

COMPOSITIONS AND METHODS FOR MODULATING A G-PROTEIN COUPLED RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/616892, filed January 2, 2024, and U.S. Provisional Application No. 63/486649, filed February 23, 2023, which are incorporated by reference in their entirety.

Field of the Disclosure

[0002] The present disclosure relates to compositions for modulating a G-protein coupled receptor (GPCR) and methods of using the same. More particularly, the present disclosure relates to compositions and methods for modulating GPCR by administering a therapeutically effective amount of an oral composition and a carrier.

BACKGROUND

[0003] Activation of several G-protein coupled receptors, for example, GPR40, GPR119, GPR120, and GPR30 have been demonstrated to produce favorable effects on glucose homeostasis, food intake, body weight gain and possibly also β -cell preservation. Free fatty acids (FFAs) appear to stimulate insulin secretion through direct islet GPCR signaling and indirect stimulation of incretin secretion via receptor-mediated mechanisms. GPR40 and GPR119 are among the several receptors to play an important physiological role in insulin release. It is now known that both GPR40 and GPR119 are expressed in pancreatic β -cells and that activating these receptors stimulates insulin secretion in a glucose-dependent manner. GPR120 is a receptor for unsaturated fatty acids, such as α -linoleic acid. Its expression has been found in both intestinal L cells and islets. Stimulation of GPR120 has been demonstrated to increase insulin levels and proliferation of β -cells. GPR30, a functional estrogen receptor, has been shown to be involved in glucose homeostasis and reduction of body weight in the DIO model in rodents. Compounds capable of activating these above-mentioned receptors could prove valuable agents for the treatment of type 2 diabetes and obesity. However, the

ligands previously identified are generally low affinity agonists and may be of limited therapeutic use.

[0004] Furthermore, most synthetic small molecule developments have had multiple safety concerns. Clearly, there remains an unmet need to develop a safe and robust GPCR agonist.

SUMMARY OF THE DISCLOSURE

[0005] Aspect of the disclosure relate to one or more compounds in a composition. Some embodiments of the disclosure relate to an oral composition. In some embodiments, the oral compositions may include, for example, a therapeutically effective amount of a compound, wherein the compound is an agonist of a G-protein coupled receptor, or a salt thereof, and one or more carriers or excipients, wherein, the agonist is capable of treating, reducing, modulating, or ameliorating a disease or condition mediated by a G-protein coupled receptor. Some embodiments of the disclosure relate to one or more compounds. In some embodiments, the compound is a GPR40 agonist. In some embodiments, the oral composition is formulated as a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition. In some embodiments, the oral composition is in a dosage form configured as one of a soft-gel capsule, a hard capsule, liquid, powder, and a tablet. In some embodiments, the oral composition comprises 1.0% to 99% w/w of a plant extract. In some embodiments, the composition further comprises a preservative. In some embodiments, the composition further comprises a sweetener. In some embodiments, the composition further comprises a coloring agent. In some embodiments, the composition further comprises an additive. In some embodiments, the composition further comprises a flavoring agent. In some embodiments, the compound is a compound of Tables 1, 2, and 3.

[0006] Some embodiments relate to a method of treating, preventing, reducing, modulating, or ameliorating a disease or disorder associated with GPR40 in a subject in need thereof. In some embodiments, the method includes administering a therapeutically effective amount of a composition as described herein. In some embodiments, the composition activates GPR40. In some embodiments, the composition is provided with food to induce activation of GPR40. In some embodiments, an activation of GPR40 by administering the composition is sufficient to control appetite and glucose metabolism in the subject.

[0007] Some embodiments relate to a method of treating, preventing, reducing, reducing a risk of, modulating, or ameliorating obesity in a subject in need thereof. In some embodiments, the method includes administering a therapeutically effective amount of a composition including an oral composition as described herein.

[0008] Some embodiments relate to a method of treating, preventing, reducing, reducing a risk of, modulating, or ameliorating diabetes in a subject in need thereof. In some embodiments, the method includes administering a therapeutically effective amount of a composition including an oral composition as described herein. In some embodiments, the diabetes is type-2 diabetes.

[0009] Some embodiments relate to a method of treating, preventing, reducing a risk of, modulating, or ameliorating metabolic syndrome in a subject in need thereof. In some embodiments, the method includes administering a therapeutically effective amount of a composition including an oral composition as described herein.

[0010] Some embodiments relate to a method of treating, preventing, reducing a risk of, modulating, or ameliorating a lipid disorder in a subject in need thereof. In some embodiments, the method includes administering a therapeutically effective amount of a composition including an oral composition as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The features and advantages of the compositions and methods described herein will become apparent from the following description, taken in conjunction with the accompanying drawings. These drawings depict certain aspects of the compositions and methods described in the present application, and thus, are not to be considered limiting. In the drawings, similar reference numbers or symbols typically identify similar components, unless context dictates otherwise. The drawings may not be drawn to scale.

[0012] FIG. 1 illustrates an *in vitro* assay setup of an example of the disclosure.

[0013] FIG. 2 illustrates a workflow of an example of the disclosure.

[0014] FIG. 3 illustrates an assay of an example of the disclosure.

[0015] FIG. 4 illustrates a counter screen with CHO parental cells of an example of the disclosure.

[0016] FIG. 5 illustrates a graph representing results from an assay depicting % activity in GPR40 +/- cells.

[0017] FIG. 6 illustrates a graph representing results from an assay comparing % hGPR40 activity to % off-target activity in CHO cells.

[0018] FIG. 7 illustrates pure compounds identified in the IP1 assay.

[0019] FIG. 8 illustrates a graph representing the TGR5 controls of DMSO and K-155 to HTRF ratio.

[0020] FIG. 9 illustrates graphs representing TGR5 pure compounds in a cAMP screen.

[0021] FIG. 10 illustrates a graph representing a GPR40 control of DMSO, K-003, and K-13 to HTRF ratio.

[0022] FIG. 11 illustrates graphs representing GPR40 pure compounds in IP1 screen.

DETAILED DESCRIPTION OF THE DISCLOSURE

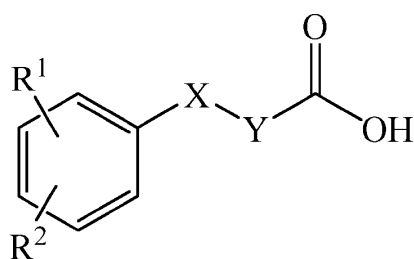
[0023] This disclosure provides, among other things, compounds, compositions, uses, and methods for providing or administering the compounds or compositions to treat, reduce, module, or ameliorate a disease or disorder or a symptom associated with a disease or disorder. In some embodiments, the disease or disorder or symptom associated with a disease or disorder is associated with a G-protein coupled receptor (GPCR). In some embodiments, the composition includes a therapeutically effectively amount of a plant extract and one or more carriers or excipients. In some embodiments, the method of treating, preventing, reducing, modulating, or ameliorating a disease or disorder is associated with GPR40 in a subject and includes providing or administering one or more compounds or a composition as described herein.

Compositions

[0024] In some aspects, a composition is provided comprising a compound capable of being useful as agonists of a G-protein coupled receptor. In some embodiments, the compound is a GPCR ligand. The term “ligand”, as used herein, shall mean a molecule (e.g., test compound) that specifically binds to a polypeptide. In some embodiments, the compound

is a GPR agonist. The term “agonist”, as used herein, shall mean an agent (e.g., ligand, test compound) that by virtue of binding to a GPCR activates (e.g., stimulates) the GPCR so as to elicit an intracellular response mediated by the GPCR. In some embodiments, the compound is a GPR partial agonist. The term “partial agonist”, as used herein, shall mean an agent (e.g., ligand, test compound) that by virtue of binding to a GPCR activates (e.g., stimulates) the GPCR so as to elicit an intracellular response mediated by the GPCR, albeit to a lesser extent or degree than does a full agonist by, for example, having a lower binding affinity and/or have lower activity of eliciting an intracellular response. In some embodiments, the compound is a GPR antagonist. The term “antagonist” shall mean an agent (e.g., ligand, test compound) that binds, and preferably binds competitively, to a GPCR at about the same site as an agonist or partial agonist but which does not activate an intracellular response initiated by the active form of the GPCR, and can thereby inhibit the intracellular response by agonist or partial agonist. An antagonist typically does not diminish the baseline intracellular response in the absence of an agonist or partial agonist. In some embodiments, the compound is a GPR inverse agonist. The term “inverse agonist” shall mean an agent (e.g., ligand, test compound) which binds to a GPCR and which inhibits the baseline intracellular response initiated by the active form of the receptor below the normal base level activity which is observed in the absence of an agonist or partial agonist. In some embodiments, the compounds are agonists of G-protein coupled receptor 40 (GPR40). In some embodiments, the compound is a selective GPR40 agonist. In some embodiments, the composition is an oral composition.

[0025] In some embodiments, a compound of the disclosure is represented by a compound of Formula (I):

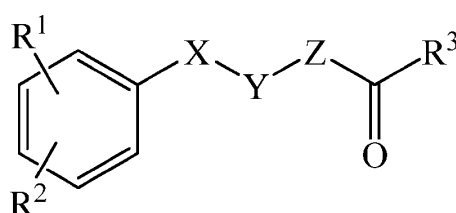


Formula (I)

[0026] In some embodiments, R^1 and R^2 are each independently selected from hydrogen, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted amino, optionally substituted C_1 - C_6 -alkyl, and optionally substituted -O- C_1 - C_6 -alkyl.

[0027] In some embodiments, X and Y are each independently selected from an optionally substituted C_1 - C_{18} alkyl, an optionally substituted C_1 - C_{18} alkenyl, and optionally substituted -O- C_1 - C_{18} -alkyl. In some embodiments, Y is absent.

[0028] In some embodiments, a compound of the disclosure is represented by a compound of Formula (II):



Formula (II)

[0029] In some embodiments, R^1 , R^2 , and R^3 are each independently selected from hydrogen, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted aryl, optionally substituted amino, optionally substituted C_1 - C_6 -alkyl, and optionally substituted -O- C_1 - C_6 -alkyl.

[0030] In some embodiments, X, Y, and Z are each independently selected from an optionally substituted C_1 - C_{18} alkyl, an optionally substituted C_1 - C_{18} alkenyl, and optionally substituted -O- C_1 - C_{18} -alkyl, optionally substituted amino, optionally substituted C-amido, optionally substituted, N-amido, or optionally substituted ester. In some embodiments, Y is absent. In some embodiments, Z is absent.

[0031] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain that comprises a fully saturated (no double or triple bonds) hydrocarbon group. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; e.g., “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon

atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, and hexyls. The alkyl group may be substituted or unsubstituted.

[0032] As used herein, “alkenyl” refers to an alkyl group, as defined herein, that contains in the straight or branched hydrocarbon chain one or more double bonds. An alkenyl group may be unsubstituted or substituted.

[0033] As used herein, “aryl” refers to a carbocyclic (all carbon) monocyclic or polycyclic aromatic ring system (including, e.g., fused, bridged, or spiro ring systems where two carbocyclic rings share a chemical bond, e.g., one or more aryl rings with one or more aryl or non-aryl rings) that has a fully delocalized pi-electron system throughout at least one of the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C₆-C₁₄ aryl group, a C₆-C₁₀ aryl group, or a C₆ aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene, and azulene. An aryl group may be substituted or unsubstituted.

[0034] The term “halogen” or “halo” as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I) groups.

[0035] Whenever a group is described as being “optionally substituted” that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being “unsubstituted or substituted” if substituted, the substituent may be selected from one or more the indicated substituents. If no substituents are indicated, it is meant that the indicated “optionally substituted” or “substituted” group may be individually and independently substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclic, aralkyl, heteroaralkyl, (heteroalicyclic)alkyl, hydroxy, protected hydroxyl, alkoxy, aryloxy, acyl, mercapto, alkylthio, arylthio, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, protected C-carboxy, O-carboxy, isocyanato,

thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, amino, mono-substituted amino group and di-substituted amino group, and protected derivatives thereof.

[0036] In some embodiments, the compound of Formula (I) or Formula (II) are a compound capable of being useful as agonists of a G-protein coupled receptor. In some embodiments, the compound of Formula (I) or Formula (II) is a GPR40 target.

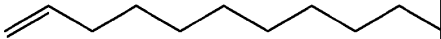
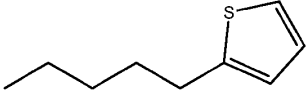
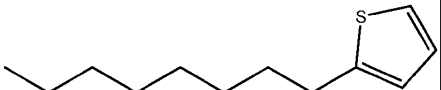
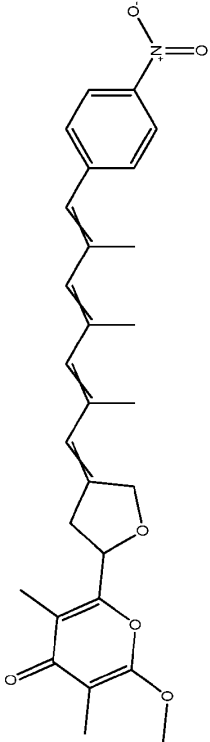
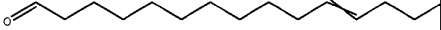
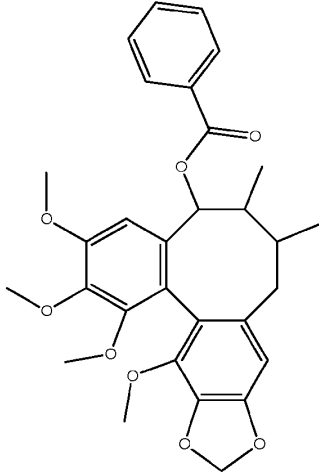
[0037] In some embodiments, the composition comprises one or more compounds according to Table 1. Table 1 depicts compounds according to the disclosure, and may include isomers and stereoisomers of the compounds portrayed. For example, compounds of Table 1 may simultaneously depict both *cis* and *trans* isomers by depicting a crossed double bond:

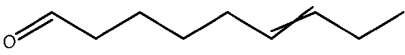
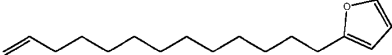
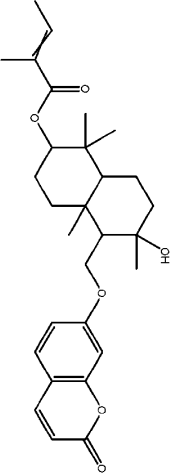
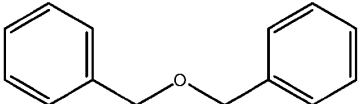
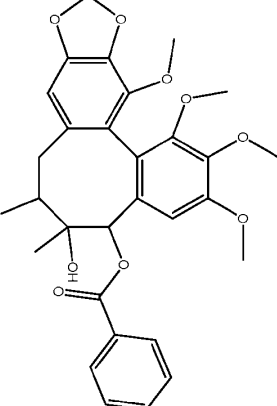
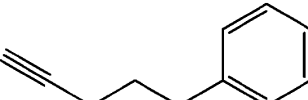
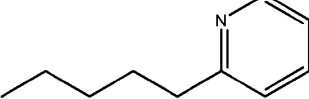
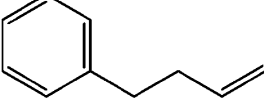
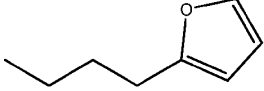
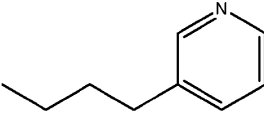


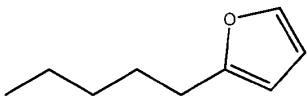
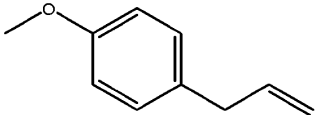
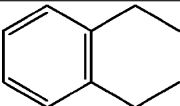
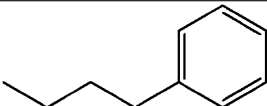
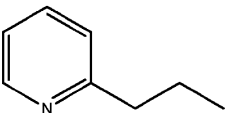
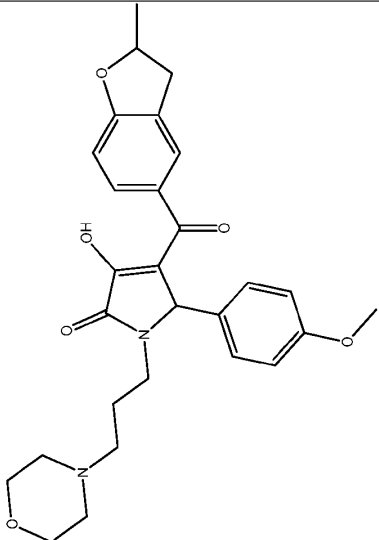
. Such depiction may represent the compound in a mixture of both the *cis* and *trans* isomers, and may also represent either of the *cis* and *trans* isomers individually.

