediate. Subsequently, the ensuing equatorial addition of the $\square$ -titanoxyl radical to the nitrile caused the generation of imine radical, which evolved into the corresponding ketone. Compound **11** was obtained exclusively in 60% yield with trace amount of side products originated from ring opening of oxirane. The structural connectivity of **11** was confirmed by single-crystal X-ray diffraction. DIBAL-H reduction of **11** to compound **2** (a mixture of triols **12** and **13**) followed by selective oxidation of primary alcohols by TEMPO (**8**) furnished 1:5 ratio of galanal A and galanal B, which can be separated by column chromatography and are identical in all respect with authentic samples isolated from HC plant and the reported data (**9**, **10**).

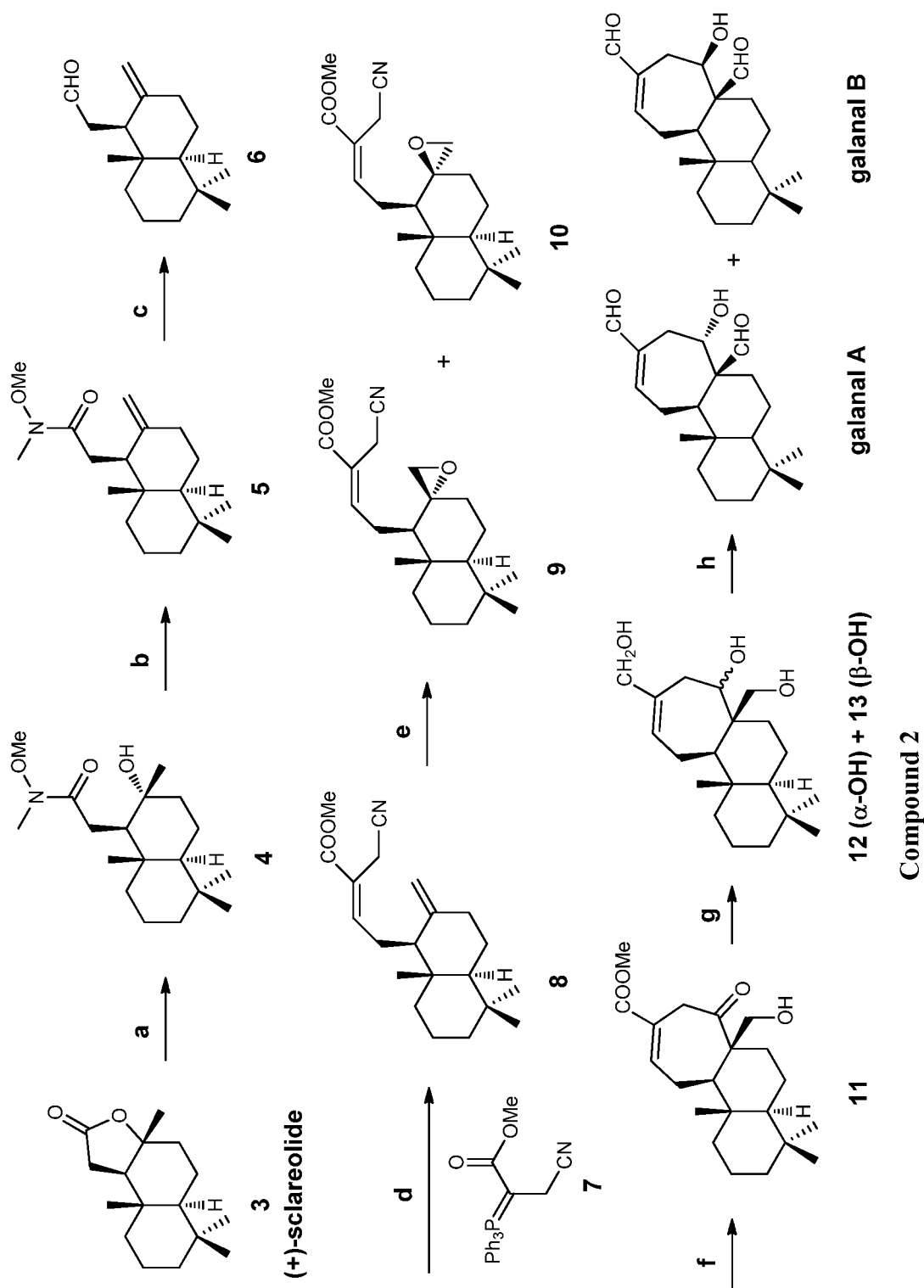
[0167] Compound **1** was synthesized according to the method shown in *Scheme 1*.



Scheme 1. Exemplary synthesis of compound 1

[0168] Compound 2 was synthesized according to the method shown in *Scheme 2*.

[0169] MeNHOMe·HCl (2 equiv.), Me₃Al (2 equiv.), CH₂Cl₂, 0°C to rt (room temperature), 85%. b) SOCl₂ (5 equiv.), pyridine (10 equiv.), CH₂Cl₂, -78°C, 80%. c) LiAlH₄ (2 equiv.), THF, rt, 90%. d) 10 (3 equiv.), toluene, reflux, 85%. e) *m*-CPBA (2 equiv.), CH₂Cl₂, rt, 85%. f) Cp₂TiCl₂ (2.2 equiv.), Zn (6.6 equiv.), THF, rt, 60%. g) DIBAL-H (8 equiv.), CH₂Cl₂, -78°C, 80%. h) TEMPO (0.2 equiv.), NCS (4 equiv.), TBACl (0.2 equiv.), NaHCO₃, K₂CO₃, CH₂Cl₂, rt, 70%).



Scheme 2. Exemplary synthesis of galanal A and galanal B (Reagents and conditions: a)

[0170] *Receptor endocytosis assay*

[0171] U2OS osteosarcoma cell line stably expressing a β -arrestin2:GFP fusion protein was obtained from Norak Biosciences (now Molecular Devices, part of MDS Inc., Mississauga, Ontario). GLP-1 receptor expression construct was used to transfect the U2OS cell stably expressing β -arrestin2:GFP fusion protein and to obtain cell line stably co-expressing GLP-1 receptor and β -arrestin2:GFP fusion protein. High-content imaging of receptor endocytosis in cells was conducted with 0.03 mg/ml of ethanol extract from 2500 edible plant to identify potentiating activity for the GLP-1 dependent GLP-1 receptor endocytosis. Extracts were supplied at a concentration of 100 mg/ml in 100% DMSO. Three replicate 384-well assay microplates were plated with U2OS cells stably expressing GFP- β -arrestin2 fusion protein and the GLP-1 receptor at a density of 3,000 cells per well. Aliquots of 2.5 μ L of $10 \times$ stocks of plant extract in phenol red free MEM containing 1, 0.3, or 0.1 mg/ml of plant extract plus 40 nM of GLP-1 were transferred to each well of the cell assay plate, which contained 22.5 μ L of phenol red free MEM. The 3 cell assay plates were incubated at room temperature for 60 min before fixation with 2% formaldehyde and labeling of the cell nuclei with 5 μ g/mL of the DNA-binding dye Hoechst 33342 (Molecular Probes, Eugene, OR) for 1 hr. Plates were washed with PBS twice and sealed and could be stored at 4 °C. The final concentration of the extract in the cell plate was 0.1, 0.03 and 0.001 mg/ml, and the final DMSO concentration was 1%.

[0172] *Bioluminescence resonance energy transfer (BRET) assay*

[0173] BRET assays were performed to examine the effect of candidate GLP-1 receptor modulators on the intracellular cAMP levels in RINm5F cells (an insulin-secreting cell line), following routine technology. See, e.g., Bertrand et al., J. Recept Signal Transduct Res., 2002, 22(1-4):533-541; Barak et al., Mol. Pharmacol., 74(3):585-594 (2008); U.S. Patent No. 8647887, and WO1999066324.

[0174] *Imaging and analysis*

[0175] Images and data of the cells were performed according to reported methods (51), using an ArrayScan® VTI HCS Reader (Cellomics, Inc. Pittsburgh, PA). Appropriate filter sets for detection of the 2 fluorophores were used, and the different fluorescent signals were recorded in 2 different image collection channels of the ARRAYSCAN VTI HCS Reader (*i.e.*, channel 1 contained the blue fluorescent Hoechst 33342-labeled nuclear images, and channel 2 contained the green fluorescent GFP- β -arrestin images). A 20×0.4 numerical aperture microscope objective was used for the imaging, 3 fields were imaged per well, and

CELLOMICS's Spot Detector BIOAPPLICATION was used to acquire and analyze the images. For these experiments, the Spot Detector BIOAPPLICATION used the Hoechst-labeled nuclei to identify individual cells and then automatically counted and analyzed the GFP-labeled spots associate with each cell. In addition to the number of spots and the sum of their areas and pixel intensities, the BIOAPPLICATION also reports properties of the individual nuclei such as their area. The extent of receptor endocytosis response was expressed as % of that elicited by 1 μ M of GLP-1.

[0176] One unit of activity is defined as the activity that will reach 50% of maximal response in a well of 384-well plate.

Results

[0177] *Primary screening herb ethanol extracts that are able to potentiate GLP-1 signaling*

[0178] To identify dietary molecules that could potentiate GLP-1 dependent receptor signaling, an ethanol extract library consisting 2500 edible plants was screened using β -arrestin2-GFP biosensor technology which is based on the observation that the β -arrestin2 binding of an activated receptor is a convergent step of GPCR signaling (45, 46). By monitoring the binding of β -arrestin2-GFP to the activated GLP-1 receptor and the following β -arrestin-mediated internalization of the activated receptors to clathrin-coated pits, a dose dependent activation of GLP-1 receptor by GLP-1 was observed. In addition, these processes can be visualized from its image (52), thus easily exclude false positive hits. As shown in *Fig. 1*, GLP1 (7-37) activates GLP1 receptor dependent β -arrestin2 translocation in a dose dependent and saturable manner, and the EC_{50} was measured to be 10 nM of GLP-1. This analysis demonstrated that 4 nM of GLP1 (7-37) is able to activate GLP-1 receptor to the level of 10 to 20% of the maximal response by 1 μ M of the peptide. To screen for extract that acts as a modulator to potentiate GLP-1 concentration dependent GLP1 receptor endocytosis, 0.1 mg/ml of plant ethanol extract was used to test its ability to enhance the agonistic effect of 4 nM of GLP-1 (7-37) on cells co-expressing GLP-1 receptor and β -arrestin2-GFP. 2500 herb ethanol extracts were screened for ability to enhance the GLP-1 receptor endocytosis elicited by 4 nM of GLP-1. 25 out of 2500 herb extracts were found to enhance the agonistic activity of 4 nM GLP-1 (7-37) from 20 % to more than 80% of the maximal response, however, 9 out these 25 primary hits were false positive as judged by visualizing the corresponding images. The remaining 16 positive hits were tested for their selectivity to potentiate GLP-1 receptor by assaying their effect on PTHR, GIPR and BRS3 signaling.

These selectivity tests revealed that 11 out of these 16 positive hits will also activate PTHR or GIPR or BRS3, thus the remaining 5 plant extracts were found specifically potentiate GLP-1 receptor signaling. 4 out of these 5 plants have been documented to display hypoglycemic effect or anti-diabetic effect on rodent or on other mammalian species, HC is the only plant has not been reported for its effect on blood glucose excursion. HC ethanol extract was further subjected to characterizing its effects on the potency and efficacy of GLP-1 signaling. As shown in *Fig. 2A*, GFP-arrestin is evenly distributed in the cytosol of cells stably co-expresses β -arrestin1-GFP and GLP-1 receptor when the receptor is at resting stage, addition of 0.06 mg/ml of HC extract alone do not change the distribution of β -arrestin1-GFP, stimulation by 4 nM of GLP-1 leads to low level formation of vesicles contains β -arrestin1-GFP and GLP-1 receptor in the cytosol and perinuclear region, much more vesicles of the receptor/ β -arrestin1-GFP complex was observed if cell co-incubated with 4 nM GLP-1 and 0.06 mg/ml of HC extract. *Fig. 2B* reveals titration of GLP-1 on GLP-1 receptor activation responses as % of that stimulated by 1 μ M of GLP-1, showing that activation increased as GLP-1 increased from 1.5 nM and reached saturation at 324 nM of GLP-1, revealing that GLP-1 elicits GLP-1 receptor endocytosis in a dose dependent and saturable manner. While in the presence of 0.06 mg/ml ethanol extract of HC, the receptor activation started with 0.44 nM of GLP-1 and reached saturation at a GLP-1 concentration of 10 nM. Comparison of the dose response data of GLP-1 titration revealed that EC_{50} was reduced from 10.7 nM to 3.8 nM and that maximal activation increased from 88.2% to 129% by the presence of 0.06 mg/ml of ethanol extract of HC. The effect of HC ethanol extract is highly dependent on the concentration of GLP-1, since HC plant extracts alone does not elicit GLP-1 receptor endocytosis, indicating that it behaves like a potentiator rather than an agonist on GLP-1 receptor. This analysis indicated HC ethanol extract potentiate GLP-1 signaling by increasing the efficacy and potency of GLP-1. Further, the potency of HC extract on GLP-1 signaling was also evaluated. A titration of HC extract was performed on the receptor endocytosis elicited by 4 nM GLP-1. *Fig. 2C* revealed the dose-response analysis of the titration of HC extract on receptor activation by 4 nM GLP-1; 4 nM of GLP-1 alone led to 20% of receptor activation while as the concentration of HC ethanol extract increased to 0.022mg/ml the receptor activation increased, and when HC increased to 0.2 mg/ml the activation by 4 nM of GLP-1 was potentiated from 20% to 70%. This analysis revealed that the HC ethanol extract potentiated GLP-1 activity in a dose dependent and saturable manner with an EC_{50} for GLP-1

signaling around 0.038 mg/ml and that maximal potentiation stimulation up to 70% of that of maximal GLP-1 titration. The potentiation effect of HC required the presence of GLP-1 as the ethanol extract of HC alone do not elicit any receptor endocytosis and has no effect on the distribution of GFP-arrestin in U2OS cells (*Fig. 1 A*).

[0179] *Isolation and purification of active components from HC ethanol extract*

[0180] Since extract from HC displayed potent activity on GLP-1 elicited receptor endocytosis, the active components was isolated according to its effect to potentiate GLP-1 elicited receptor endocytosis. Solvent partition with hexane, ethyl acetate, butanol, and water revealed that most of the activity was recovered in the ethyl acetate fraction (*Table I*), while little activity was noted in the layer of dH₂O. There is a 6-fold increase in the affinity of the fraction to potentiate GLP-1 elicited GLP-1 receptor endocytosis in ethyl acetate fraction as the EC₅₀ of the fraction was reduced from 0.045 mg/ml to 0.007 mg/ml. The recovery of the activity was more than 100% in this step of fractionation, indicating some of the negative activity was removed. Chromatography of the ethyl acetate fraction on silica gel resolved into 36 fractions, activity assay of each fraction showed a significant activity was recovered between fraction 4 to fraction 12 (*Fig. 3*). These active fractions (fraction I) were pooled and subjected to reverse phase silica gel chromatography and resolved into 106 fractions (*Fig. 4*). There are 30 fractions showing activity significantly higher than that of 4 nM GLP-1 alone. Fraction 26 is one of the fractions able to potentiate GLP-1 response from 20% to 40% at a concentration of 0.0002 mg/ml and its EC₅₀ to potentiate 4 nM of GLP-1 was measured to be EC₅₀ = 0.00024 mg/ml, and its potentiation effect is selective for GLP-1 but not for PTH (*Figs. 5 A and 5B*). Since this fraction displayed purity more than 90 % thus was subjected to structure elucidation, and its structure turn out to be galanal B which increase the affinity of GLP-1 by 4 folds (*Fig. 5 C*).

[0181] Table 1. Partition of ethanol extract of HC

HC Fraction	Weight (gram)	EC ₅₀ at 4 nM GLP1 (mg/ml)	Specific Activity ^a (U/mg)	Total Activity ^b (U) × 10 ³
Dried plant	1400			
Ethanol extract	209.65	0.045	0.42×10^3	8.8×10^7
Hexane	33.42	0.032	1.25×10^3	4.2×10^7
Ethyl acetate	19.3	0.007	5.71×10^3	1.1×10^8
Butanol	28.6	nd	nd	nd
dH ₂ O	124.6	nd	nd	

^a One arbitrary unit is defined as the activity that will induce 50% of maximal response in a well of 384-well plate with a volume of 25 μ L for each well.

^b Total activity is obtained by multiplying the specific activity to the total weight.

[0182] Characterization of galanal B, compound 1, and compound 2

[0183] Galanal B, Compound 1, and Compound 2 were synthesized as described above.

Their effects on GLP-1 induced receptor endocytosis were investigated. As shown in *Fig. 7*, dose response curve of GLP-1 and receptor endocytosis was left shifted by the presence of 0.003 mg/ml of these compounds. The EC₅₀ values and efficacy of galanal B, compound 1, and compound 2 are shown in Table 2 below. These results show that the potentiating effect of these compounds on GLP-1 dependent receptor endocytosis is highly dependent on the presence of GLP-1 since reduced levels of GLP-1 resulted in a decrease of the activity. The potentiating effects of these compounds are all blocked by GLP-1 receptor antagonist – exendin 9 (*Fig. 8*), indicating their effects are mediated via GLP-1 receptor.

[0184] Table 2. Effect of galanal B, compound 1, and compound 2 on the EC₅₀ and efficacy of GLP-1 to elicit receptor endocytosis

	GLP-1 only	Compound 2 + GLP-1	Galanal B + GLP-1	Compound 1 + GLP-1
EC ₅₀ (nM)	8.1	0.80	1.1	4.8
Efficacy (100%)	83.2	82	115.2	106.6

[0185] GLP-1 receptor is coupled to G α s and leads to generation of cAMP in pancreatic β cells, to examine if the receptor endocytosis potentiating activities of the present compounds will translate into the ability to potentiate cAMP production, the effect of these compounds on the GLP-1 induced intracellular cAMP generation in RINm5F cell was tested via a BRET assay, using a cAMP biosensor as known in the art, which monitored the bioluminescence energy transferring as intracellular cAMP level increased (53). It has been demonstrated that cAMP binding induced a remarkable conformational change of the cAMP sensor expressed in RINm5F cells and the conformational change was determined by measuring the bioluminescence resonance energy transfer between the donor and acceptor in the cAMP sensor. In the resting stage when the intracellular cAMP is minimal, a large BRET ratio was observed. When cells were incubated with GLP-1 or forskolin, an increase of the intracellular levels of cAMP and a decrease of the BRET ratio were observed. However, this dose response was eliminated by the presence of 250 μ M of adenylyl cyclase inhibitor MDL 12330A. To analyze the effect of compounds on the GLP-1 elicited cAMP production, it was examined if the potency of GLP-1 be changed by the presence of galanin b, compound 1, and compound 2. As shown in *Fig. 9A*, the dose response curve of GLP-1 was left shifted by 2.5 orders of magnitude when cells were co-incubated with 0.0025mg/ml of compound 2 and EC₅₀ was reduced from 7.8 nM to 0.0025 nM. The effect of compound 2 on GLP-1 elicited cAMP production decreased as GLP-1 concentration reduced and was diminished when GLP-1 concentration reduced to 0.1 pM, indicating that compound 2 alone is not able to induce cAMP production, but to increase the potency of GLP-1 to stimulate cAMP production. The potentiating effect of compound 2 on GLP-1 stimulated cAMP production was blocked by the presence of GLP-1 receptor antagonist - exendin 9 (*Fig. 10A*) or by MDL12330A - cyclase inhibitor (*Fig. 10B*), indicating the requirement of GLP-1 receptor and production of cAMP in the potentiation by compound 2. To measure the affinity of compound 2 to potentiate GLP-1 dependent cAMP production, the effect of compound concentration on the enhancement of cAMP production elicited by 3 nM of GLP-1 was titrated. As shown in *Fig. 9B*, the production of cAMP by 3 nM of GLP-1 increased as the concentration of compound increased and became saturated as the concentration of compound 2 reach 0.03 mg/ml. The affinity of compound 2 to enhance GLP-1 was determined to be 0.001 mg/ml. Similar dose of galanin B did not facilitate GLP-1 to stimulate cAMP production (*Fig. 9A*), galanin B did not significantly affect the dose-response curve of GLP-1 and cAMP production by 3 nM of GLP-1 was not changed by galanin B up to 0.04

mg/ml (*Fig. 9B*). By contrast, compound **1** remarkably suppresses GLP-1 elicited cAMP production in RINm5F cells and the dose response curve of GLP-1 on cAMP production was right shifted by almost 2 orders of magnitude, the EC₅₀ was increased from 7.8 to 360 nM (*Fig. 9A*). The affinity of compound **1** on GLP-1 elicited cAMP production was obtained by analyzing the dependence of compound **1** concentration on the cAMP production elicited by 60 nM of GLP-1. As revealed in *Fig. 9C*, 60 nM of GLP-1 generated cAMP more than 80% of that of saturation dose, as the concentration of compound **1** increased, the cAMP production reduced and reached bottom saturation at 0.003 mg/ml of compound **1**. The affinity of compound **1** for GLP-1 in this assay was measured to be 0.0003 mg/ml. The effect of galanin B, compound **1** and compound **2** on the affinity of GLP-1 to elicit cAMP production in RINm5F cells are summarized in *Table 3*. To examine if these modulation effects of compound **1** and compound **2** is specific for GLP-1, 0.03 and 0.01 mg/ml of these compounds were included in the analysis of dose dependence of GIP and glucagon on cAMP production in RINm5F cells. As shown in *Fig. 11*, compound **1** and compound **2** at a concentration of 0.025 mg/ml do not affect the cAMP production elicited by GIP or glucagon, indicating their modulation effects are specific for GLP-1. The above studies revealed that galanin B, compound **1**, and compound **2** are modulator without intrinsic agonistic or antagonistic activity, their actions are dependent on both GLP-1 and GLP-1 receptor.

[0186] Table 3. Effect of compound 1, 2, and galanin B on the affinity of GLP-1 dependent cAMP production in RINm5F cells

	GLP-1 only	Compound 1* + GLP-1	Compound 2* + GLP-1	Galanin B* + GLP-1
EC ₅₀ (nM)	7.86	365	0.0025	4.93

* Titration of GLP-1 on the production of cAMP in RINm5F cells with 0.003 mg/ml of the indicated compounds.

Discussion

[0187] Plants remain either the source of or the inspiration for a significant proportion of the new small-molecule chemical entities. GLP-1 receptor mediated signaling is a major target for treatment of type 2 diabetes, further its role in Alzheimer's disease and psoriasis is under clinical investigation. Currently GLP-1 therapeutics are GLP-1 analogs or compounds with agonistic activity which may cause serious adverse effect upon chronic use. In an attempt to

find compound that function as a GLP-1 modulator, instead of agonist, HC plant was identified that displays positive modulating action on GLP-1 elicited receptor endocytosis which requires the presence of GLP-1, indicating the identified activity functions as a GLP-1 potentiator with little intrinsic agonistic activity. After activity directed fractionation and purification, the structure of one of the active compounds was found to be galanal b. The purified galanal b displayed potent activity to potentiate GLP-1 to elicit recruiting β -arrestin2 to GLP-1 receptor and the following receptor endocytosis. This activity of galanal b is specific for GLP-1 as it did not show similar effect on PTH and its cognate receptor. The effect is highly dependent on the presence of GLP-1 and is abolished by the presence of GLP-1 receptor antagonist exendin 9. To confirm this activity of purified galanal B, galanal B and its modified analogs were synthesized, followed by characterizing their ability (galanal b, compound **1**, and compound **2**) with respect to potentiating GLP-1 in eliciting receptor endocytosis and in stimulating cAMP production.

[0188] Though galanal b, compound **1**, and compound **2** are all able to potentiate GLP-1 to elicit receptor endocytosis in a GLP-1 and GLP-1 receptor dependent manner, their ability to modulate GLP-1 in stimulating cAMP production is quite distinct, in that compound **1** selectively reduce the affinity of GLP-1 by a factor of 50, galanal b is neutral, while compound **2** selectively potentiate the affinity of GLP-1 up to 1000 fold. This finding demonstrates that compound **1** negatively modulate GLP-1 induced cAMP production pathway while compound **2** positively modulate the same pathway, though they display comparable activity on GLP-1 elicited receptor endocytosis. It was demonstrated that these activities and selectivity are dependent on the GLP-1, GLP-1 receptor and specific for the GLP-1 signaling, as they are GLP-1 concentration dependent, are all blocked by GLP-1 receptor antagonist exendin 9 and do not affect cAMP production elicited by the other incretin GIP or by glucagon. Galanal b, compound **1**, and compound **2** share similar scaffolds but are structurally distinct, the present disclosure identifies a critical chemical space of galanal b relevant to its selectivity in modulating GLP-1 receptor coupling efficiency to its intracellular receptor signaling pathway. The present data show that galanal b, compound **1**, and compound **2** can display quite distinct effect on the coupling efficiency of GLP-1 receptor to $G\alpha_s$ while display similar effect on the coupling efficiency to β -arrestin2. The simplest explanation for this observation is that each compound will dictate a unique conformation of receptor-GLP-1-compound complex, thus the conformation of GLP-1 receptor is highly dependent on whether galanal b, compound **1**, or compound **2** is in the

complex. This is consistent with the finding that GPCR can exist in multiple active conformations, distinct conformation of the receptor is stabilized by distinct ligand structure and may lead to distinct signaling selectivity (55). The present findings raise question as how galanin b and its analogs share similar structure but stabilize quite distinct conformation of GLP-1 receptor which coupled comparably to β -arrestin-2 but display opposite coupling efficiency to the pathway of cAMP production. There are at least two possible mechanisms to account for these observations. The first explanation is that the compound may bind to and modify the structure of GLP-1 receptor such that manifest as a pathway-dependent change in the signaling capacity upon binding to its orthosteric ligand GLP-1. By binding to and modifying structural conformation of the receptor, the allosteric inhibitor of parturition (PDC113.824) induces biased signaling when an orthosteric ligand is co-bound to the prostaglandin F₂ α receptor (56). Alternatively, these compounds bind to GLP-1 to form a complex with distinct conformation which will stabilize a distinct set of receptor conformation upon binding and leads to positively or negatively modulate coupling efficiency to G α s pathway while display similarly the coupling efficiency to β -arrestin2 mediated receptor endocytosis. Subtle conformation changes in peptide agonists can lead to selective coupling of the receptor to its downstream signaling pathway. As it has been shown in the case of biased agonist for the type 1 parathyroid hormone receptor (PTH1R) (25) and angiotensin II type 1A receptor ligands (57), subtle structure change of the peptide ligands can profoundly stabilize a distinct conformation of the receptor protein that selectively affects the coupling efficiency of a particular downstream signaling pathway. Two preliminary observations in the present communication are consistent with the second mechanism that requires the binding of these compounds to GLP-1 peptide to stabilize compound-GLP-1 complex in a distinct conformation different from that of free GLP-1. First, free GLP-1 peptide is quickly degraded by limited trypsin digestion, while galanin b protects GLP-1 from trypsin degradation. Furthermore, compound 2 potentiates GLP-1 to stimulate cAMP production in RINm5F cells, but has little effect on cAMP production by a small molecule agonist Boc5, though 1000 fold higher of Boc5 is needed to stimulate low level cAMP production in RINm5F cells.