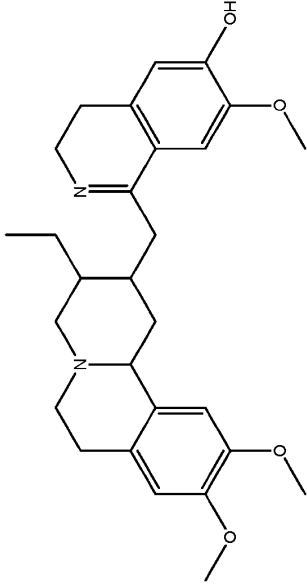
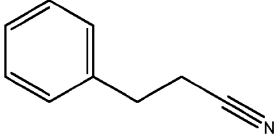
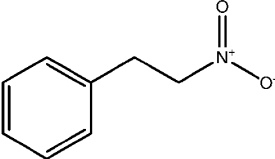
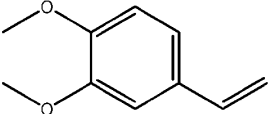
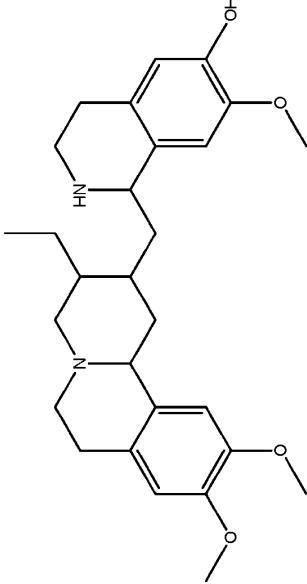
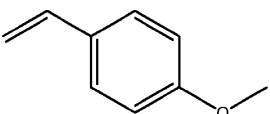
Table 1