[0189] The chronic administration of glucagon-like peptide-1 (GLP-1) analogs widely used to treat type-2 diabetes was associated with a potential risk of pancreatitis (37-41) or pancreatic/thyroid cancers (42), though with benefits far outweighing the potential risks (58). Physiologically, plasma level of GLP-1 is stringently controlled by ingestion of food and by

DPP-4, the plasma level of active GLP-1 will be raised from 5 pM to 20-25 pM 15 min after glucose challenge and return to basal level 2 hr later. However, a constant high plasma concentration of GLP-1 analogs in type 2 diabetes receive GLP-1 analogs therapy (59,60) leads to stimulating target tissues constitutively and may cause the adverse undesired consequences reported in the literatures. Compound **2** which potentiate GLP-1 dependent cAMP production by 1000 fold in RINm5F cells is a “true” positive modulator for GLP-1 because it lacks intrinsic agonistic activity as it does not elicit cAMP production in the absence of GLP-1. GLP-1 positive modulator function as a dimmer switch that amplifies the signaling depends on the plasma level of endogenous GLP-1, the intensity of activation of GLP-1 receptor is controlled by the physiologic concentration of GLP-1 secreted from intestine, thus will not stimulate target tissues constitutively. Since GLP-1 secretion in type 2 diabetes is comparable to or slightly defective as compare to healthy subject (43,44), GLP-1 positive modulator will be a potential compound to treat type 2 diabetes in the future. Positive modulator without intrinsic agonistic activity but only function to potentiate the activity of endogenous GLP-1 is expected to overcome the undesired effects by skipping the step of constitutive stimulation of the target tissues (58) associated with the chronic administration of GLP-1 analogs.

[0190] GLP-1 receptors are also expressed in extra-pancreatic tissues, and trial data suggest GLP-1RAs also have effects beyond their glycaemic actions. GLP-1 signaling has been shown to be potential target for the treatment of immune dysfunction (Ahern *et al.*, J Eur Acad Dermatol Venereol. 2013 Nov;27(11):1440-3) (15), neurodegenerative diseases and cardiovascular disorders (Seufert *et al.*, Diabetes Obes Metab. 2013 Dec 24. doi: 10.1111/dom.12251; Egebjerg *et al.*, Dan Med J. 2012 Oct;59(10):A4519). Biological effects triggered by GLP-1 receptor often result from the activation of multiple intracellular signaling pathways. Deciphering which signaling pathways are engaged following GLP-1 receptor activation appears to be primordial to reveal their contribution in the physiological and pathological processes. The development of pathway selective GLP-1 modulators to elucidate the role of the different signaling mechanisms mediated by GLP-1 receptor activation may allow the generation of new therapeutic agents with improved efficacy and reduced side effects. In this regard, the identification of GLP-1 modulator selectively promoting insulin secretion without inducing pro-inflammatory effects would offer therapeutic benefit. For many GPCR targets, the required spectrum of signaling needed to attain optimal therapeutic benefit is currently unknown, which limits the rational selection of

drug candidates. Therefore, drug discovery at these tractable targets is considerably challenging. There are evidences showing that many adverse side effects can be avoided with such pathway selective compounds and provide improved treatments. The angiotensin II type 1A receptor, the β -arrestin-biased ligand Sar1, D-Ala8 angiotensin II (TRV120027) has been shown to increase cardiac performance in anesthetized rats, whereas unbiased ligands reduce cardiac performance. There is also potential for improved PTH receptor agonists used for the treatment of osteoporosis. The β -arrestin-biased ligand (D-Trp12,Tyr34)-PTH(7-34) stimulates β -arrestin while blocking G-protein signaling and promotes anabolic bone formation in the absence of bone resorption. Screening signaling pathway selective compounds provides considerable scope for the identification of compounds that selectively target clinically useful GLP-1 signaling pathways and are more neutral or even block alternative pathways, which give rise to undesirable side effects. Given the risk of chronic usage of GLP-1 agonist in type 2 diabetes and potentially in other disorders, creating small molecules which modulates GLP-1 signaling pathway selectivity in a potent unique manner, may dramatically accelerate the rate at which critical pathway are selected.

OTHER EMBODIMENTS

[0191] All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

[0192] From the above description, one skilled in the art can easily ascertain the essential characteristics of the present present disclosure, and without departing from the spirit and scope thereof, can make various changes and modifications of the present disclosure to adapt it to various usages and conditions. For example, compounds structurally analogous the compounds described herein of this present disclosure also can be made, screened for their anti-cancer activities, and used to practice this present disclosure. Thus, other embodiments are also within the claims.

[0193] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference for the purposes or subject matter referenced herein.

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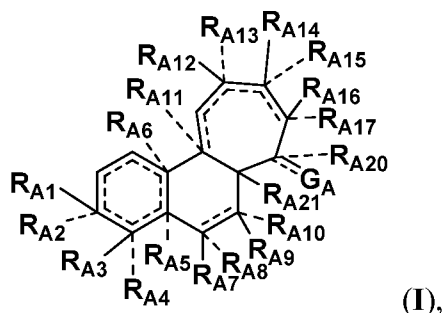
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What is claimed is:

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

G_A is hydrogen, =O, =S, -OR'', -SR'', -N(R'')₂, alkenyl, alkynyl, an amide group, an ester group, a phosphate group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, wherein each instance of R'' is independently hydrogen, a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

R_{A1}, R_{A2}, R_{A3}, R_{A4}, R_{A5}, R_{A6}, R_{A7}, R_{A8}, R_{A9}, and R_{A10} are each independently hydrogen, halogen, -OR'', -N(R'')₂, a carboxyl group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbons, or R_{A1} and R_{A2} are joined to form =O, or R_{A3} and R_{A4} are joined to form alkenyl;

R_{A11}, R_{A13}, R_{A15}, and R_{A17} are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R_{A12}, R_{A14}, and R_{A16} are each independently halogen, -N(R'')₂, -SR'', -OR'', alkyl, alkenyl, alkynyl, an amide group, a carboxyl group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a urea group, a carbamate group, or a thiocarbamate group, or R_{A14} and R_{A15} are joined to form =O or =S;

R_{A20} is hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms; and

R_{A21} is hydrogen, halogen, $-N(R'')_2$, $-SR''$, $-OR''$, $-CH_2OR''$, alkenyl, alkynyl, an amide group, a carboxyl group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

provided that:

- (i) at least one of R_{A1} , R_{A2} , R_{A5} , R_{A7} , R_{A8} , R_{A9} , R_{A10} , R_{A11} , R_{A12} , R_{A13} , R_{A15} , R_{A16} , and R_{A17} is not hydrogen;
- (ii) at least one of R_{A3} , R_{A4} , and R_{A6} is not $-CH_3$; or
- (iii) when R_{A21} is $-CHO$ and G_A is $-OH$ or $=O$, R_{A14} and R_{A15} are each not $-CHO$.

2. The compound or pharmaceutically acceptable salt of claim 1, wherein:

G_A is hydrogen, $=O$, $=S$, $-OR''$, $-SR''$, $-NR''H$, alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, wherein each instance of R'' is independently hydrogen, a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

R_{A1} , R_{A2} , R_{A3} , R_{A4} , R_{A5} , R_{A6} , R_{A7} , R_{A8} , R_{A9} , and R_{A10} are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbons;

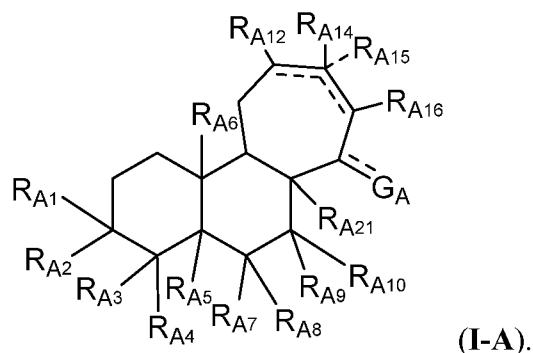
R_{A11} , R_{A12} , R_{A13} , R_{A15} , R_{A16} , and R_{A17} are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R_{A14} is halogen, $-NR''H$, $-SR''$, $-OR''$, alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, or a thiocarbamate group;

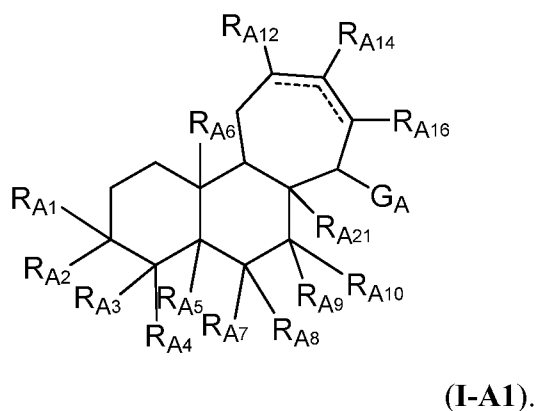
R_{A20} is hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms; and

R_{A21} is hydrogen, halogen, $-NR''H$, $-SR''$, $-OR''$, alkenyl, alkynyl, an amide group, an ester group, an aldehyde group, a nitrile group, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms.

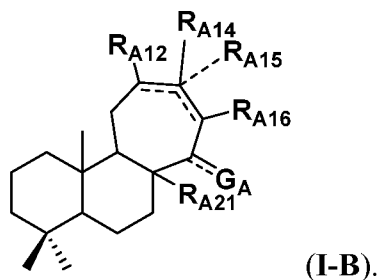
3. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is of Formula (I-A):



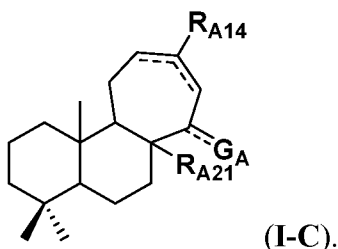
4. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is of the formula (I-A1):



5. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is of Formula (I-B):

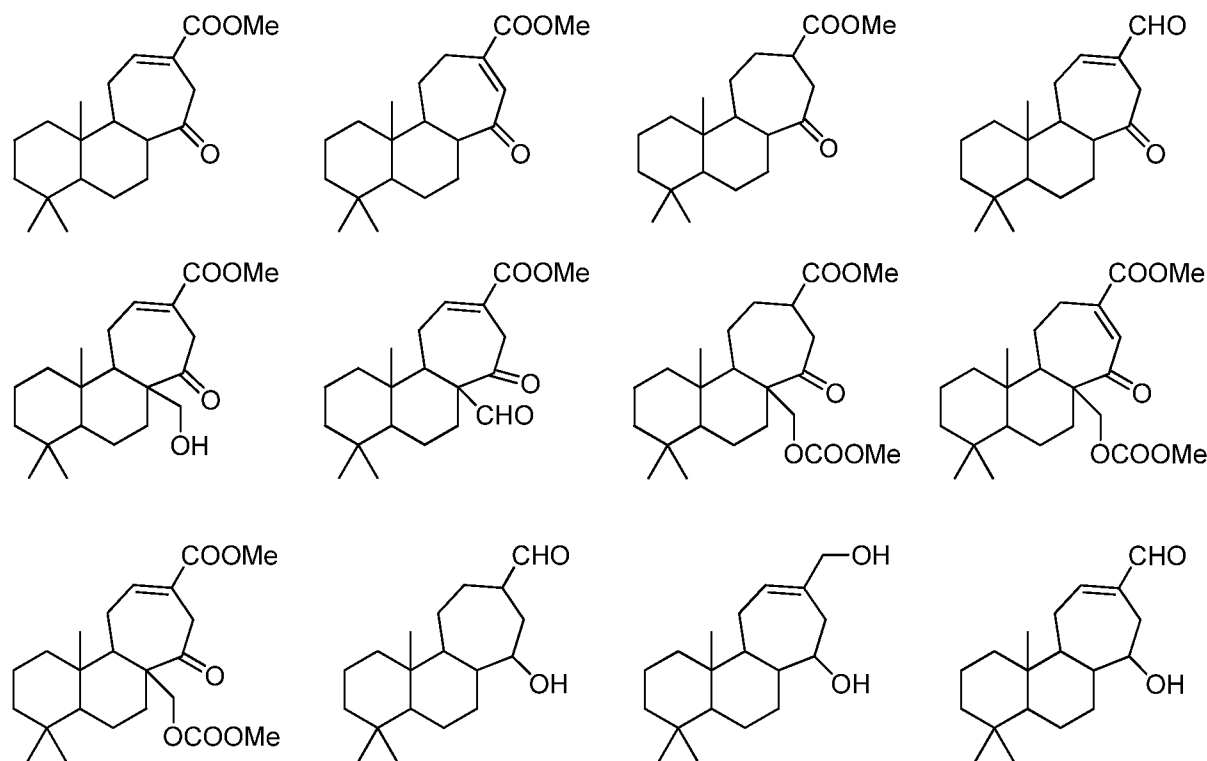


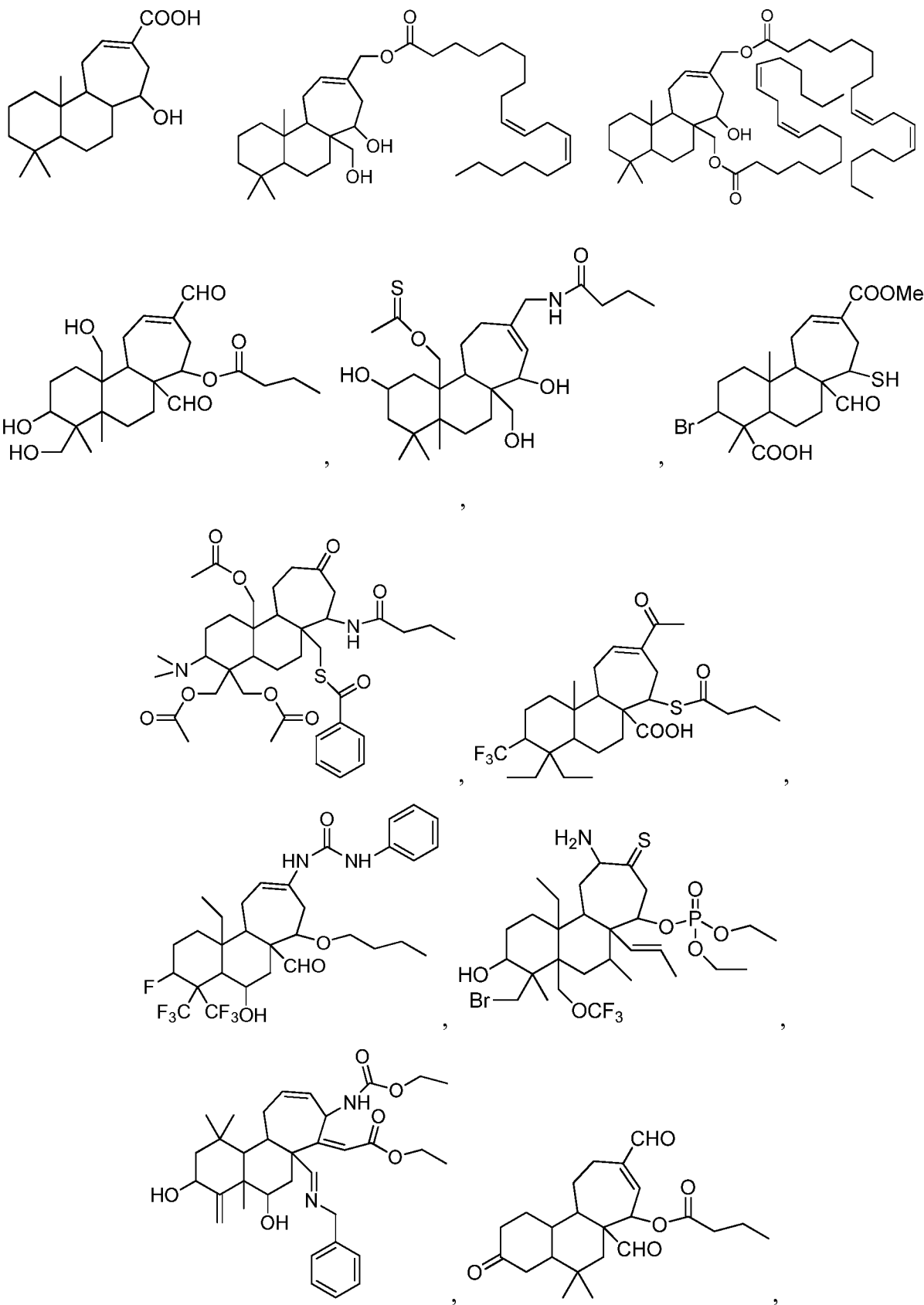
6. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is of Formula (I-C):

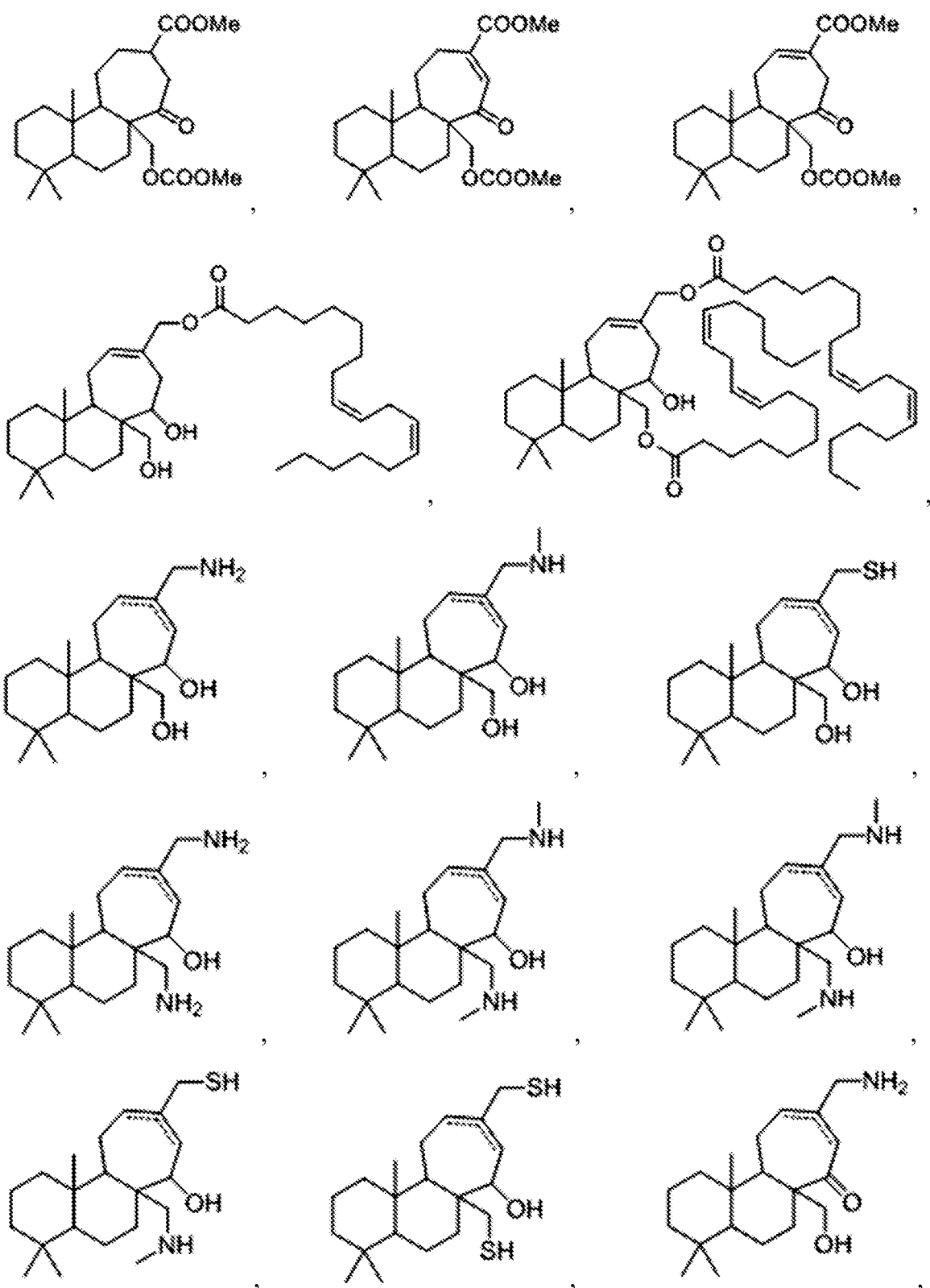


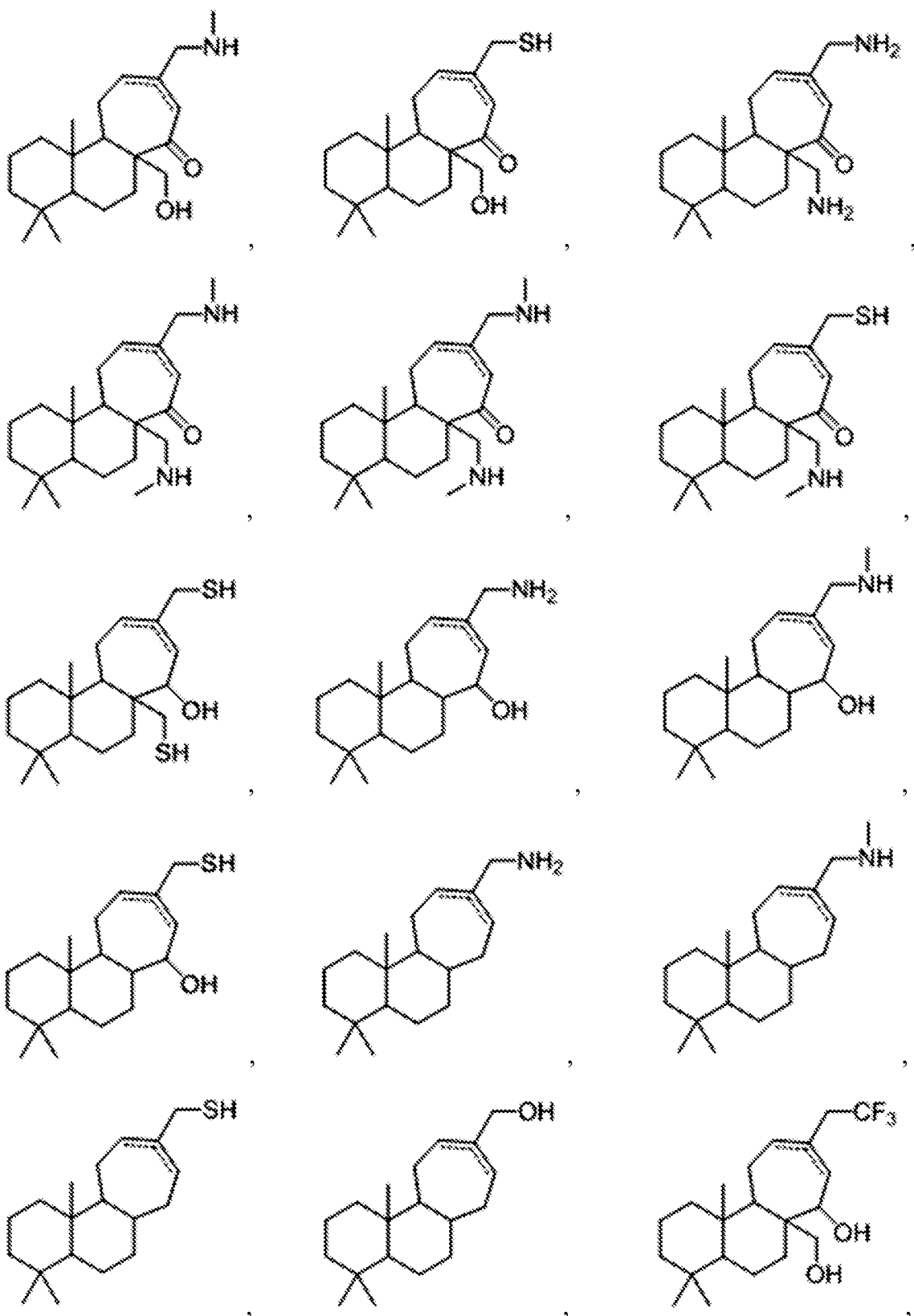
7. The compound or pharmaceutically acceptable salt of any one of claims 1 to 6, wherein G_A is $=O$, $=S$, $-SR''$, $-OR''$, $-N(R'')_2$, $-OH$, $-SH$, or $-NH_2$.
8. The compound or pharmaceutically acceptable salt of any one of claims 1 to 6, wherein G_A is $=O$ or $-OR''$.
9. The compound or pharmaceutically acceptable salt of any one of claims 1 to 4, wherein R_{A6} is acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl.
10. The compound or pharmaceutically acceptable salt of claim 9, wherein R_{A6} is methyl.
11. The compound or pharmaceutically acceptable salt of any one of claims 1 to 10, wherein R_{A14} is an ester group, an aldehyde group, or a ketone group.