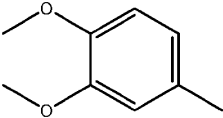
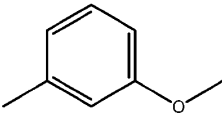
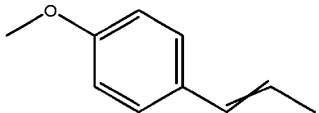
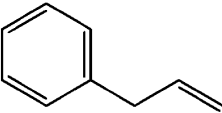
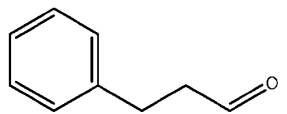
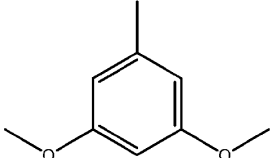
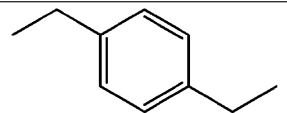
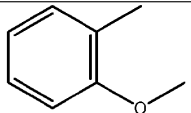
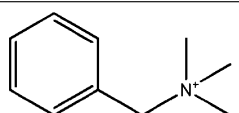
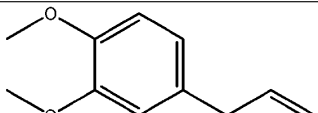
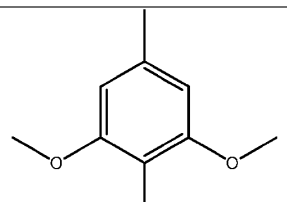
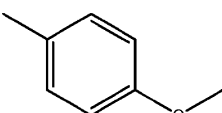
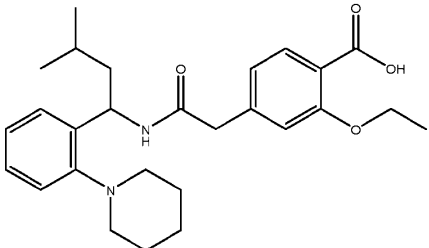
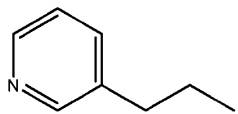
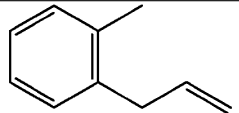
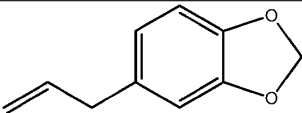
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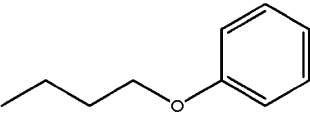
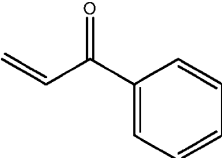
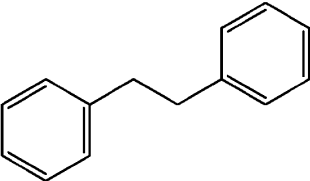
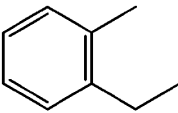
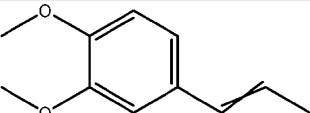
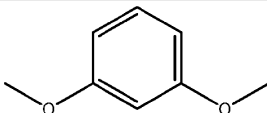
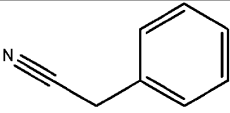
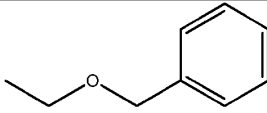
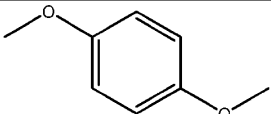
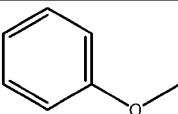
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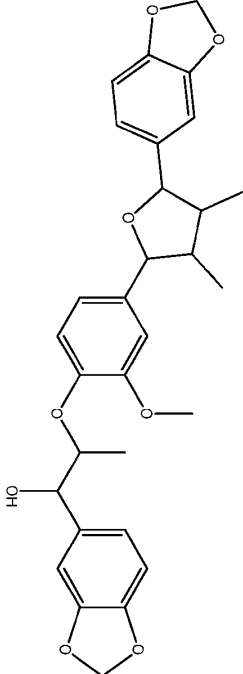
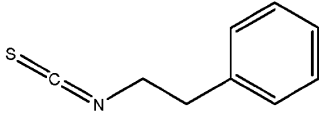
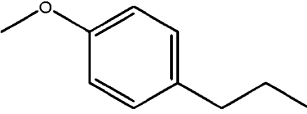
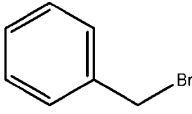
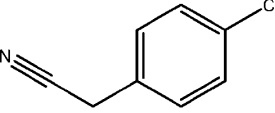
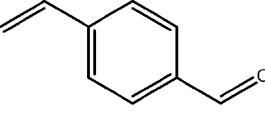
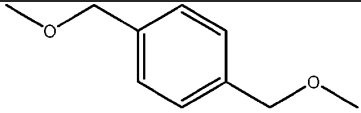
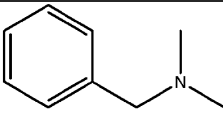
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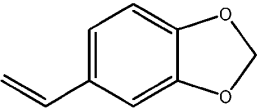
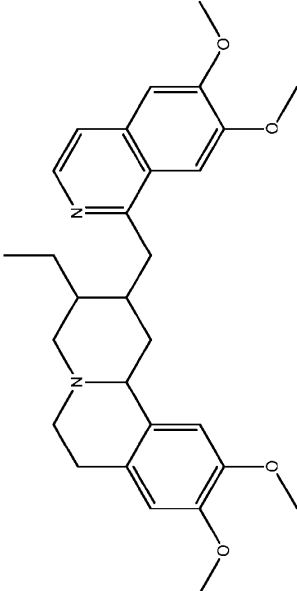
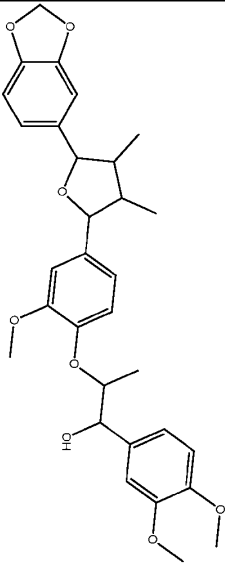
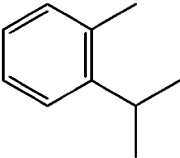
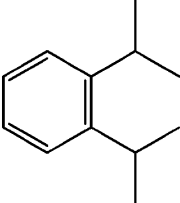
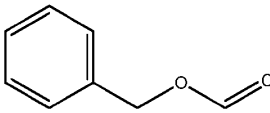
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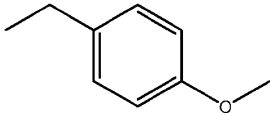
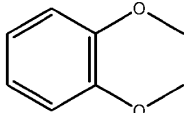
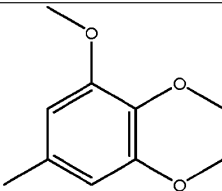
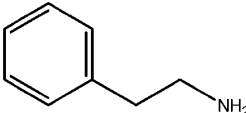
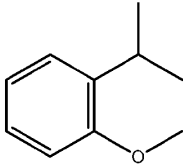
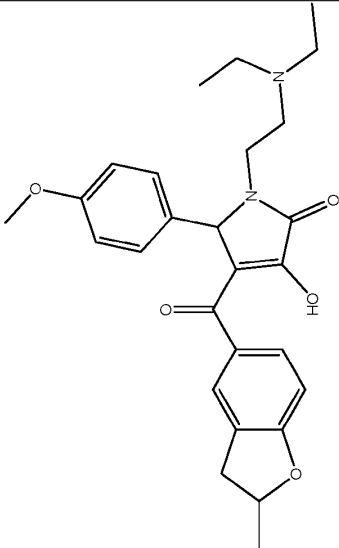
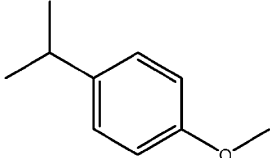
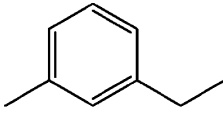
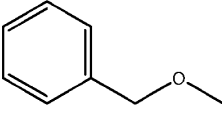
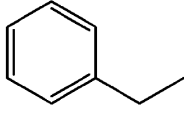
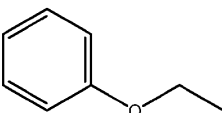
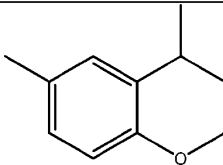
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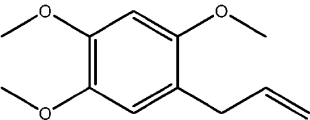
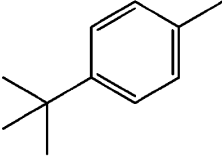
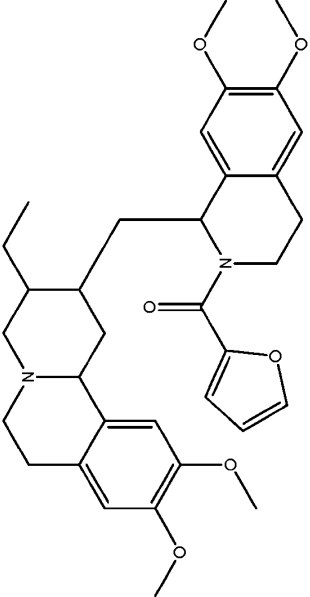
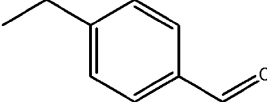
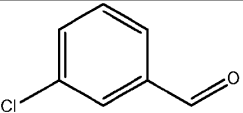
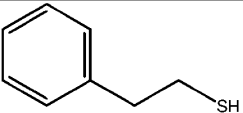
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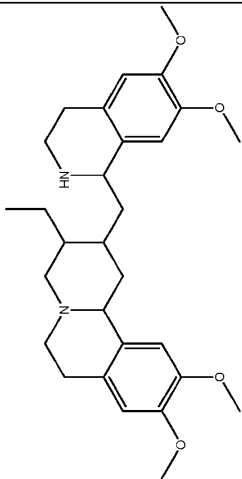
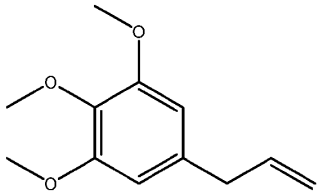
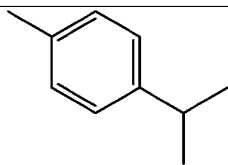
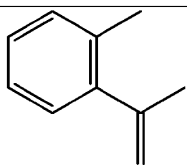
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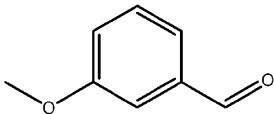
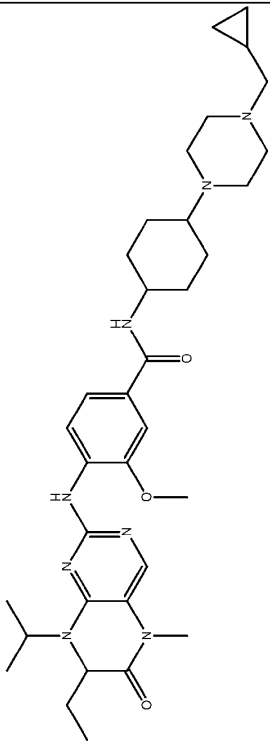
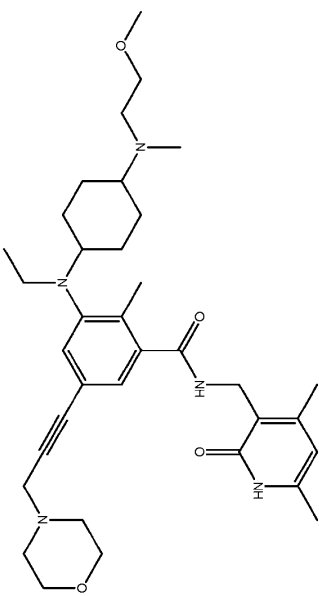
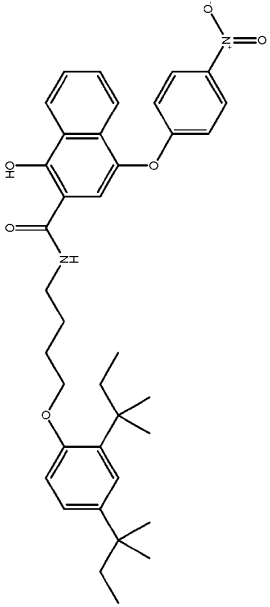
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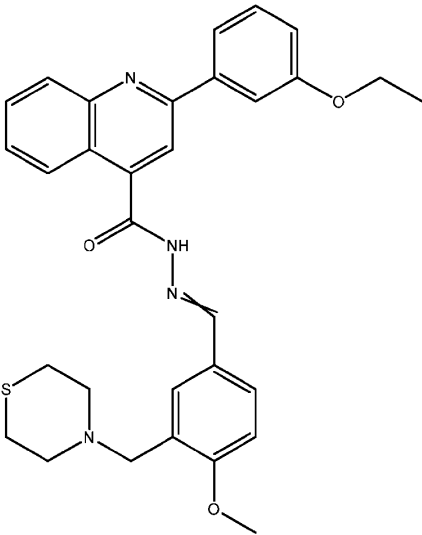
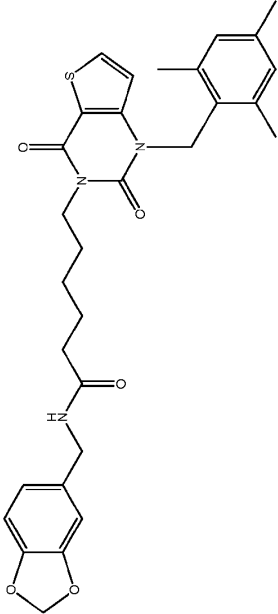
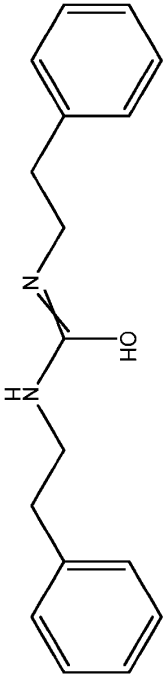
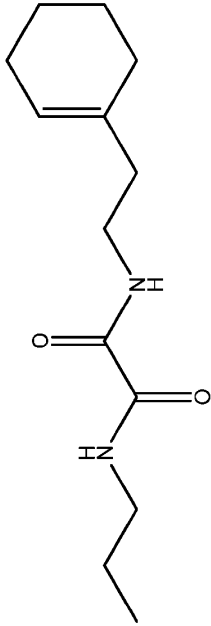
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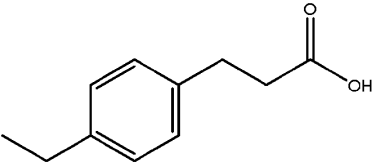
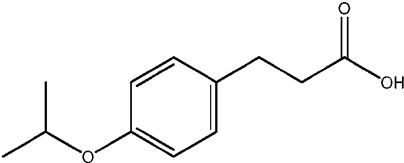
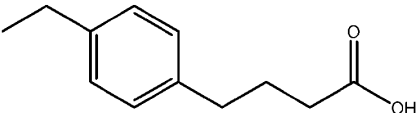
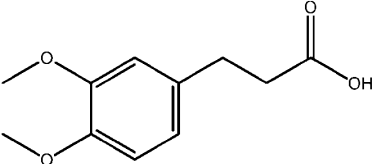
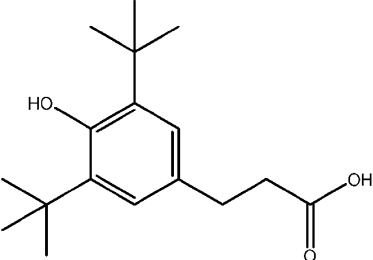
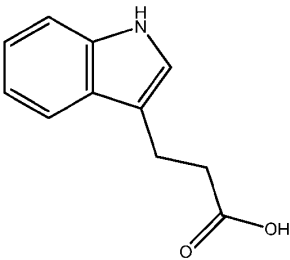
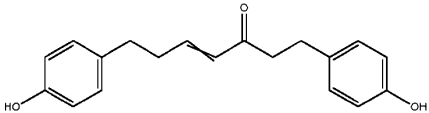
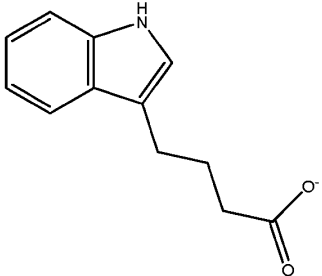
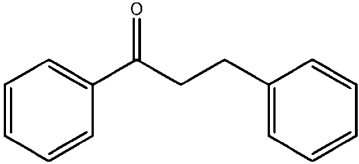
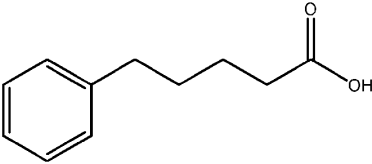
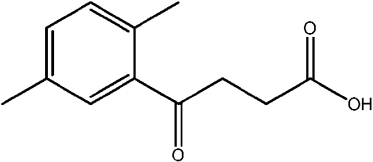
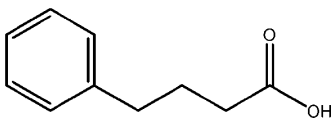
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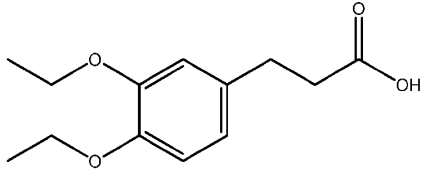
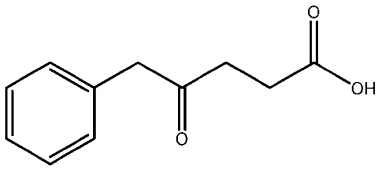
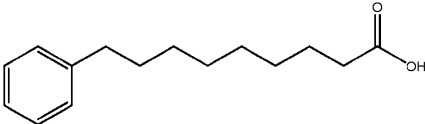
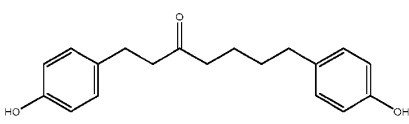
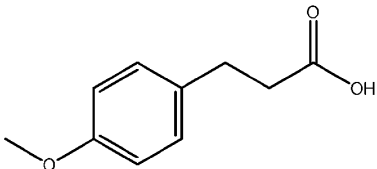
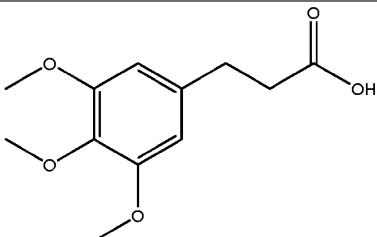
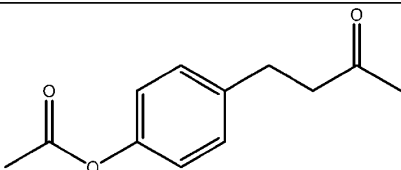
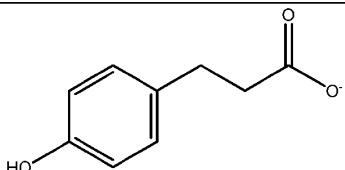
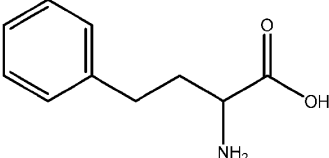
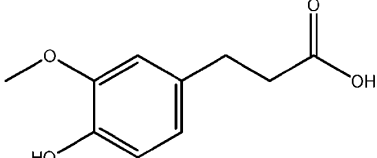
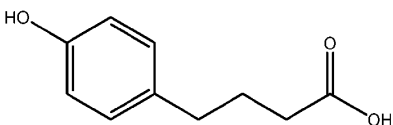
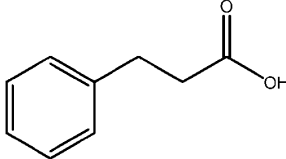
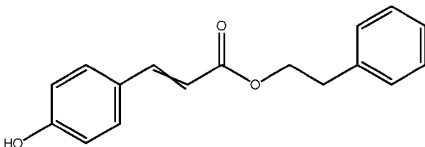
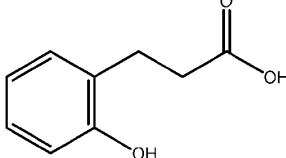
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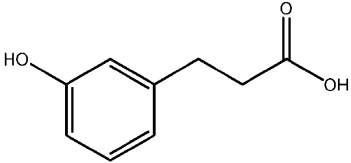
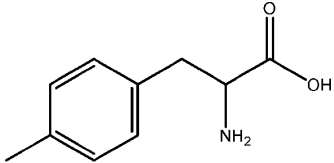
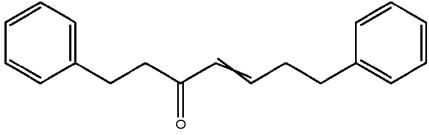
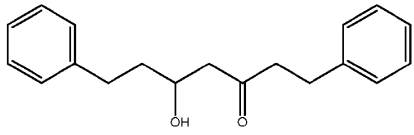
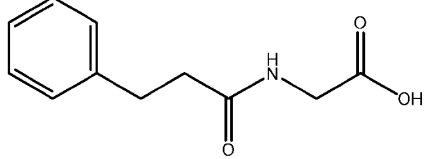
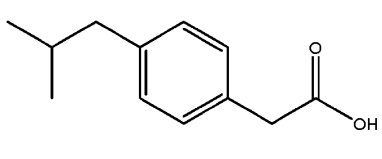
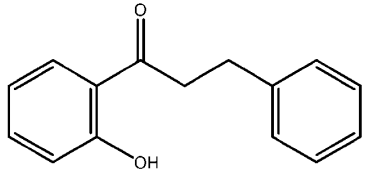
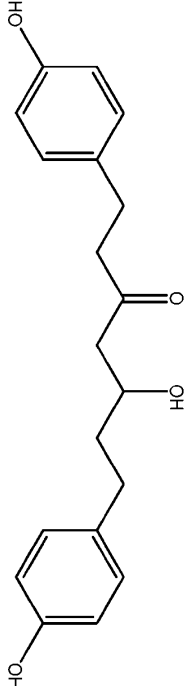
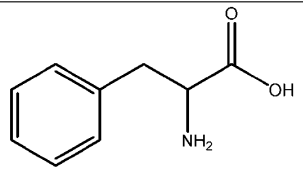
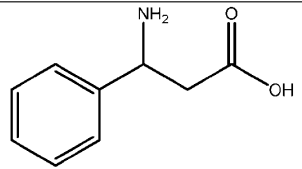
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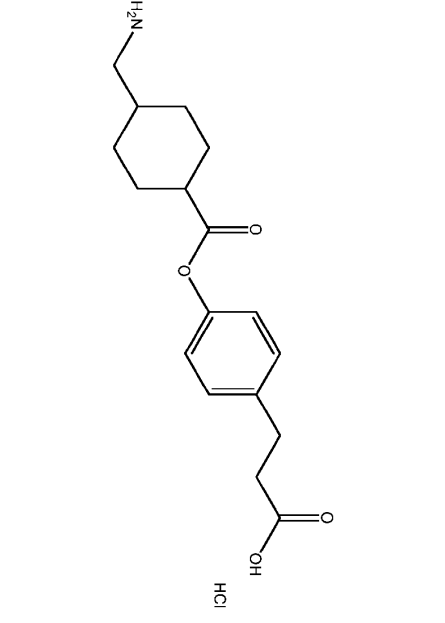
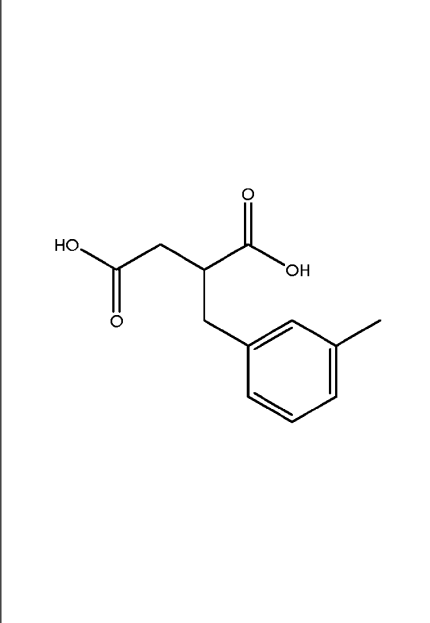
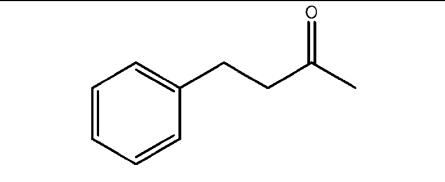
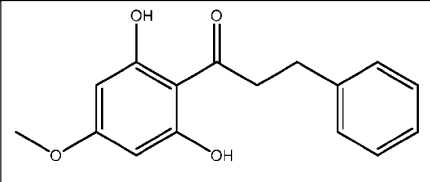
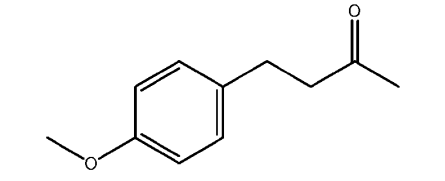
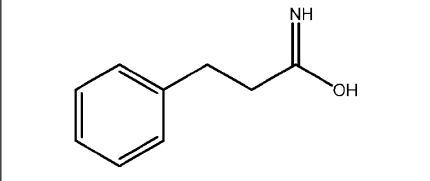
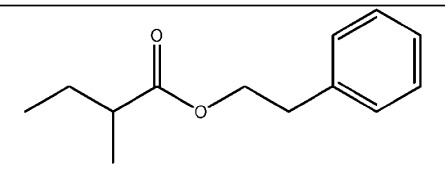
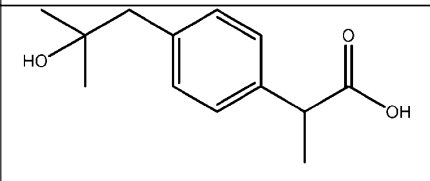
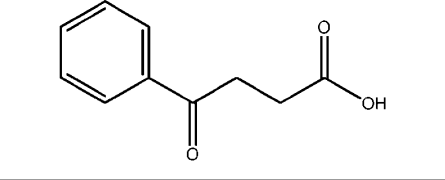
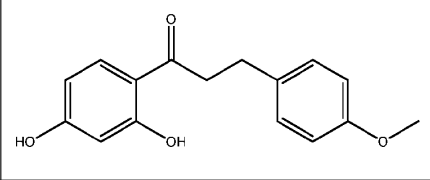
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ID	Structure	ID	Structure
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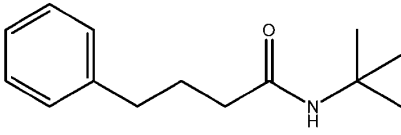
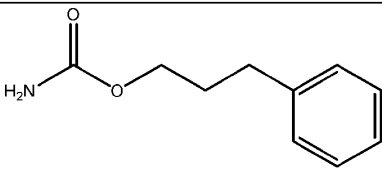
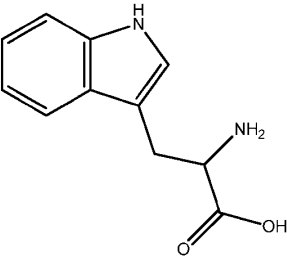
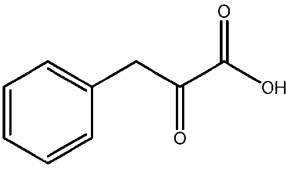
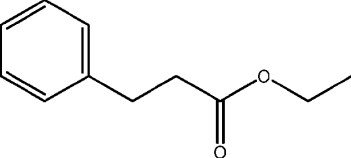
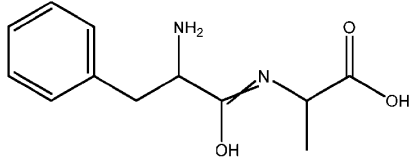
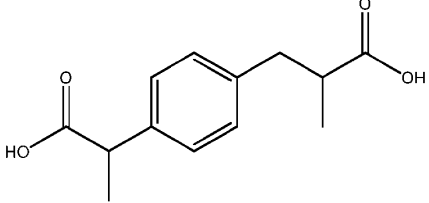
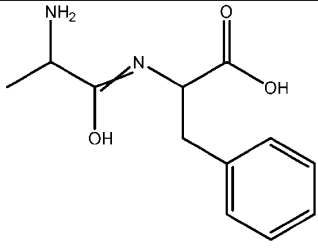
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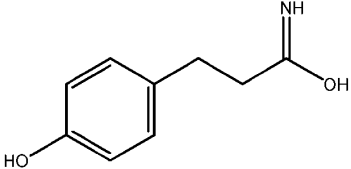
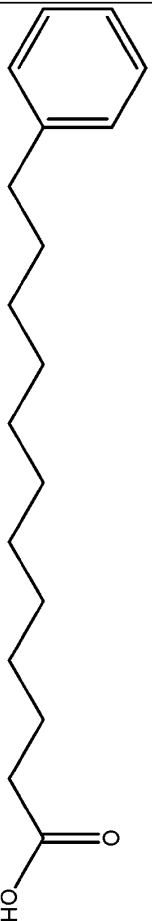
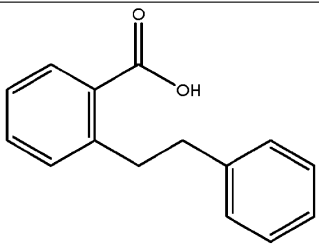
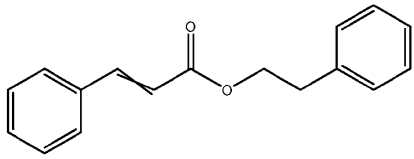
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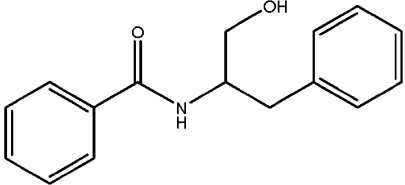
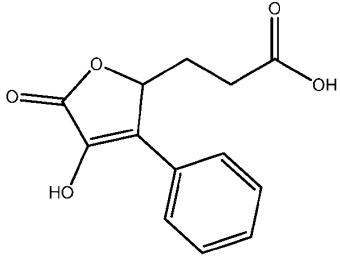
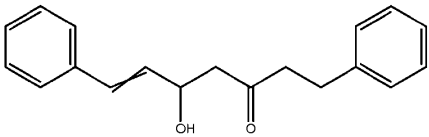
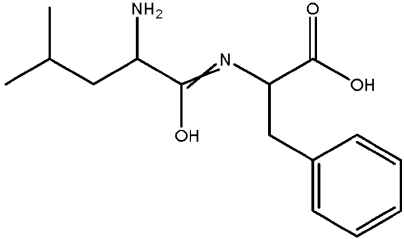
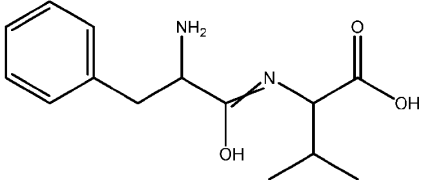
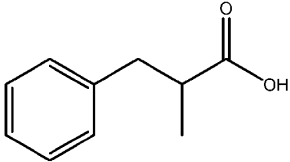
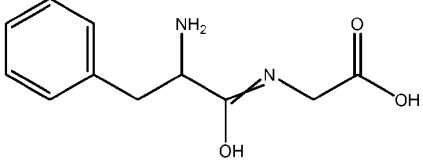
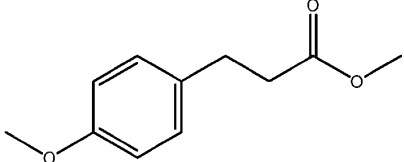
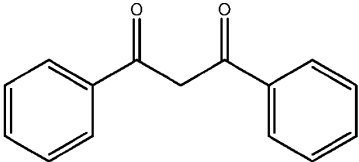
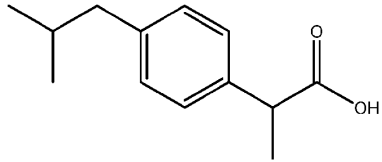
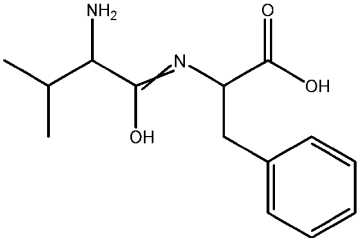
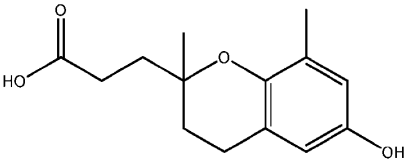
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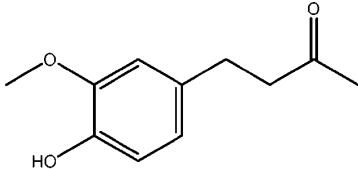
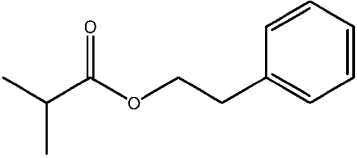
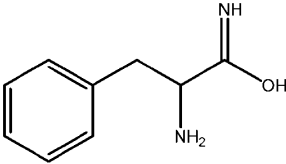
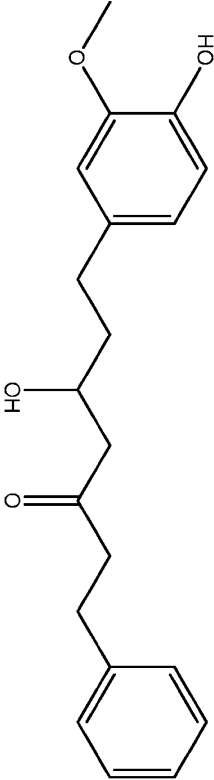
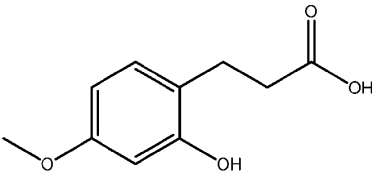
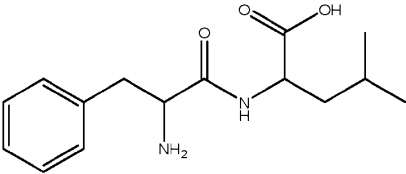
ID	Structure	ID	Structure
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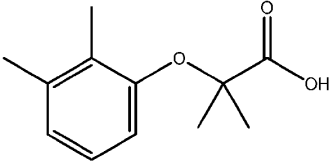
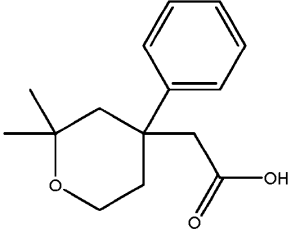
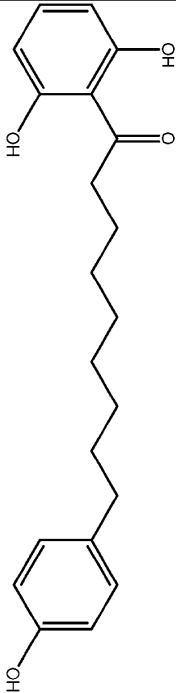
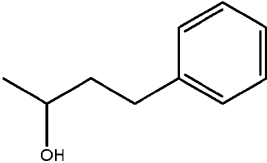
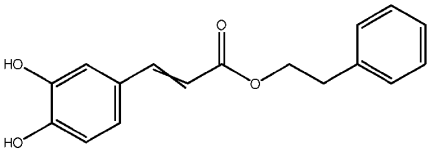
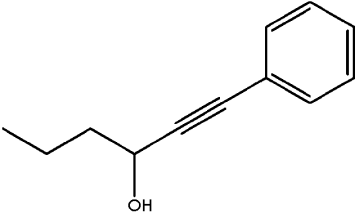
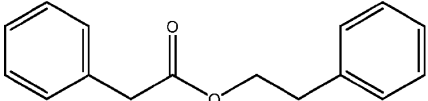
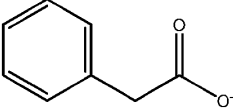
ID	Structure	ID	Structure
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161	<chem>OC1=CC=C(C=C1O)CC(=O)O[O-]</chem>	162	<chem>CC(=O)OCCc1ccccc1</chem>
163	<chem>COC(=O)OCCc1ccc(O)cc1</chem>	164	<chem>CC(=O)OCCCCc1ccccc1OCC#C</chem>
165	<chem>CC(=O)OCCc1ccc(O)cc1</chem>	166	<chem>CC1=C(C2=CC=CC=C2N1)CC(N)C(=O)O</chem>
167	<chem>CC(=O)OCC(N)CCc1ccccc1</chem>	168	<chem>CC(C)C(=O)OCCc1ccccc1</chem>
169	<chem>CCC(=O)Cc1ccccc1</chem>	170	<chem>COc1ccc(cc1)C(N)C(=O)O</chem>

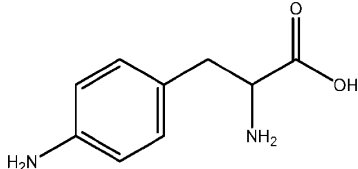
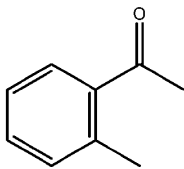
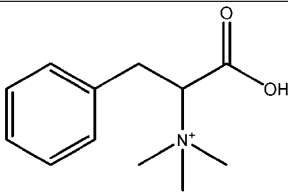
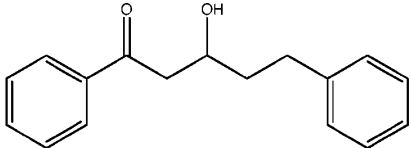
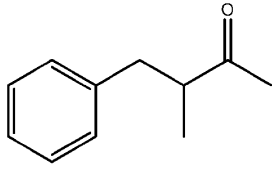
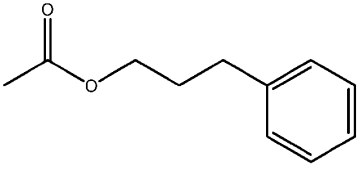
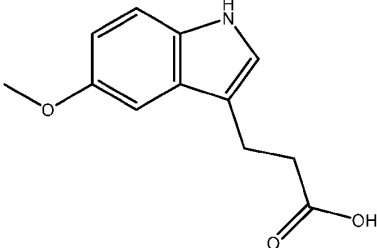
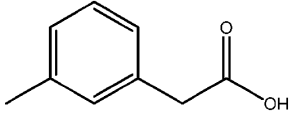
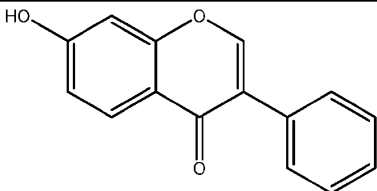
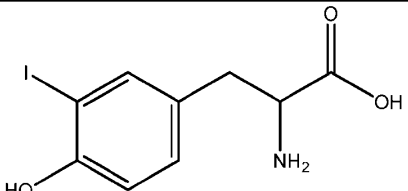
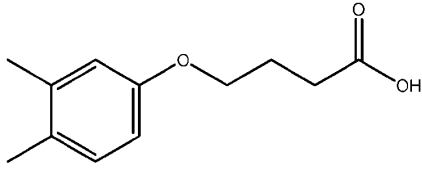
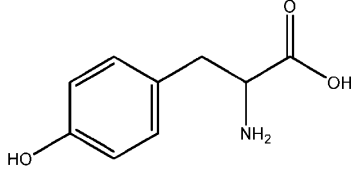
ID	Structure	ID	Structure
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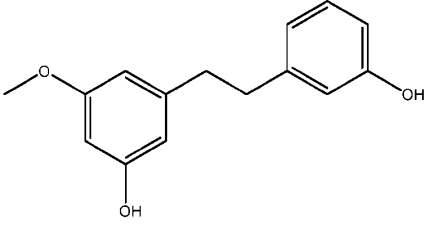
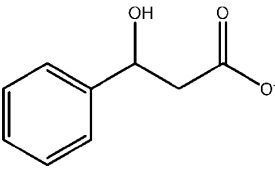
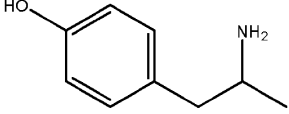
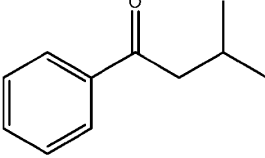
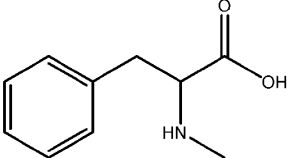
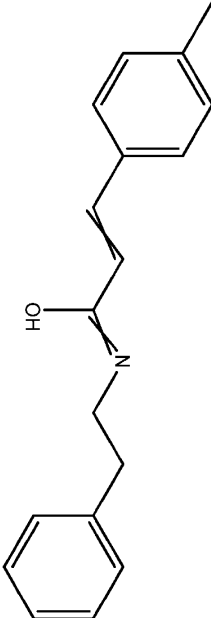
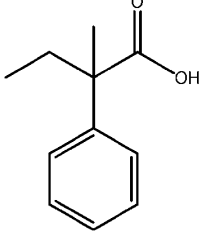
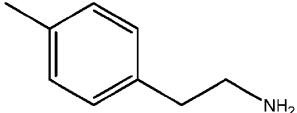
ID	Structure	ID	Structure
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181	 <chem>OC(=O)C1=CC=CC=C1CCC2=CC=CC=C2</chem>	182	 <chem>OC(=O)C1=CC=CC=C1CCC2=CC=CC=C2</chem>