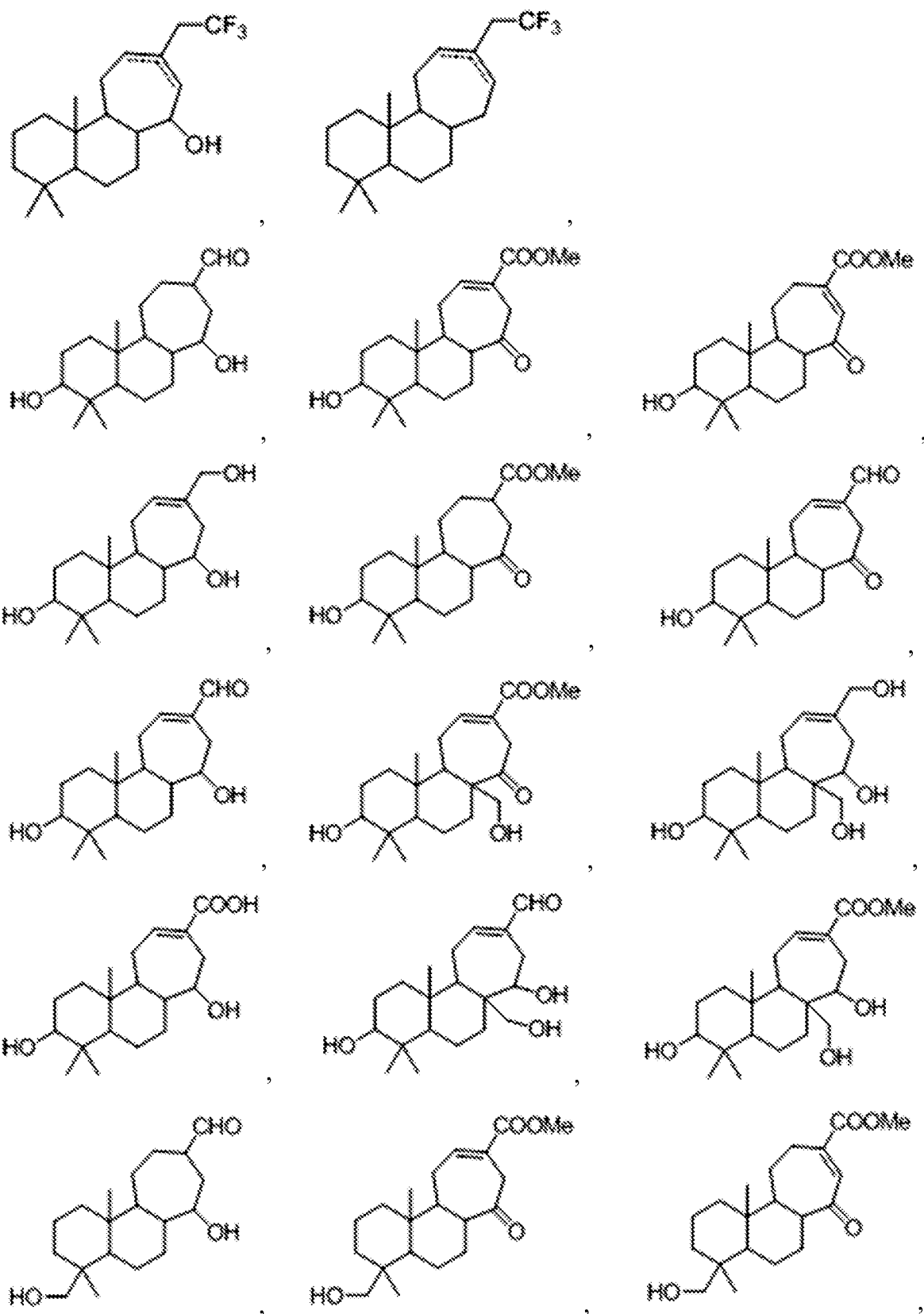
12. The compound or pharmaceutically acceptable salt of any one of claims 1 and 3 to 10, wherein R_{A14} is alkyl, a carboxyl group, or a urea group.
13. The compound or pharmaceutically acceptable salt of any one of claims 1 to 12, wherein R_{A21} is hydrogen.
14. The compound or pharmaceutically acceptable salt of any one of claims 1 to 12, wherein R_{A21} is substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl.
15. The compound or pharmaceutically acceptable salt of any one of claims 1 and 3 to 12, wherein R_{A21} is $-\text{CH}_2\text{OR}''$.
16. The compound or pharmaceutically acceptable salt of any one of claims 1 to 12, wherein R_{A21} is an aldehyde group.
17. The compound or pharmaceutically acceptable salt of claim 1, wherein the compound is of the formula:

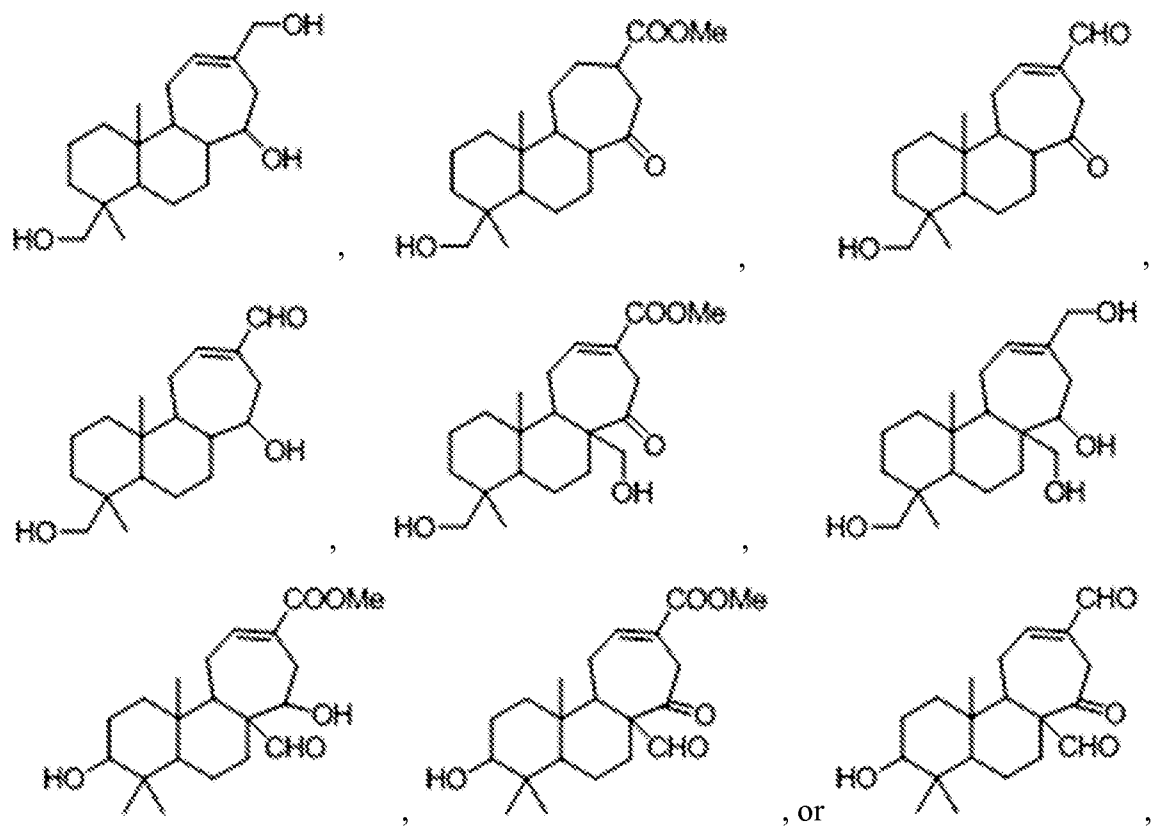






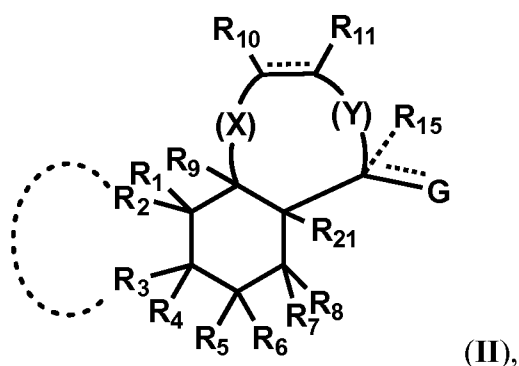






or a pharmaceutically acceptable salt thereof, wherein  is , , or .

18. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

G is hydrogen, =O, =S, -NR'H, -SR', or -OR', wherein R' is hydrogen, an ester group, a ketone group, a thione group, or a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 16 carbon atoms;

W is -O-, -S- or -NR'-;

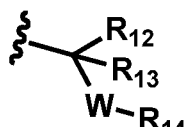
X and Y are each independently a single bond or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 3 carbon atoms;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₂ and R₁₃ are each independently hydrogen, halogen, or a cyclic or acyclic, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms, or R₂ and R₃ may join to form cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

R₁₀ and R₁₁ are each independently hydrogen, halogen, an amino group, an amide group, an ester group, an aldehyde group, a nitrile, an imino group, a ketone group, a thione group, an isonitrile group, an isothiocyanide group, a carbamate group, a thiocarbamate group, or a cyclic or acyclic, saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1 to 6 carbon atoms;

R₁₄ is hydrogen or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1-16 carbon atoms;

R₁₅ is hydrogen or a saturated or unsaturated, substituted or unsubstituted, branched or unbranched, (hetero)aliphatic group having 1-6 carbon atoms; and

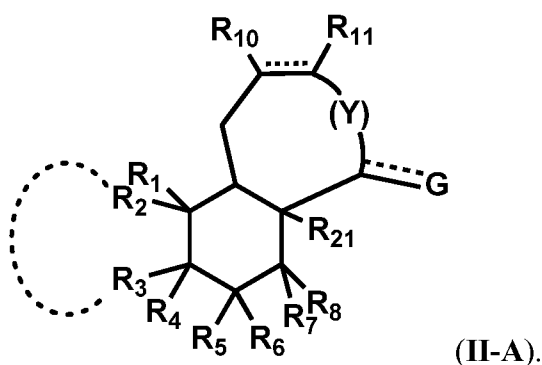


R₂₁ is

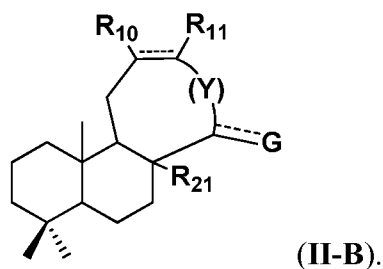
provided that:

- (i) at least one of R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀ is not hydrogen;
- (ii) R₁ is not -CH₃; or
- (iii) when R₂₁ is -CHO and G is -OH or =O, R₁₁ is not -CHO.

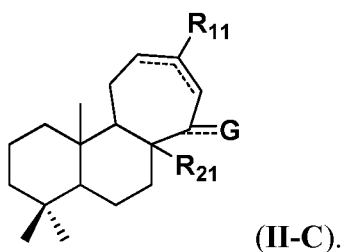
19. The compound or pharmaceutically acceptable salt of claim 18, wherein the compound is of Formula (II-A):



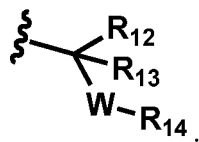
20. The compound or pharmaceutically acceptable salt of claim 18, wherein the compound is of Formula (II-B):



21. The compound or pharmaceutically acceptable salt of claim 18, wherein the compound is of Formula (II-C):



22. The compound or pharmaceutically acceptable salt of any one of claims 18-21,



wherein R₂₁ is

23. The compound or pharmaceutically acceptable salt of claim 22, wherein R₂₁ is –CH₂OH.

24. The compound or pharmaceutically acceptable salt of any one of claims 18-21, wherein R₂₁ is an aldehyde group.

25. The compound or pharmaceutically acceptable salt of any one of claims 18-24, wherein G is =O.

26. The compound or pharmaceutically acceptable salt of any one of claims 18-24, wherein G is –OR'.

27. The compound or pharmaceutically acceptable salt of any one of claims 18-21 and 25-26, wherein W is $-O-$.
28. The compound or pharmaceutically acceptable salt of any one of claims 18 and 22-27, wherein X is methylene.
29. The compound or pharmaceutically acceptable salt of any one of claims 18-20 and 22-28, wherein Y is methylene.
30. The compound or pharmaceutically acceptable salt of any one of claims 18-29, wherein R_{11} is an ester group, an aldehyde group, a ketone group, or acyclic, substituted or unsubstituted, branched or unbranched, C_{1-6} alkyl.
31. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt of any of claims 1-30, and a pharmaceutically acceptable carrier.
32. A pharmaceutical composition for use in activating a glucagon-like peptide 1 (GLP-1) receptor in a subject in the presence of GLP-1, the composition comprising a compound or pharmaceutically acceptable salt of any of claims 1-30, and a pharmaceutically acceptable carrier.
33. The pharmaceutical composition for use of claim 32, wherein the subject has, is suspected of having, or is at risk for a disease or disorder selected from the group consisting of type I diabetes, type II diabetes, gestational diabetes, obesity, excessive appetite, insufficient satiety, and a metabolic disorder.