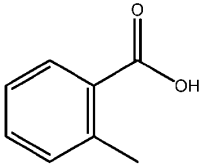
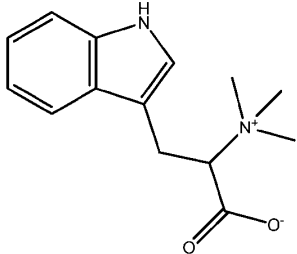
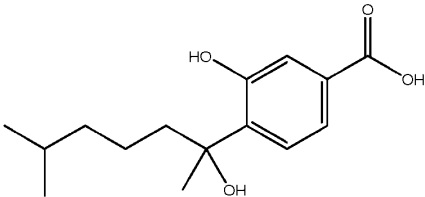
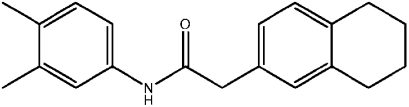
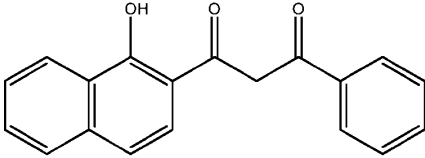
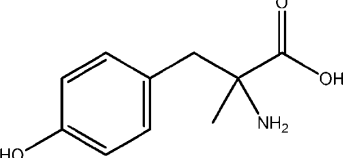
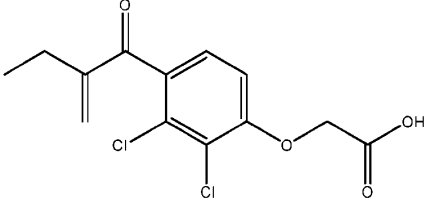
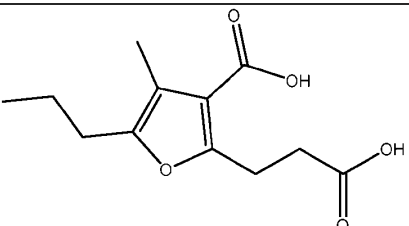
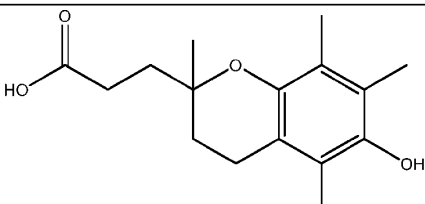
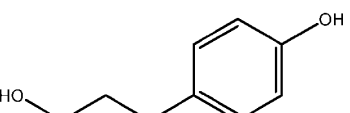
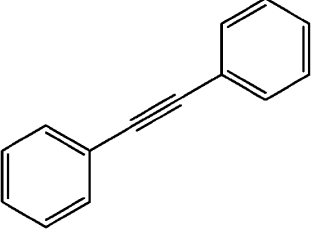
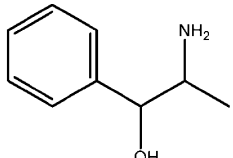
ID	Structure	ID	Structure
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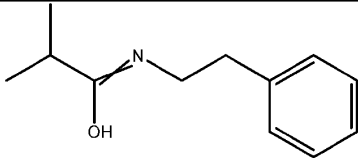
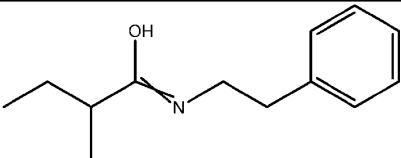
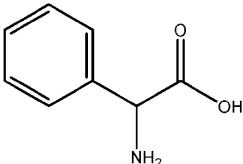
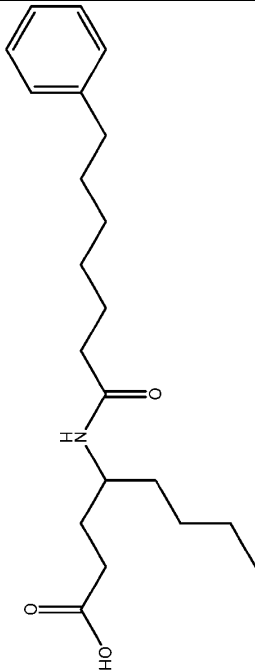
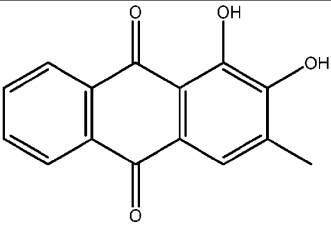
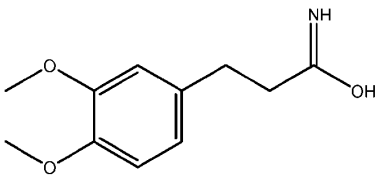
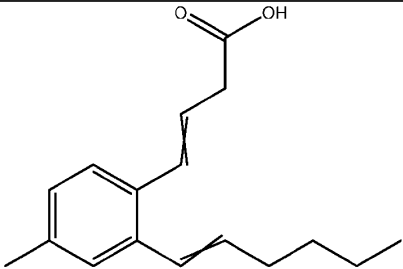
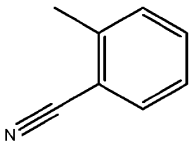
ID	Structure	ID	Structure
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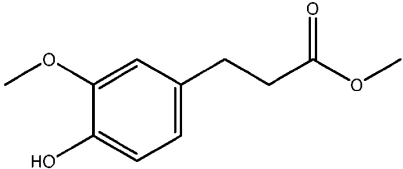
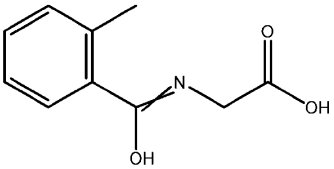
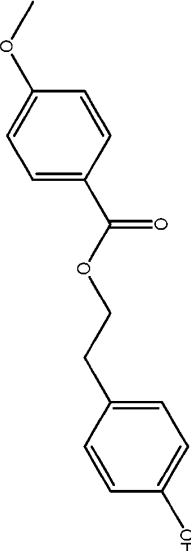
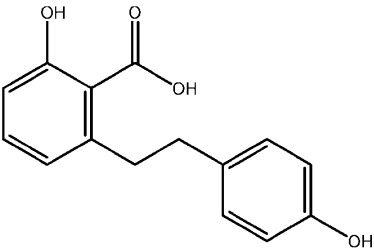
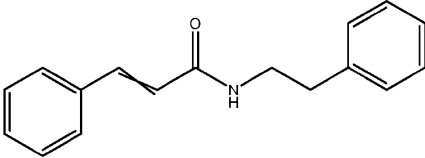
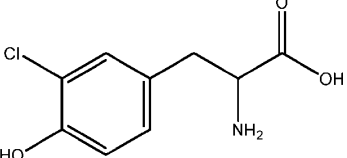
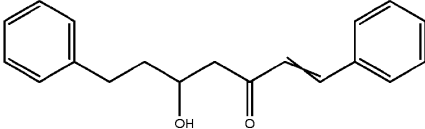
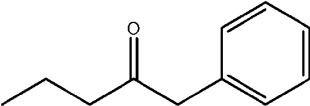
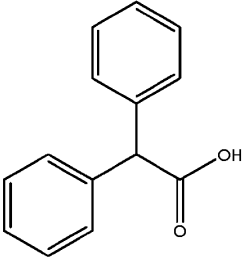
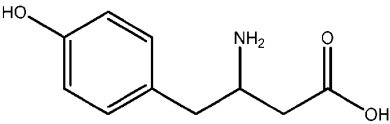
ID	Structure	ID	Structure
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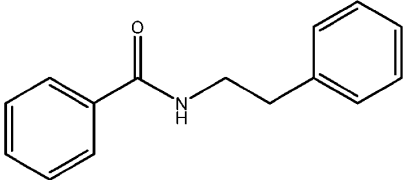
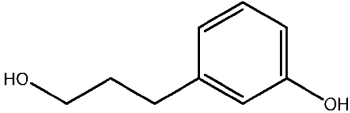
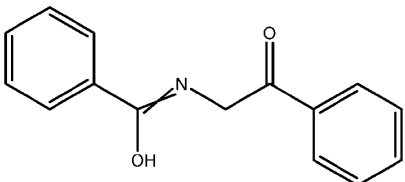
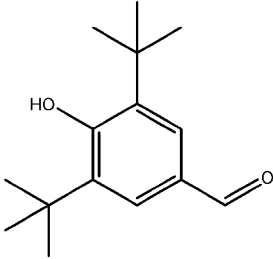
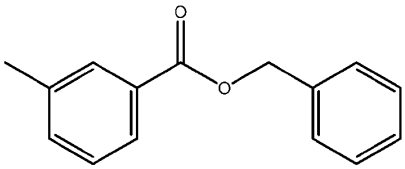
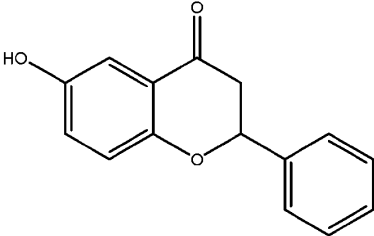
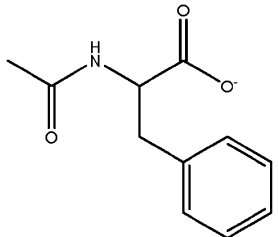
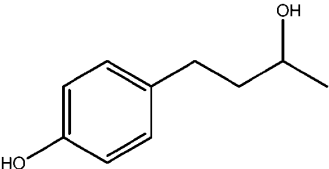
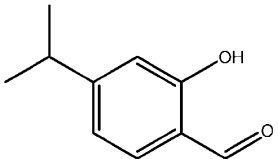
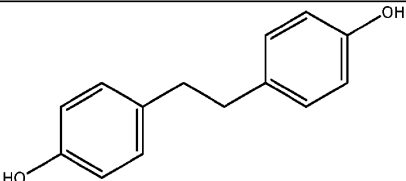
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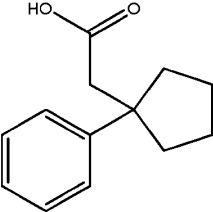
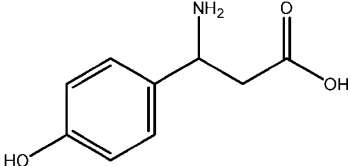
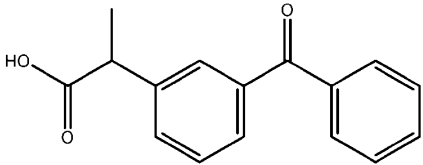
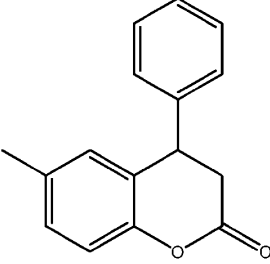
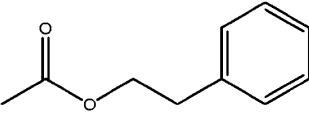
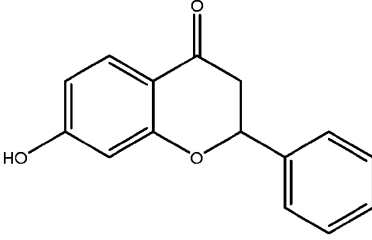
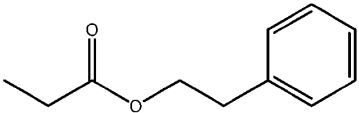
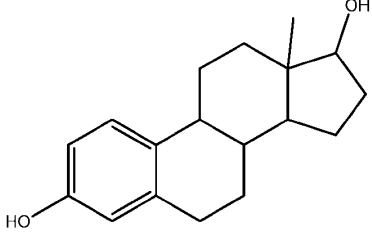
ID	Structure	ID	Structure
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225	 <chem>CCNC(=O)Cc1ccccc1</chem>	226	 <chem>CCc1ccc(cc1)/C=C/C(=O)O[N+](C)(C)CCc2ccccc2</chem>
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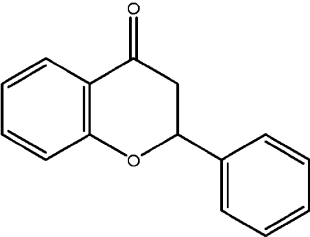
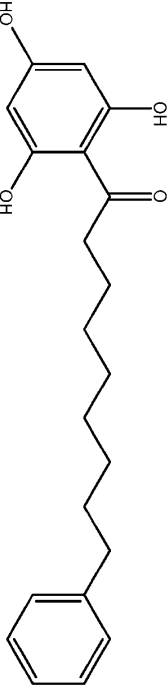
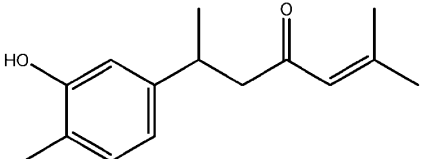
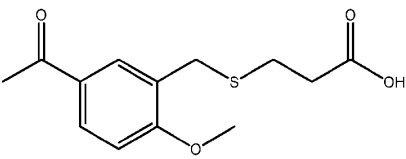
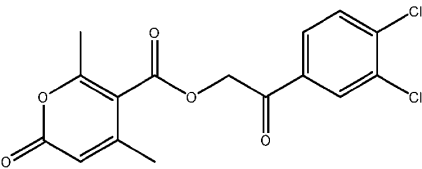
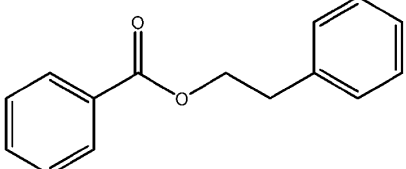
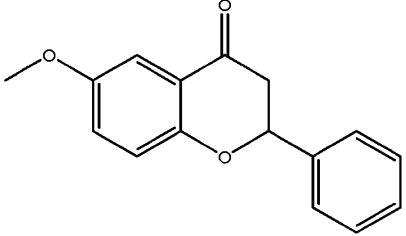
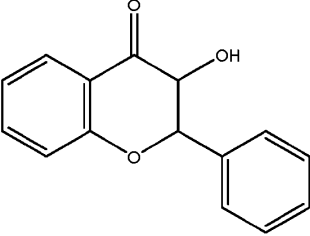
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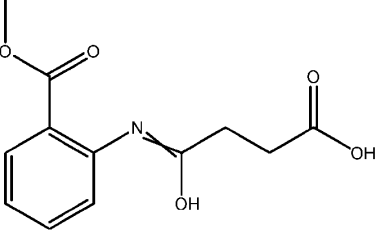
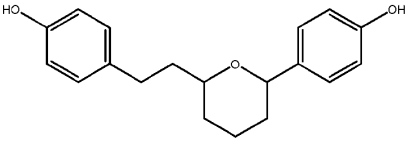
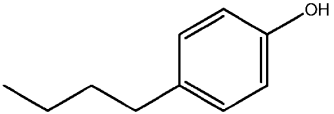
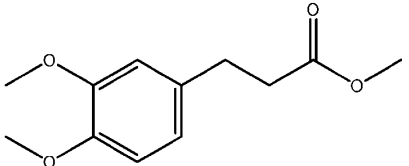
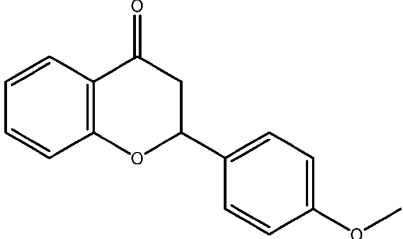
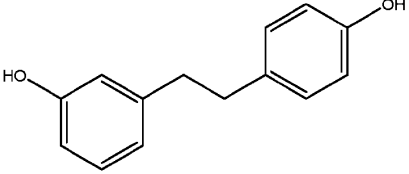
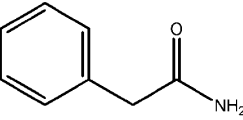
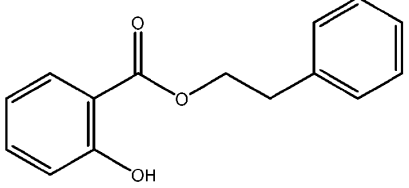
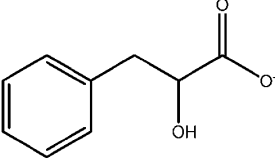
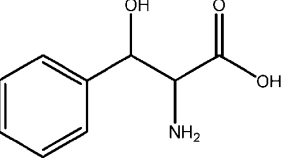
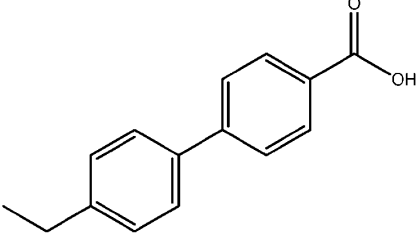
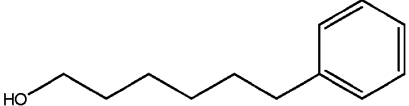
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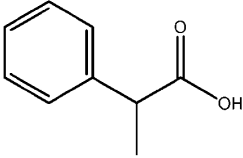
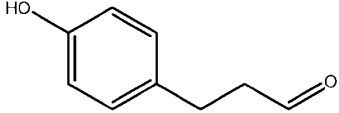
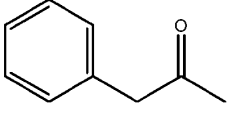
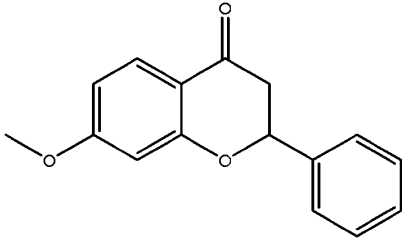
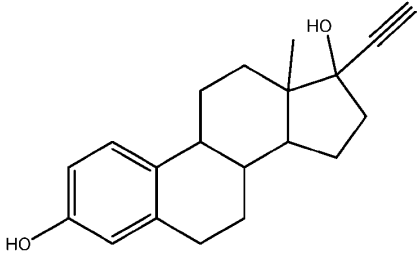
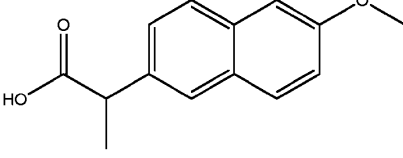
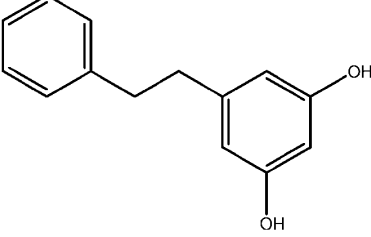
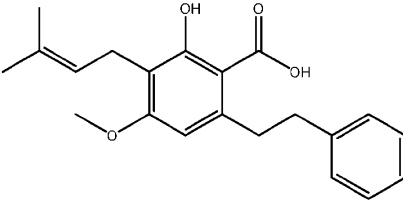
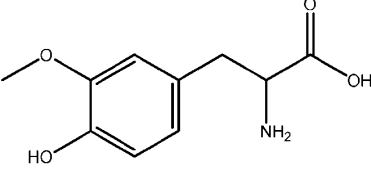
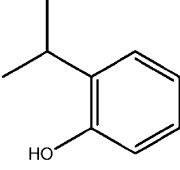
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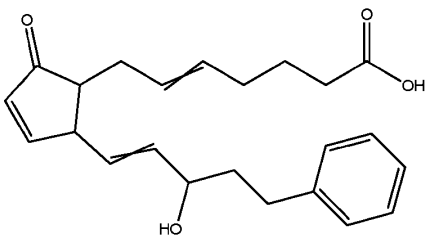
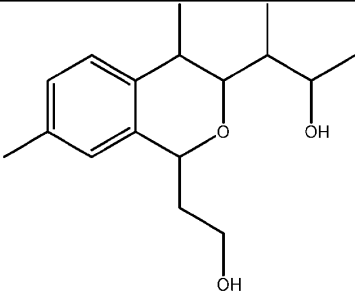
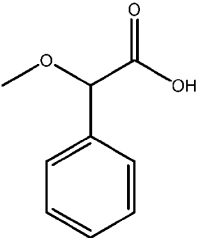
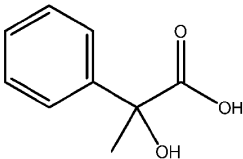
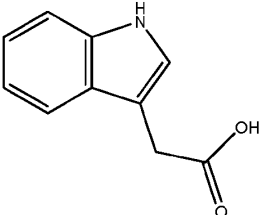
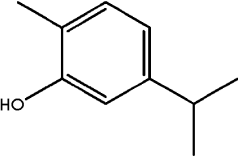
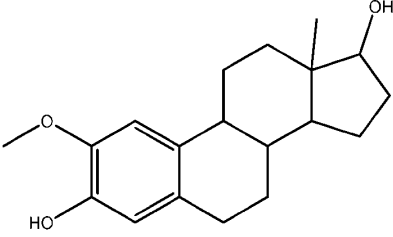
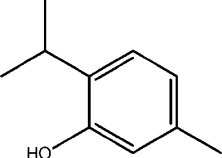
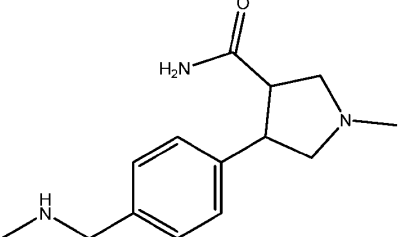
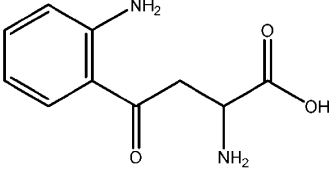
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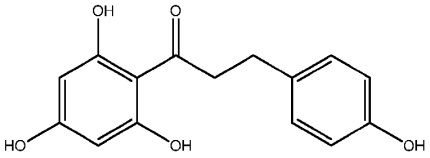
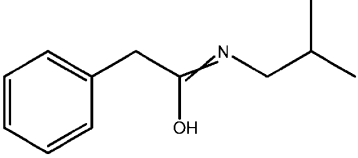
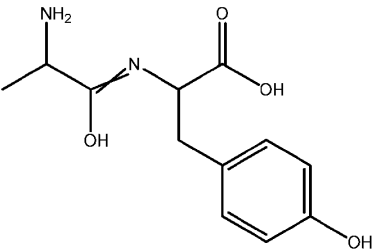
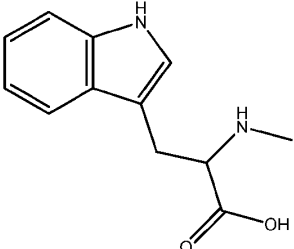
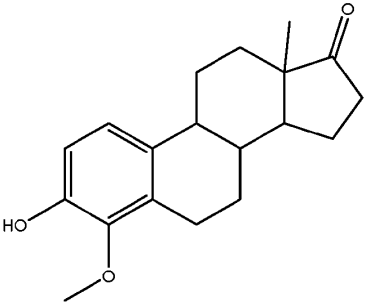
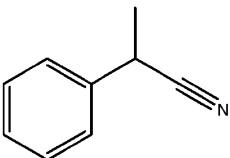
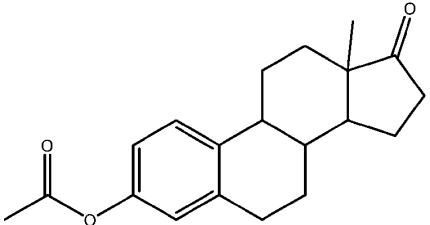
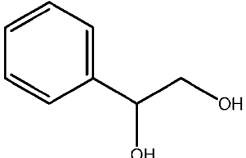
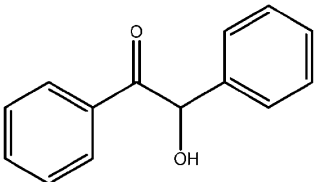
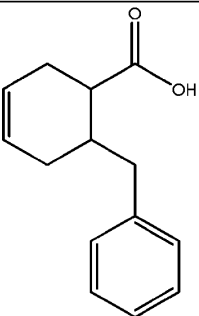
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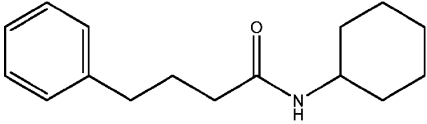
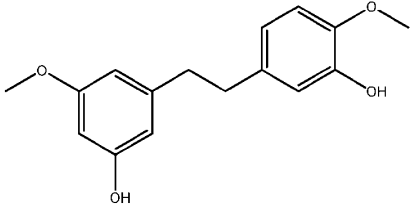
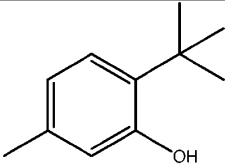
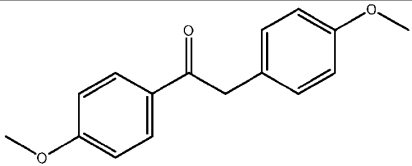
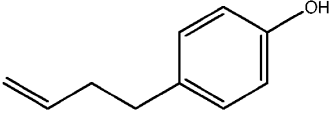
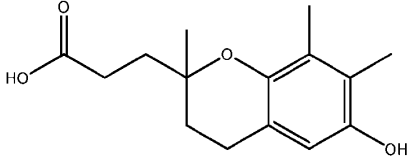
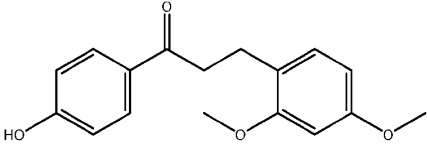
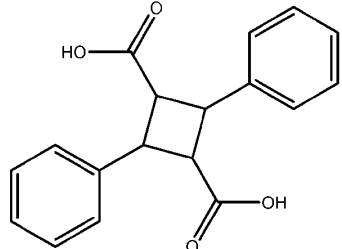
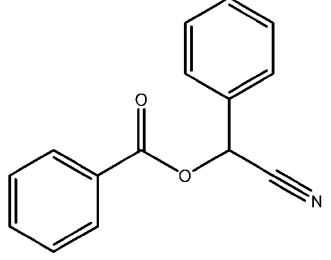
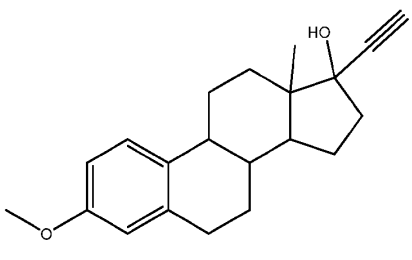
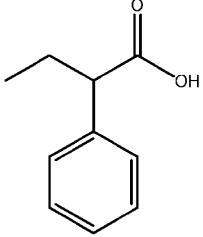
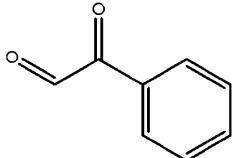
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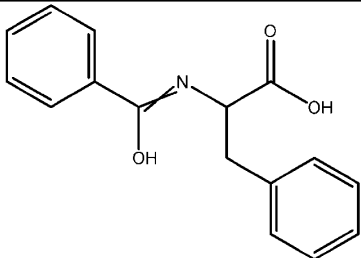
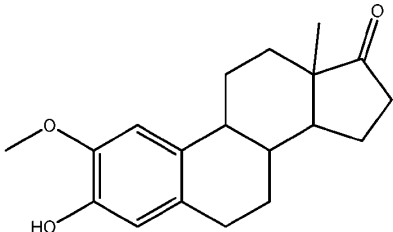
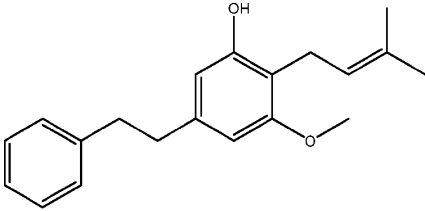
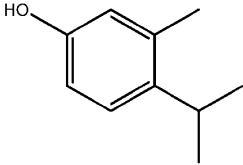
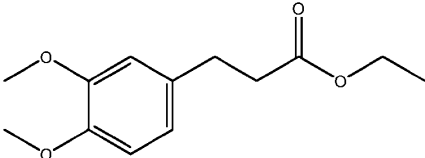
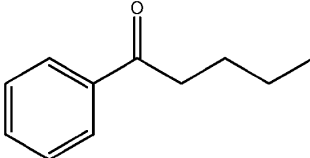
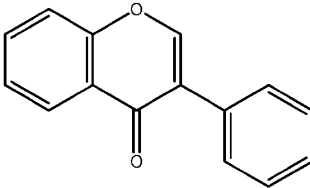
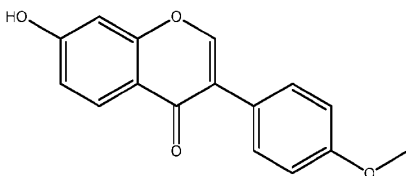
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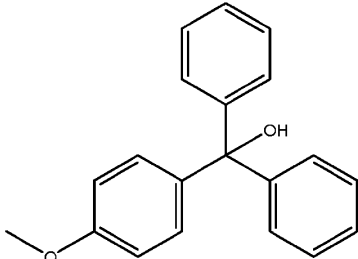
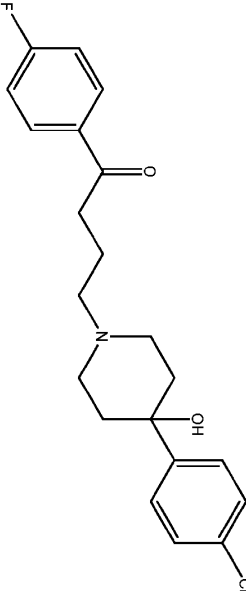
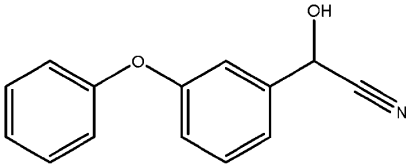
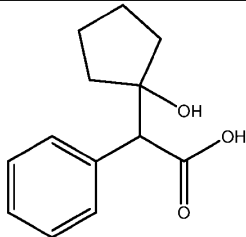
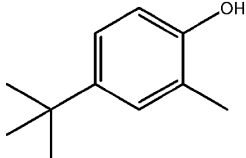
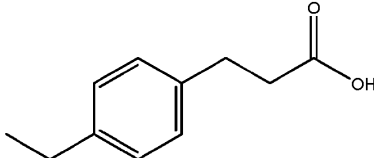
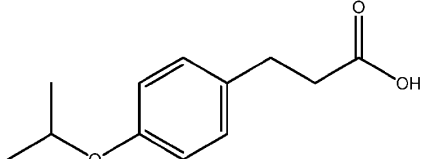
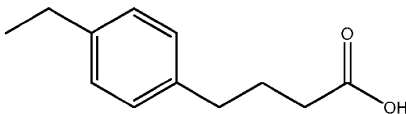
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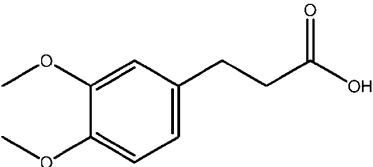
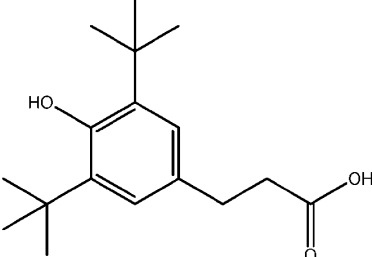
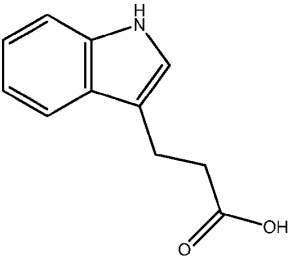
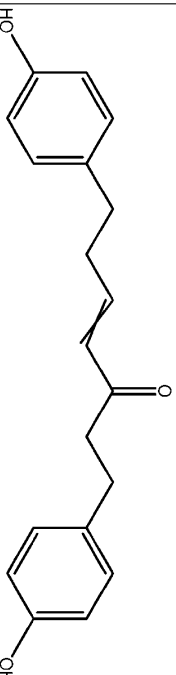
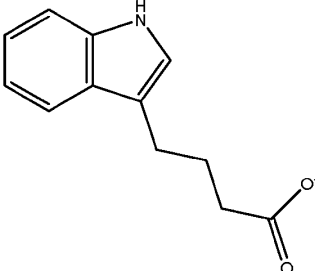
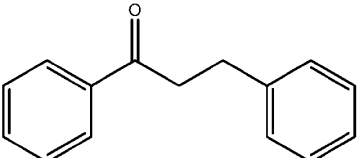
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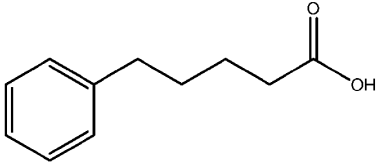
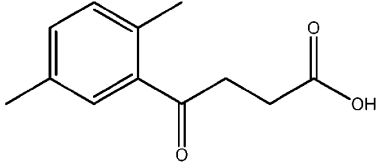
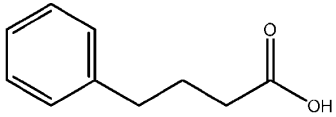
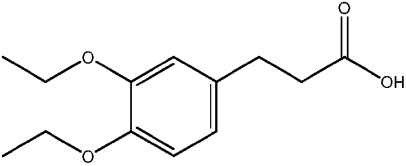
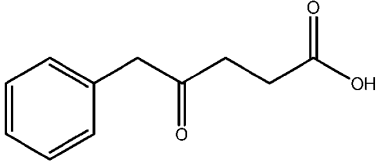
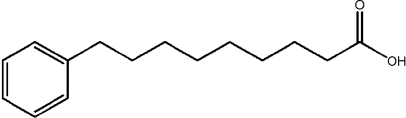
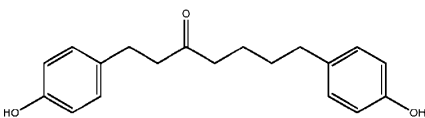
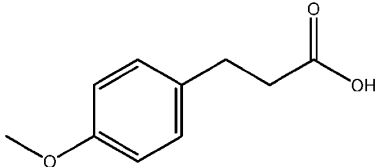
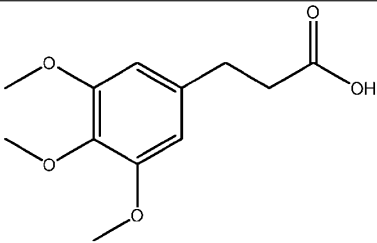
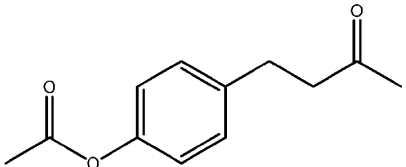
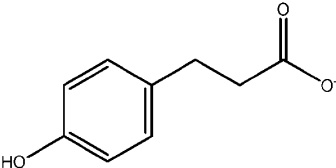
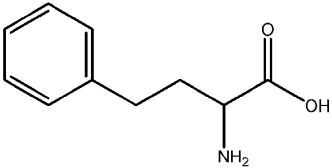
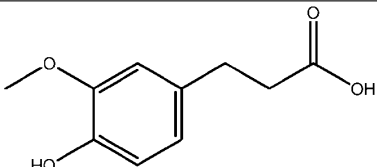
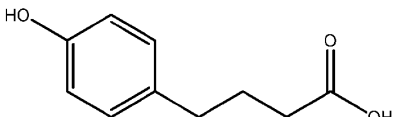
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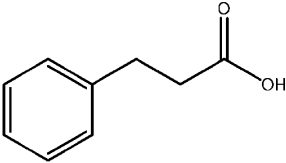
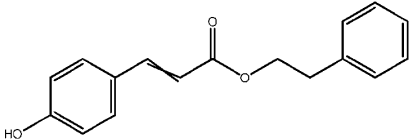
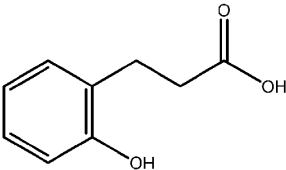
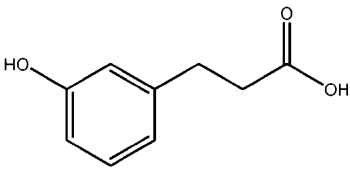
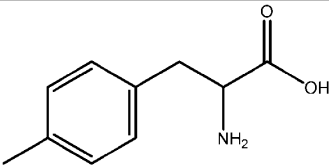
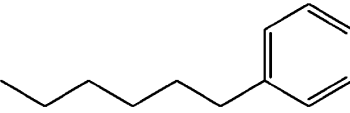
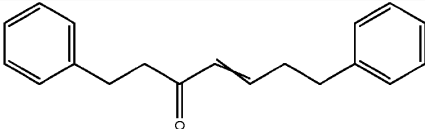
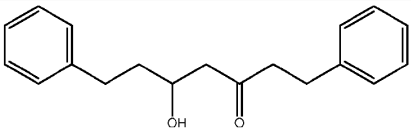
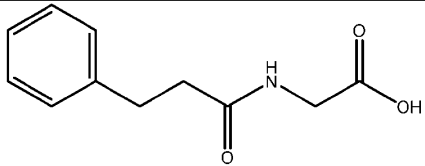
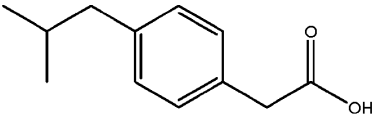
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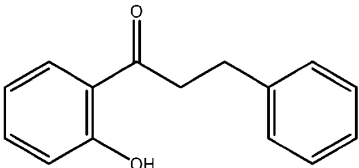
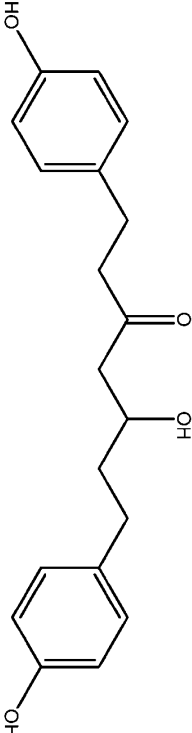
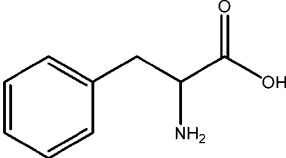
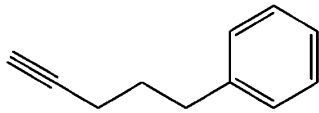
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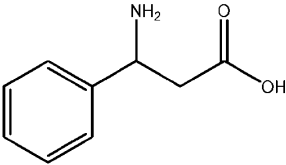
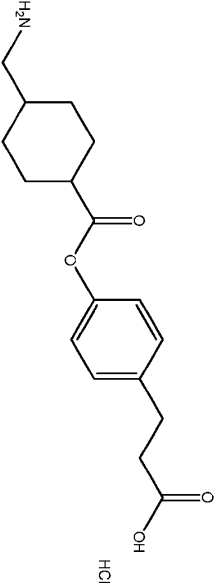
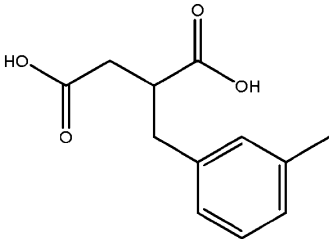
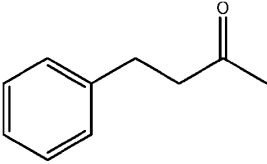
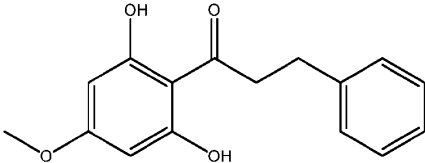
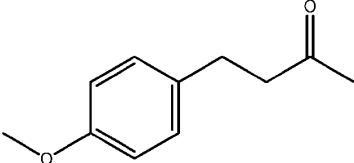
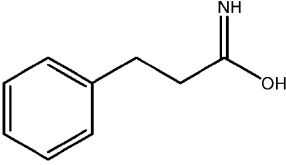
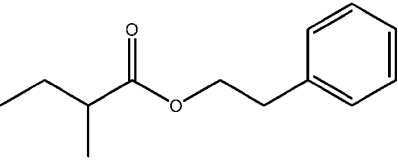
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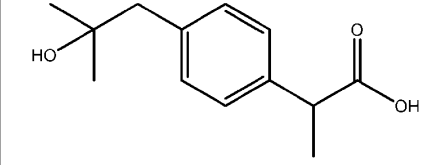
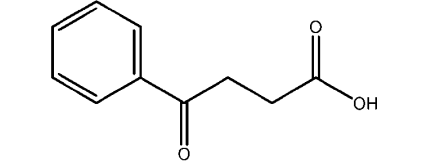
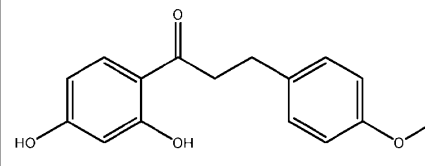
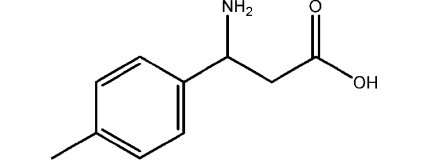
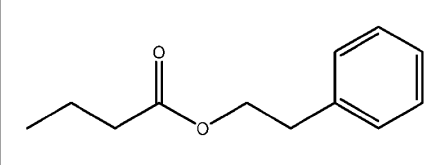
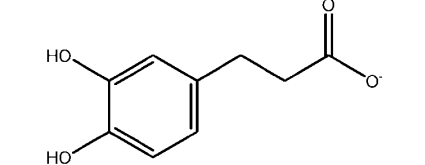
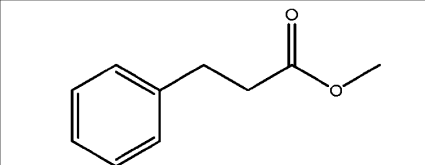
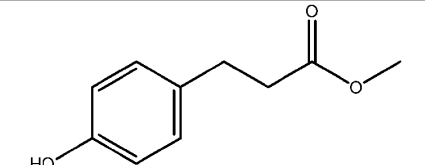
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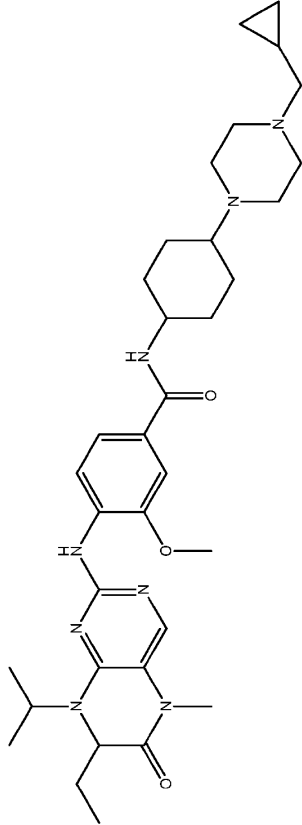
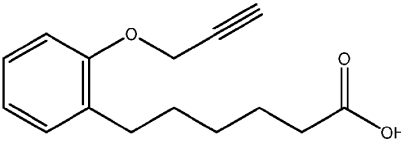
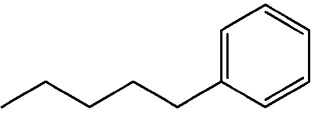
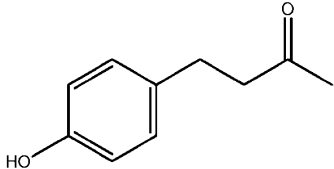
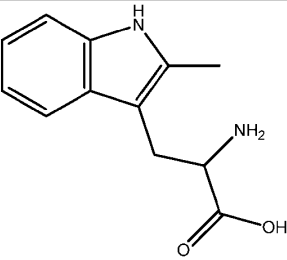
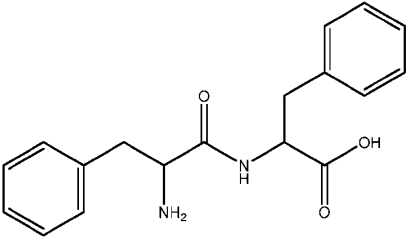
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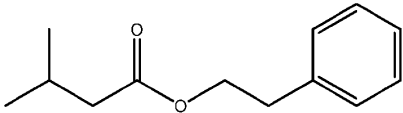
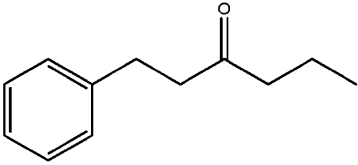
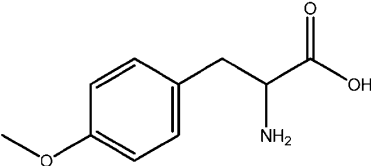
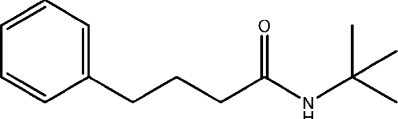
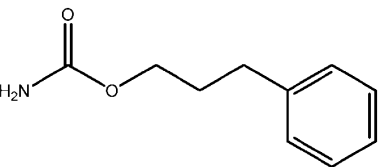
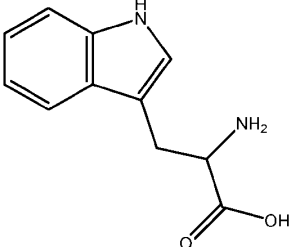
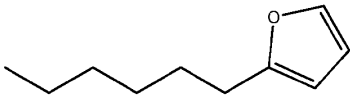
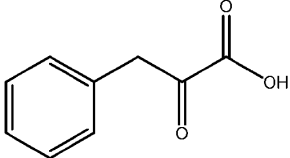
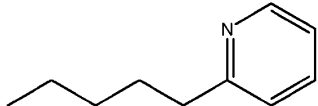
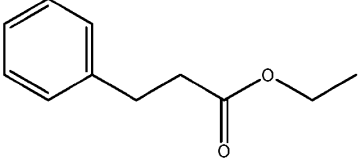
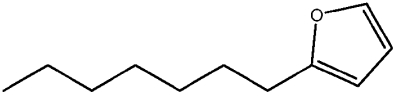
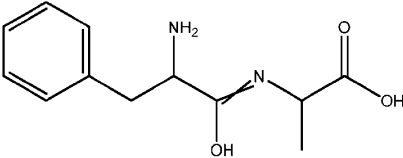
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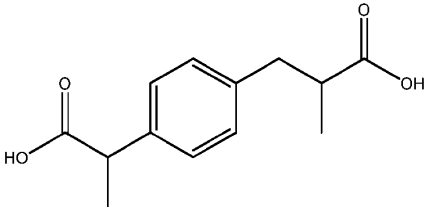
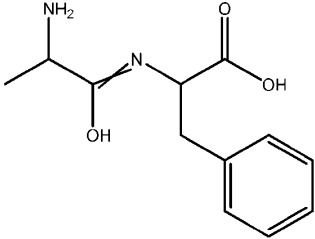
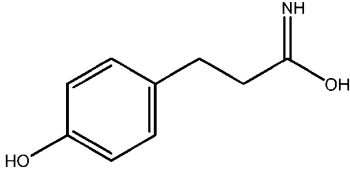
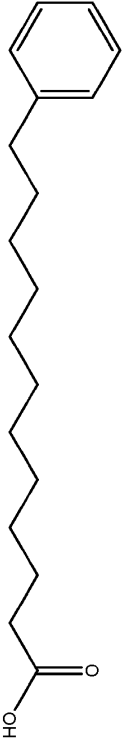
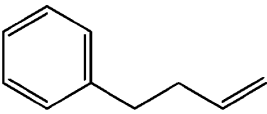
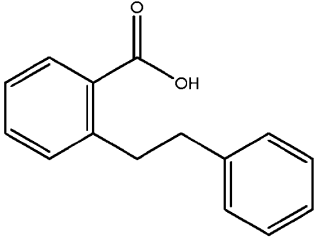
ID	Structure	ID	Structure
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387	 <chem>NC(Cc1ccccc1)C(=O)O</chem>	388	 <chem>C#CCCCc1ccccc1</chem>