Fig. 1

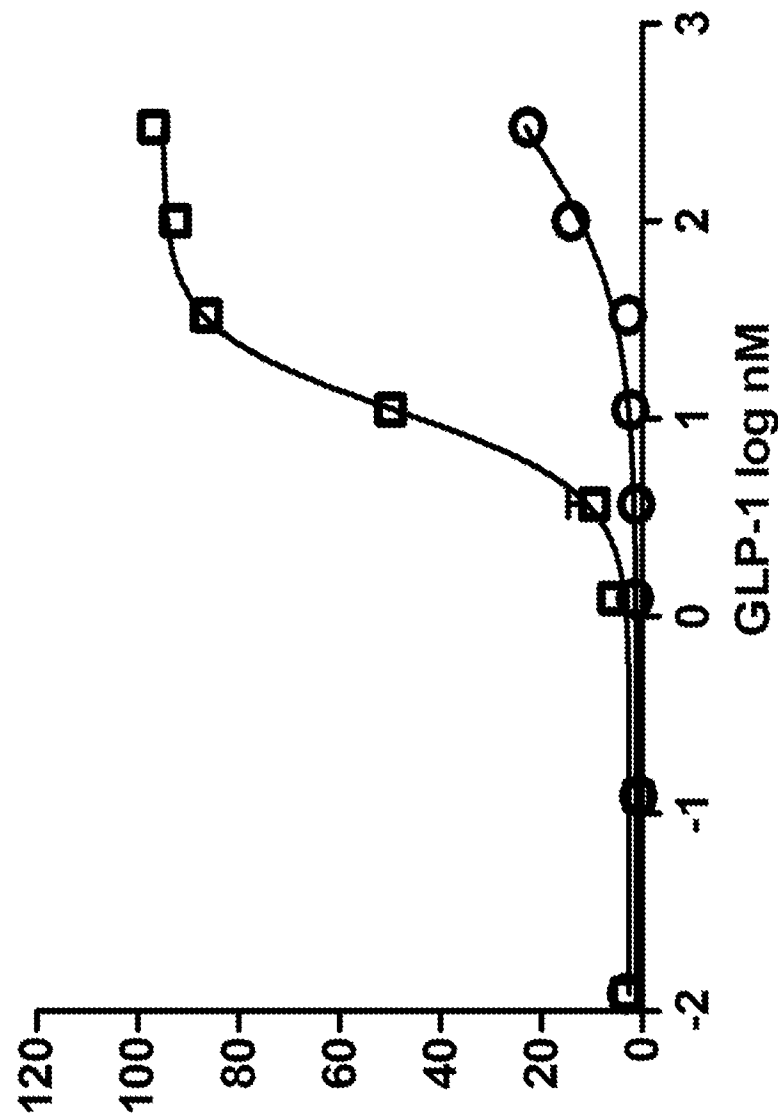


Fig. 2

A.

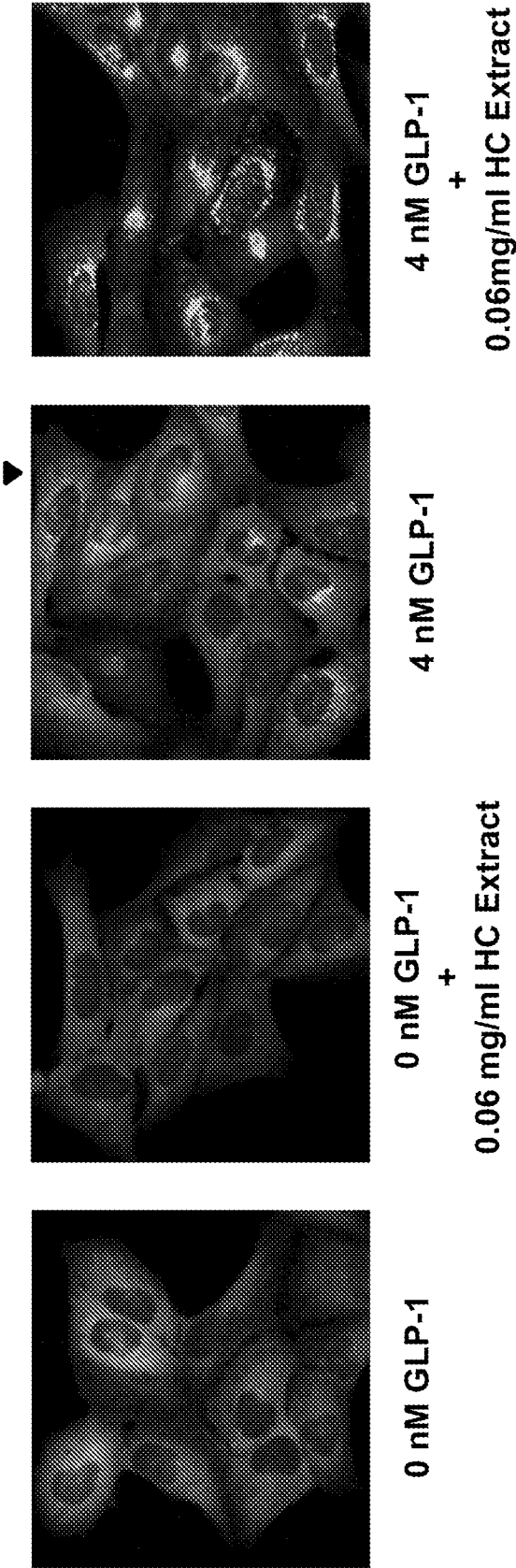


Fig. 2 (Cont'd)