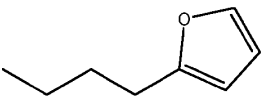
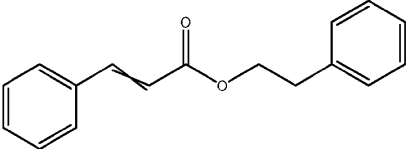
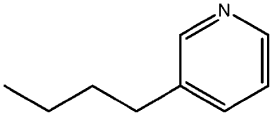
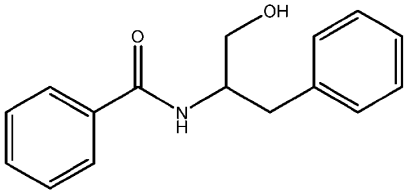
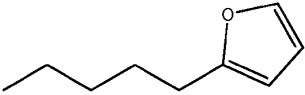
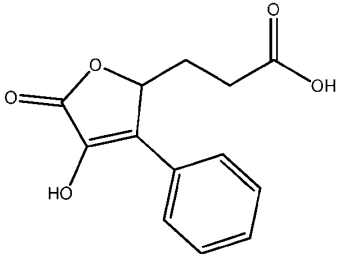
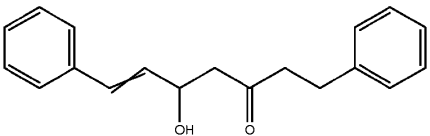
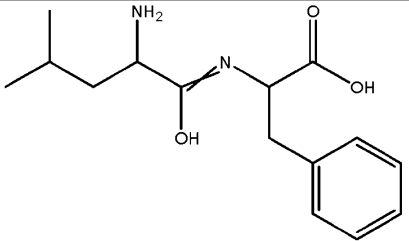
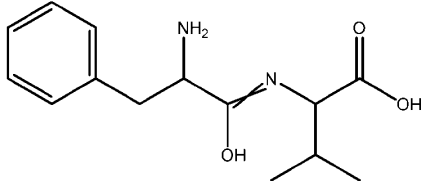
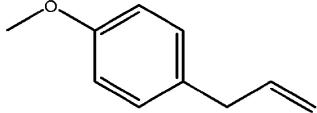
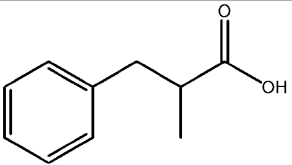
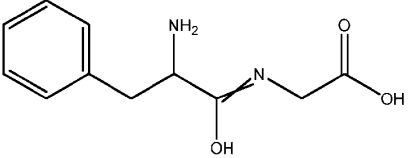
ID	Structure	ID	Structure
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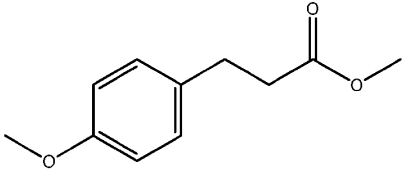
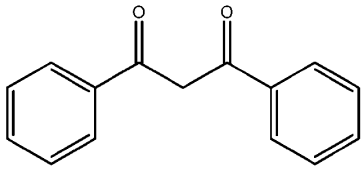
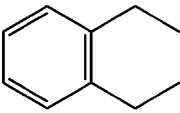
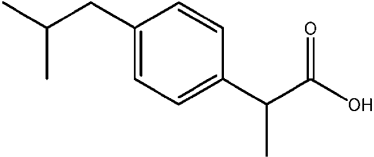
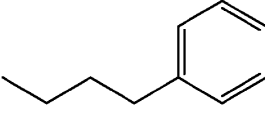
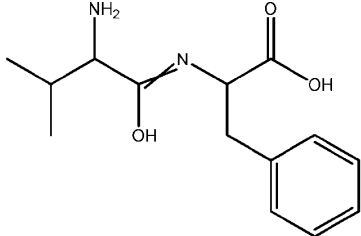
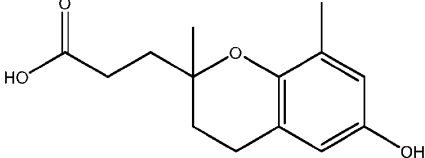
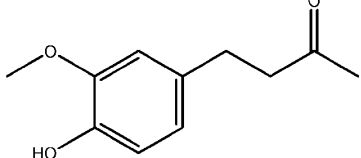
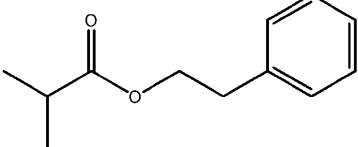
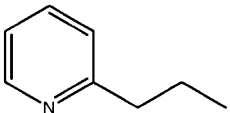
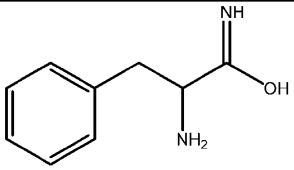
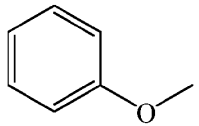
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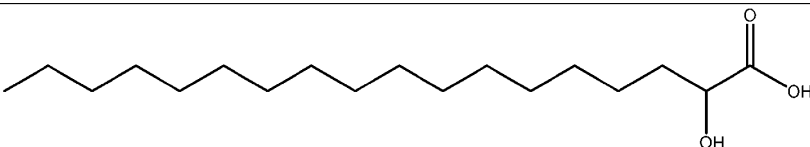
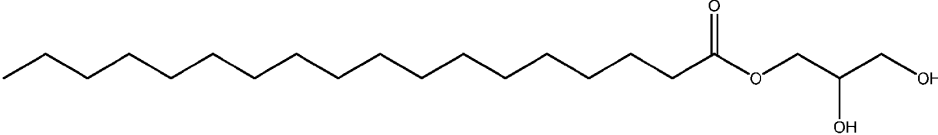
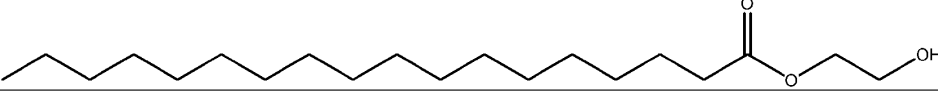
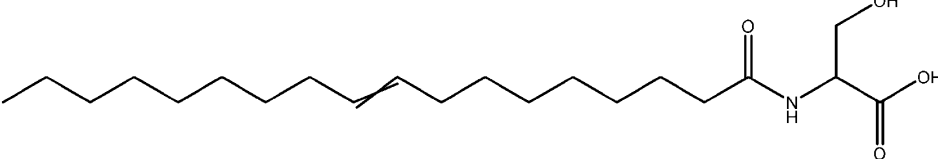
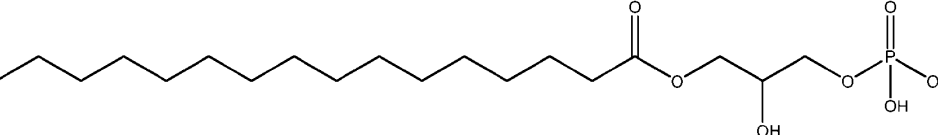
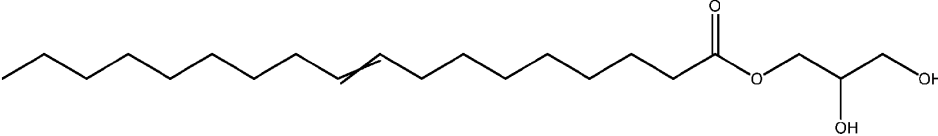
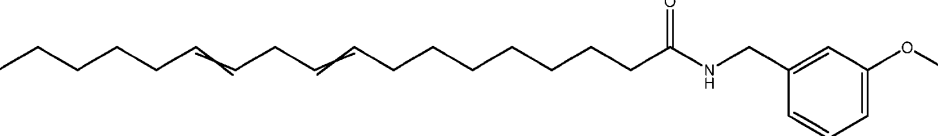
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[0038] In some embodiments, a composition is provided comprising a compound capable of being useful as agonists of GPR119. The term “GPR119 agonist,” as used herein, refers to a compound that binds to GPR119 receptor and acts as an agonist. GPR119 is a G-protein-coupled receptor primarily expressed in pancreatic β -cells and enteroendocrine cells in