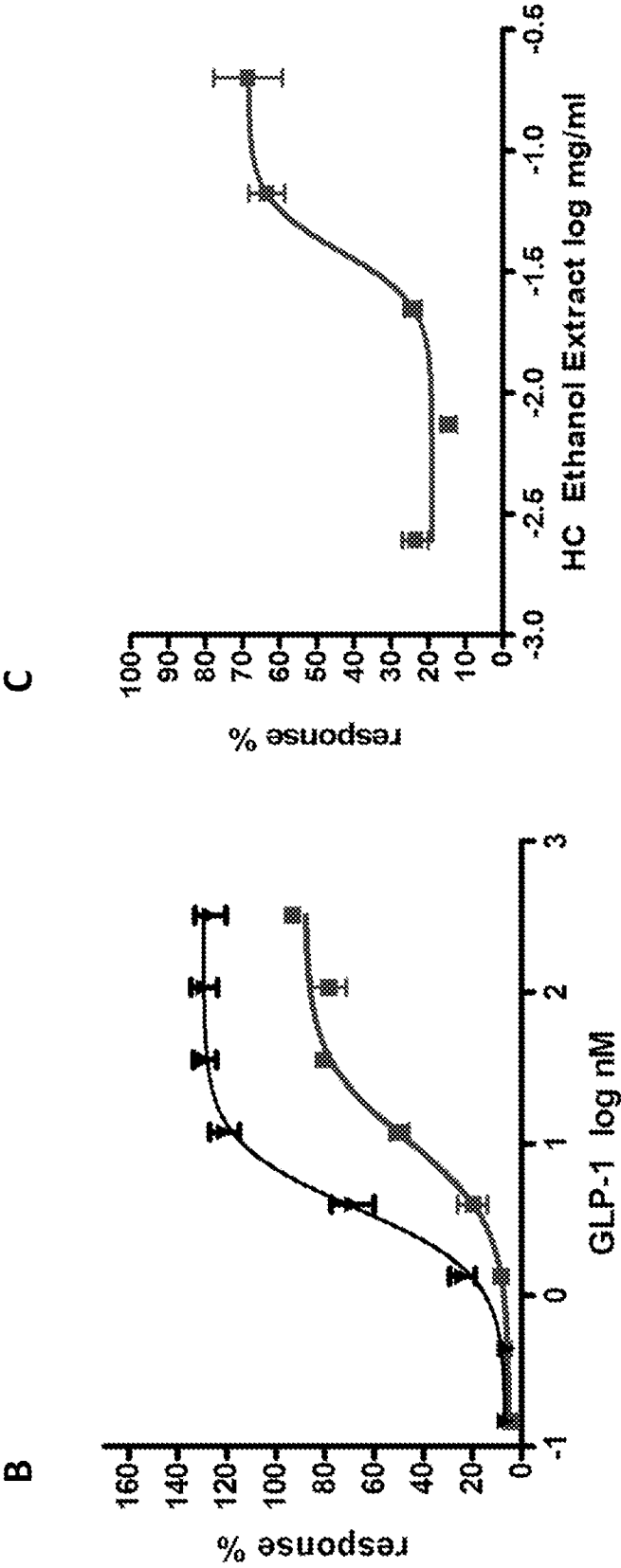


Fig. 3

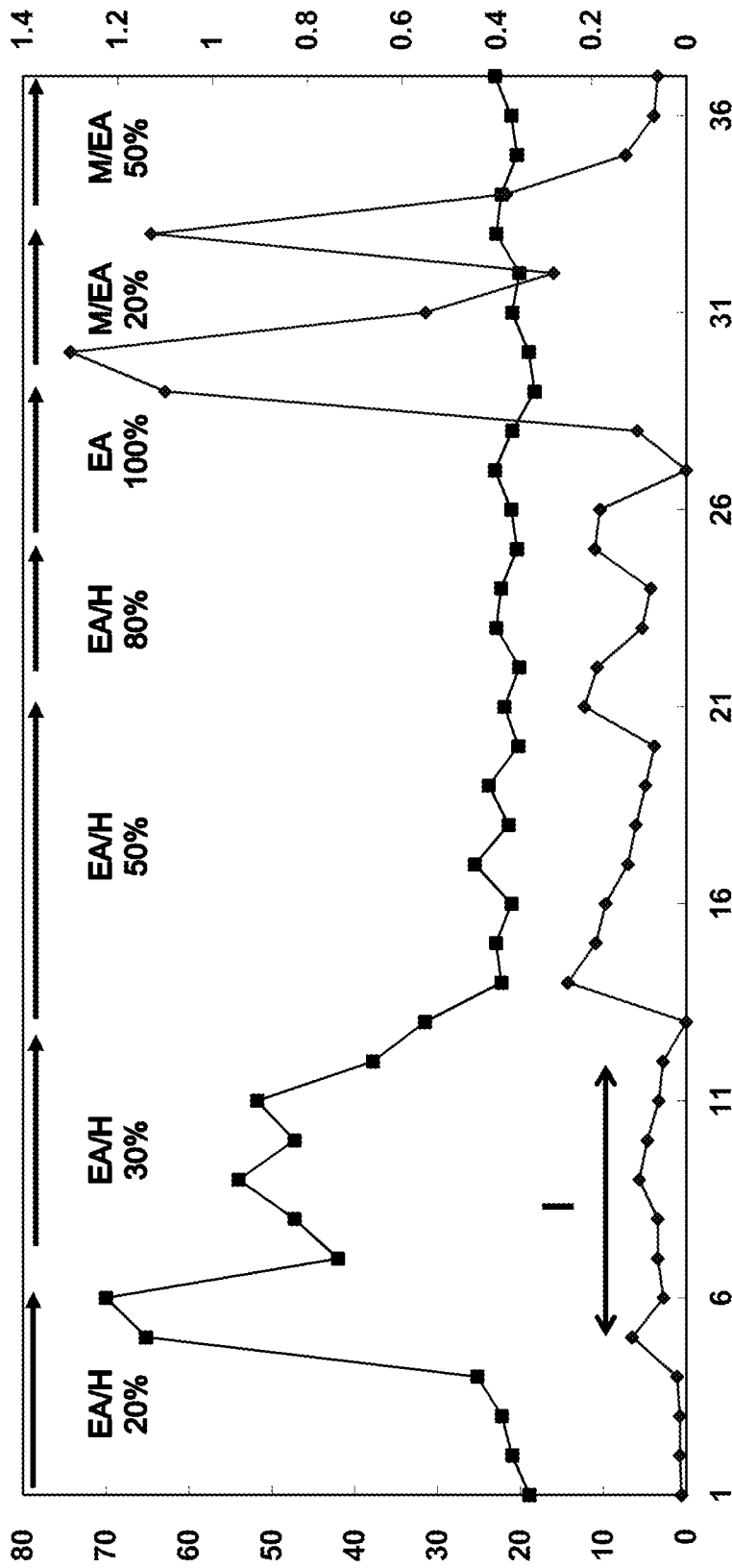


Fig. 4

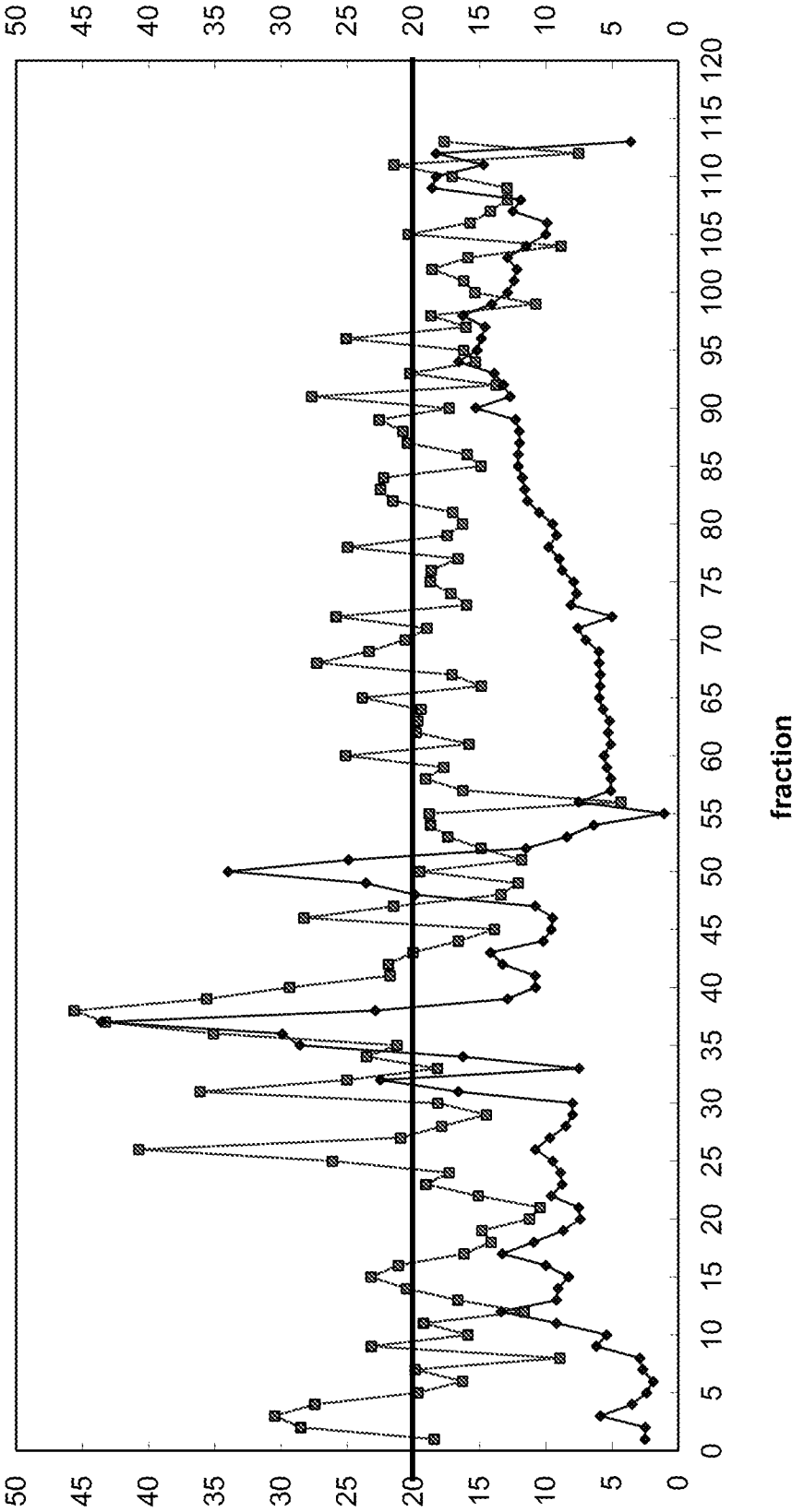


Fig. 5

A

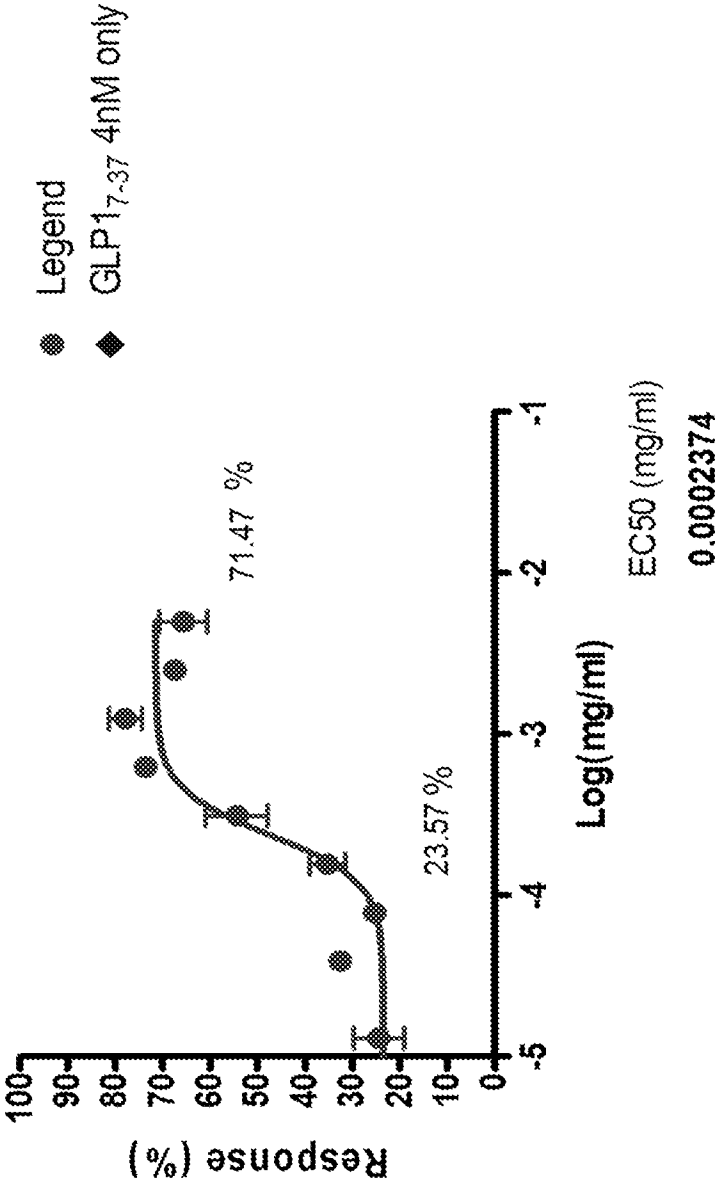


Fig. 5 (Cont'd)

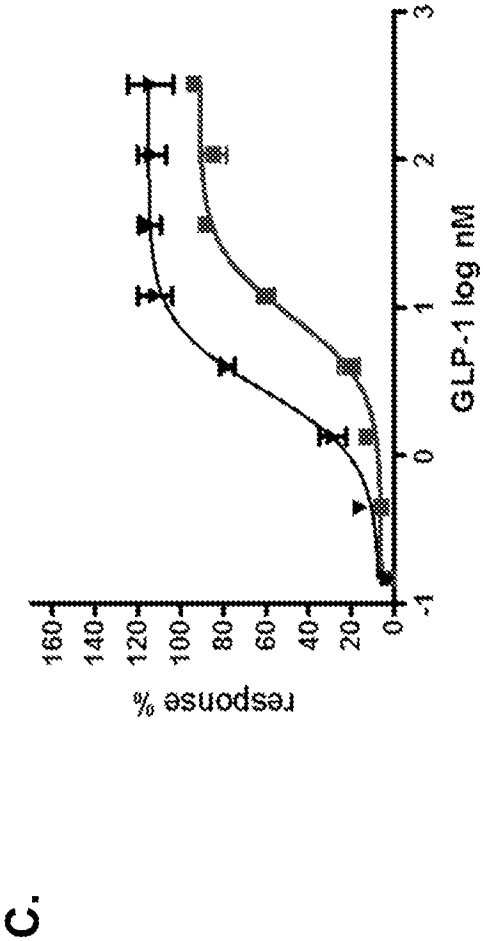
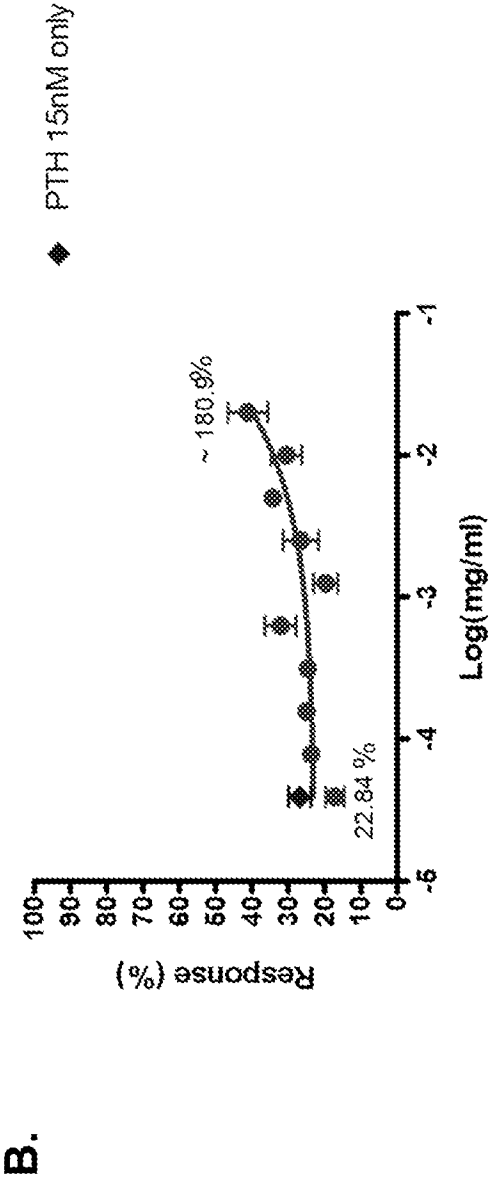


Fig. 6

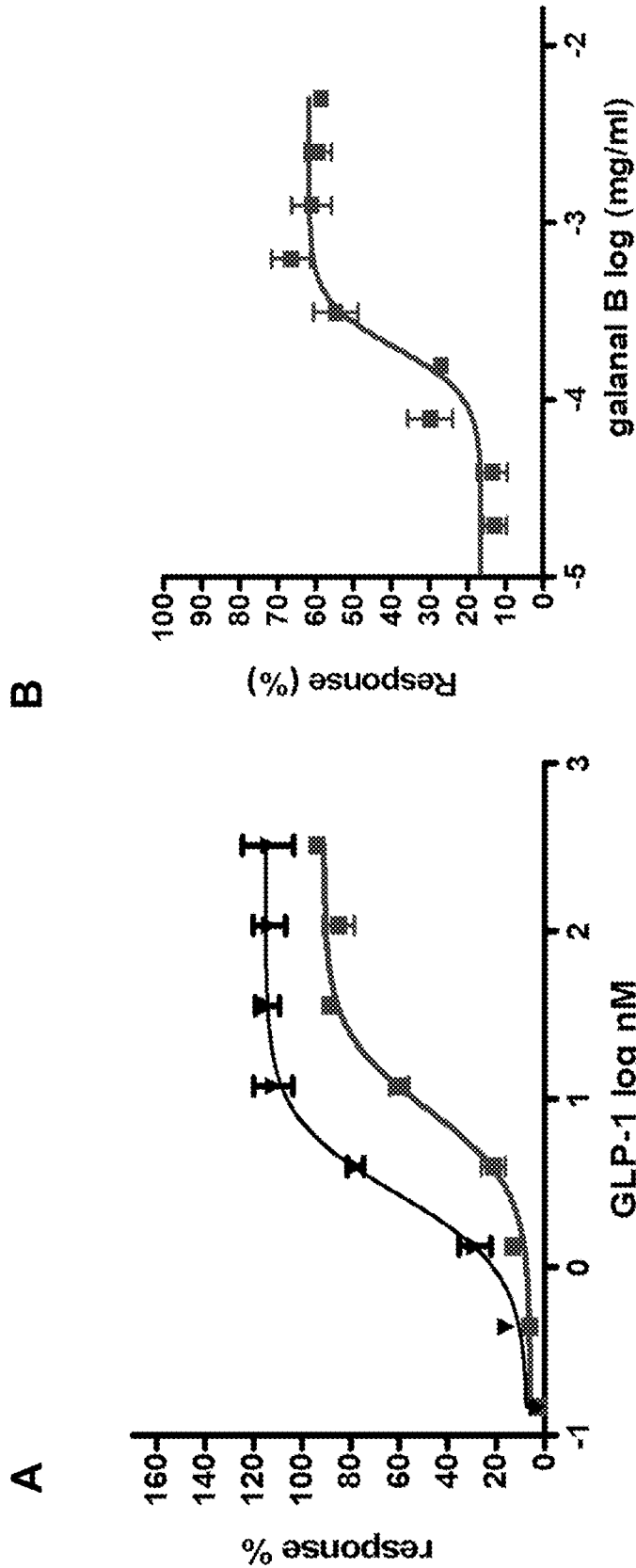


Fig. 7

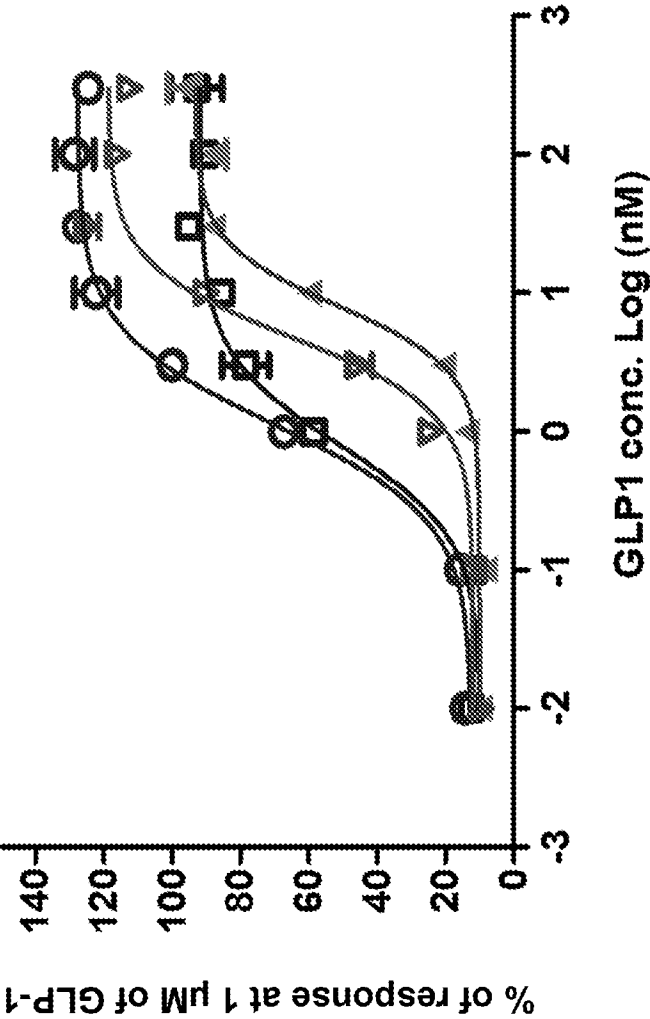


Fig. 8

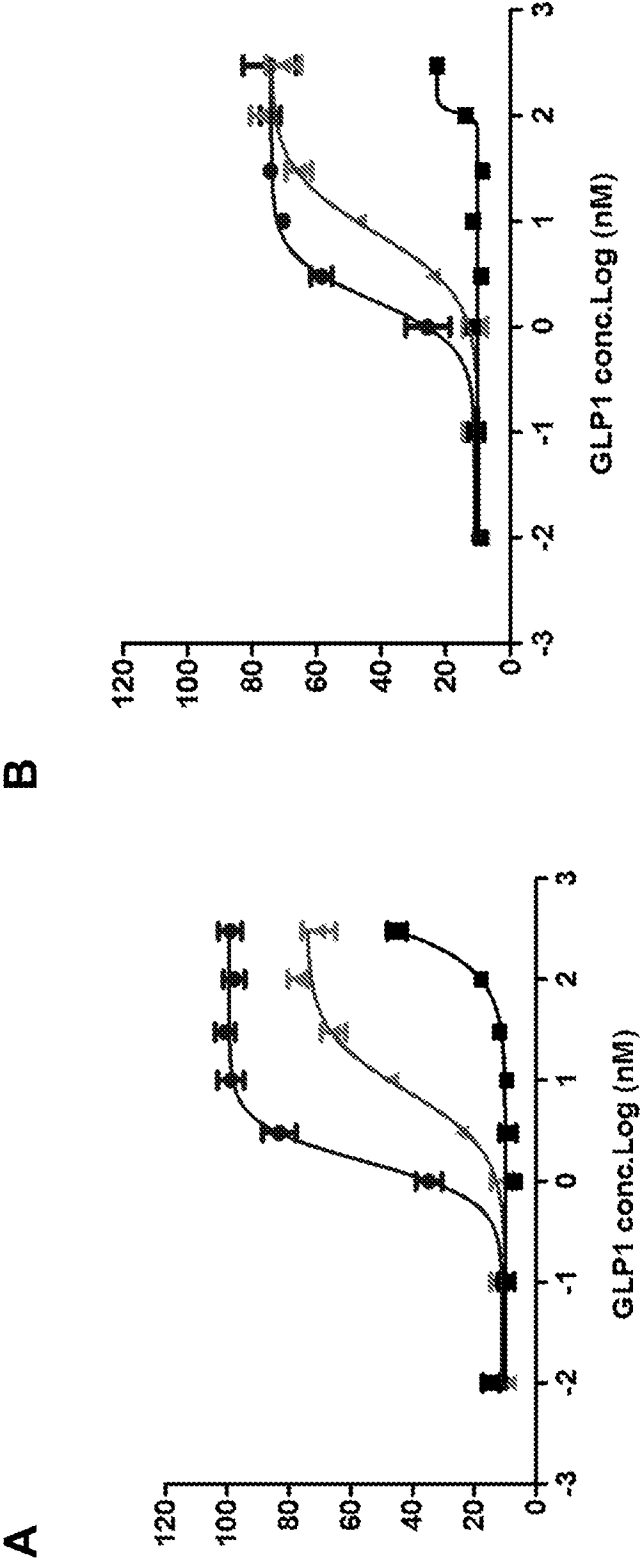


Fig. 8 (Cont'd)

C

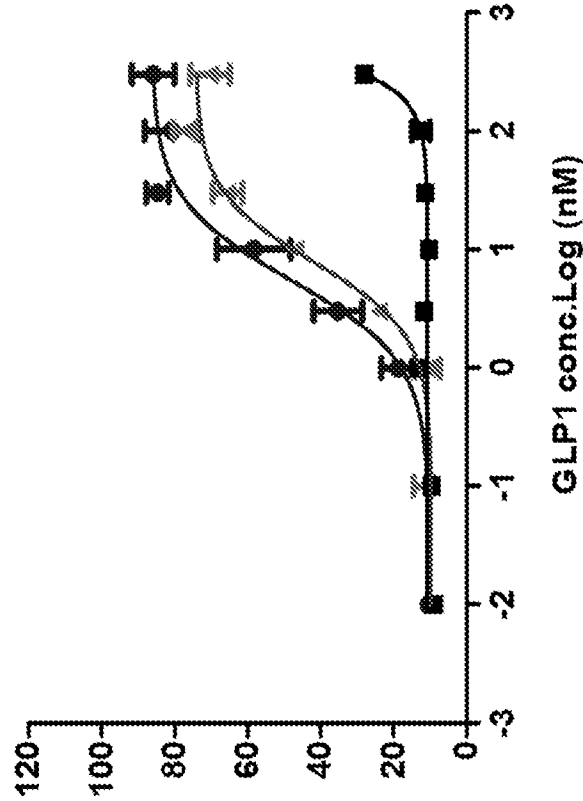


Fig. 9

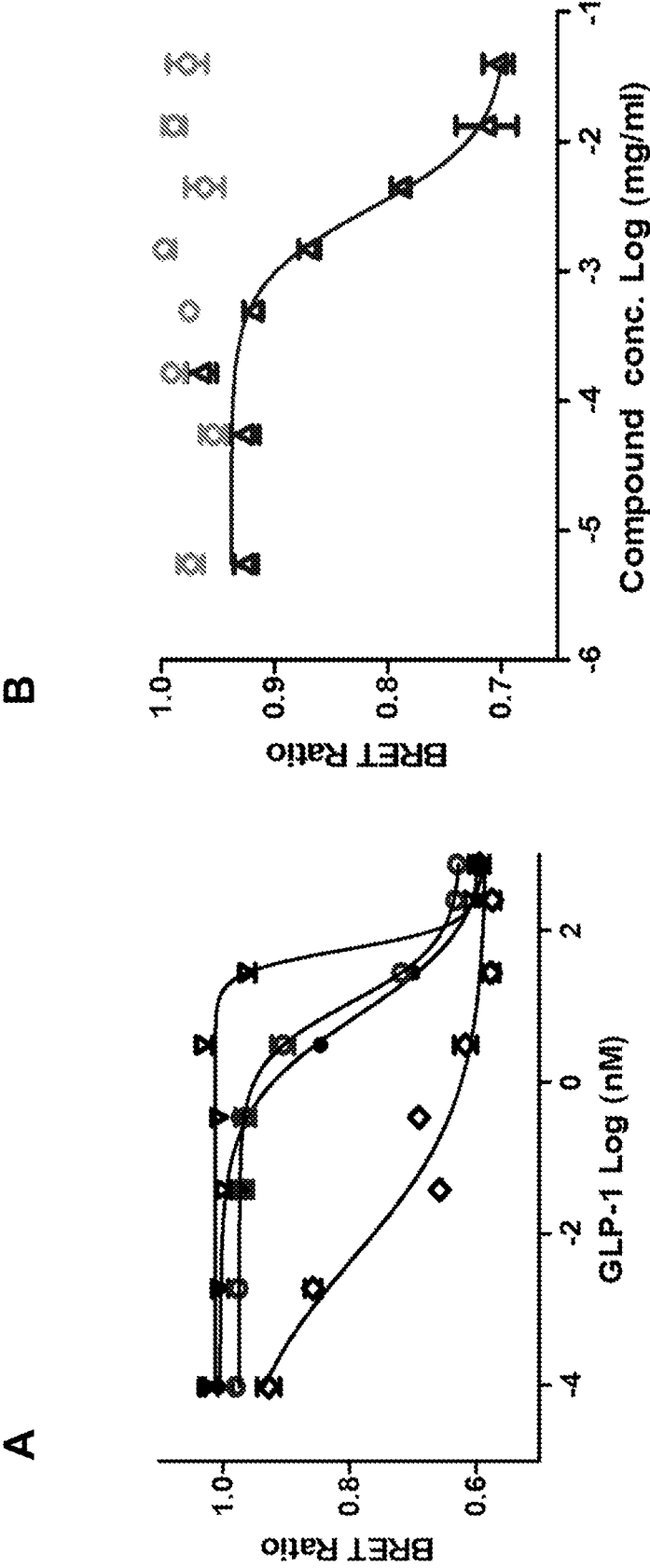


Fig. 9 (Cont'd)

C

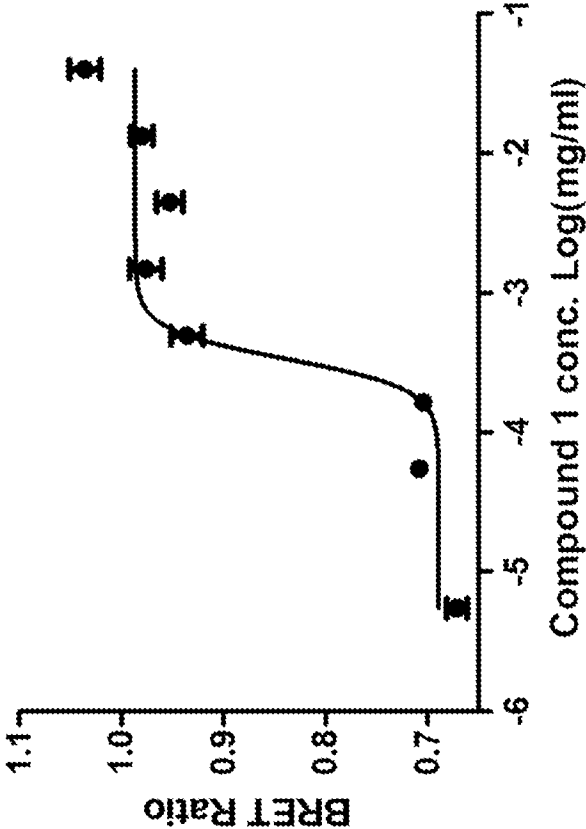
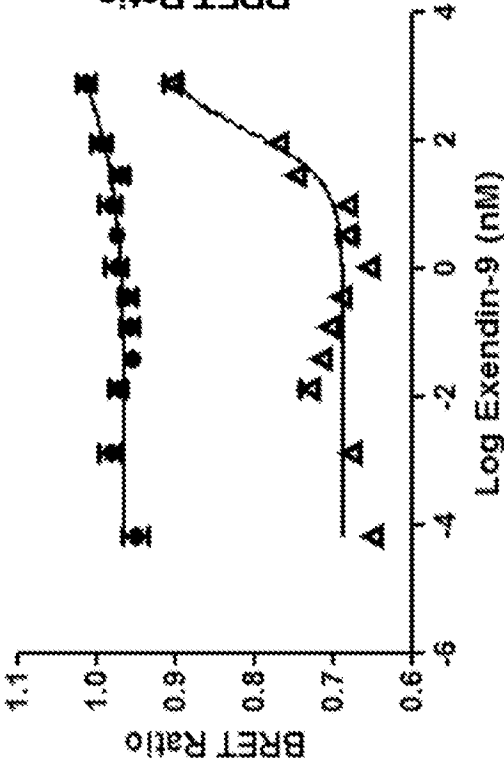


Fig. 10

A.



B.

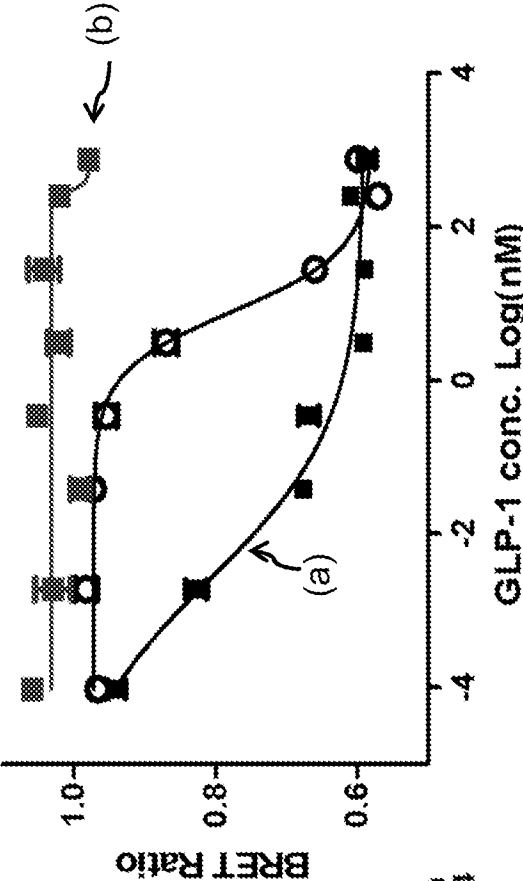


Fig. 11