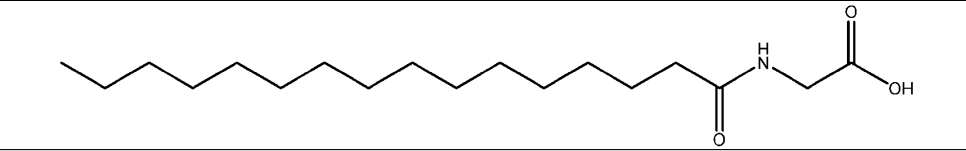
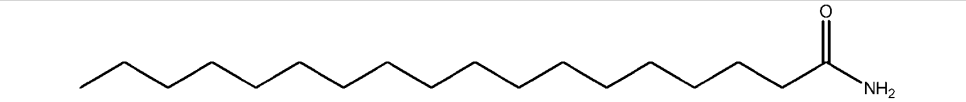
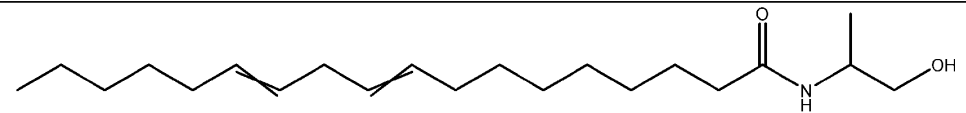
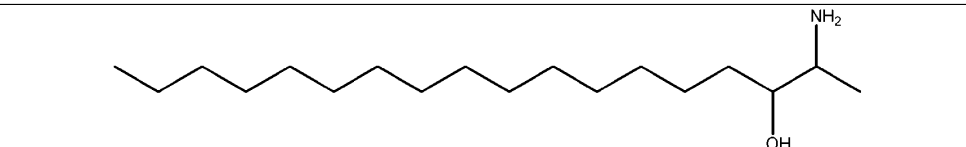
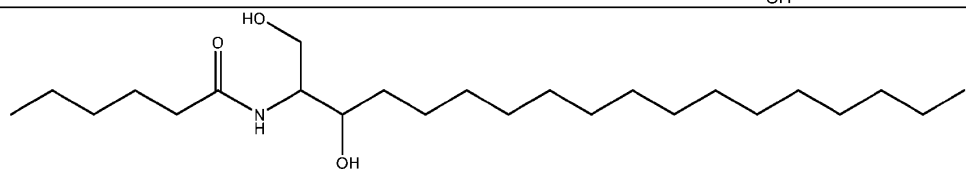
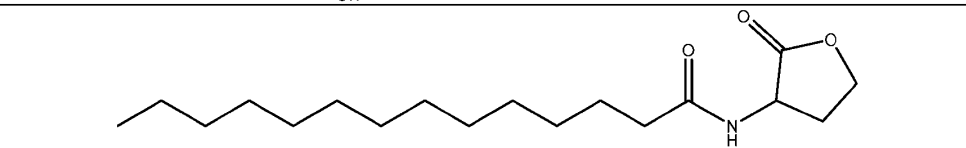
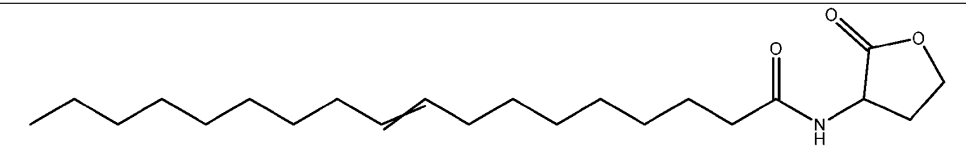
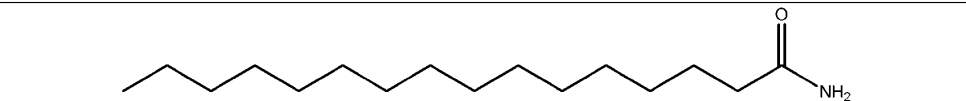
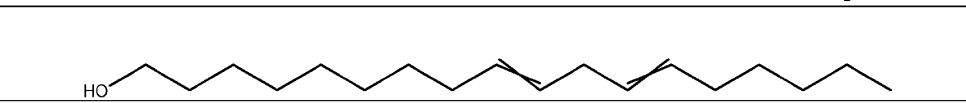
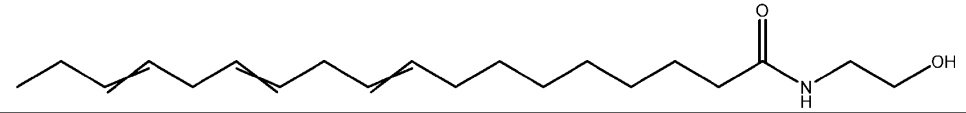
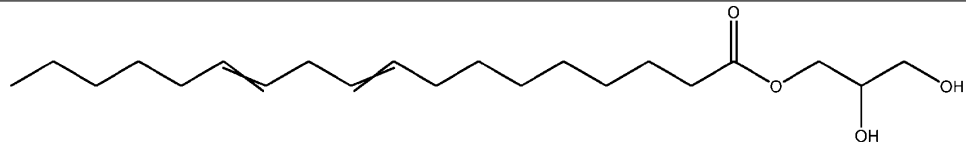
the gastrointestinal tract, including L-cells, which are responsible for the secretion of incretin hormones. The term “selective GPR119 agonist,” as used herein, refers to a GPR119 agonist having selectivity for GPR119 receptor over one or more related receptors, such as corticotrophin-releasing factor-1 (CRF-1) receptor. GPR119 is a G protein-coupled receptor (GPR119; e.g., human GPR119, GenBank® Accession No. AAP72125 and alleles thereof; e.g., mouse GPR119, GenBank® Accession No. AY288423 and alleles thereof). GPR119 stimulation as by an agonist leads to elevation of the level of intracellular cAMP, consistent with GPR119 being coupled to Gs. In the patent literature, GPR119 has been referred to as RUP3 (e.g., WO 00/31258); GPR119 has also been referred to as Glucose-Dependent Insulinotropic Receptor (GDIR). In some embodiments, the compound is a PYY secretagogue. The term “PYY secretagogue” shall mean an agent (e.g., ligand, test compound) that promotes (e.g., stimulates) secretion of PYY in a cell, e.g., an enteroendocrine cell, or that increases a level of total PYY, e.g., a level of blood or plasma total PYY, on administration to an individual such as a vertebrate or a mammal. In certain embodiments, a PYY secretagogue is a compound suitable for increasing a level of total PYY in an individual, for example a level of blood or plasma total PYY. In some embodiments, the compound is capable of modulating by PYY. As used herein, the term “condition modulated by PYY” refers to a condition modulated by PYY₁₋₃₆ or by a fragment thereof that is capable of modulating a G protein-coupled receptor. In certain embodiments, the term “condition modulated by PYY” refers to a condition modulated by PYY₃₋₃₆. In certain embodiments, the term “condition modulated by PYY” refers to a condition modulated by an NPY Y2 receptor (Y2R) agonist. In certain embodiments, the term “condition modulated by PYY” refers to a condition modulated by stimulation of Y2R. In certain embodiments, the term “condition modulated by PYY₃₋₃₆” refers to a condition modulated by a Y2R agonist. In certain embodiments, the term “condition modulated by PYY₃₋₃₆” refers to a condition modulated by stimulation of Y2R. In some embodiments, the compound may include PYY-related activity. As used herein, the term “PYY-related activity” refers to an activity for modulating a level of PYY or to an activity associated with PYY. In certain embodiments, the term “PYY-related activity” refers to an activity for increasing a level of PYY or to an activity associated with PYY. In some embodiments, the composition is an oral composition. In some embodiments, the composition comprises a compound according to Table 2. Table 2 depicts compounds according to the

disclosure, and may include isomers and stereoisomers of the compounds portrayed. For example, compounds of Table 2 may simultaneously depict both *cis* and *trans* isomers by depicting a crossed double bond: . Such depiction may represent the compound in a mixture of both the *cis* and *trans* isomers, and may also represent either of the *cis* and *trans* isomers individually.

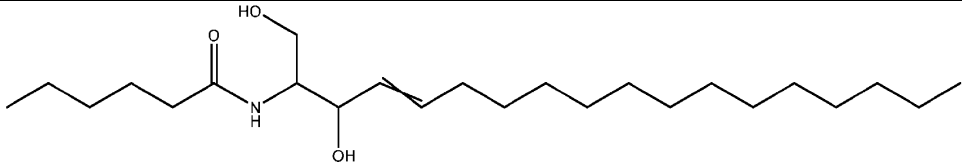
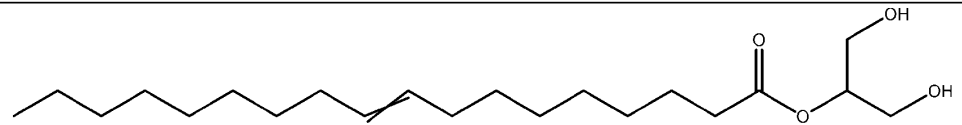
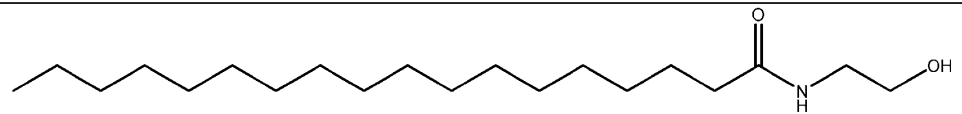
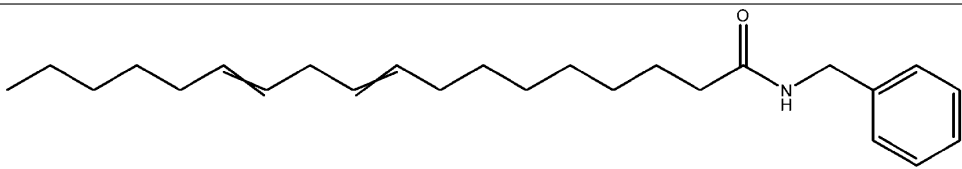
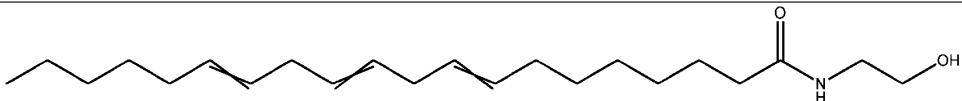
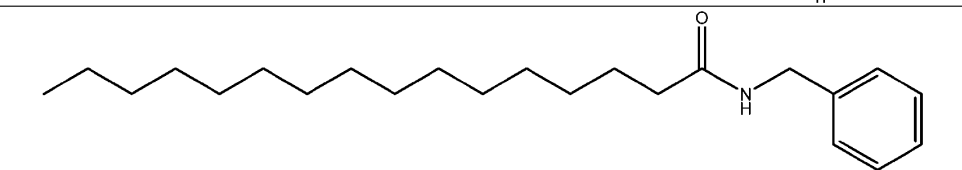
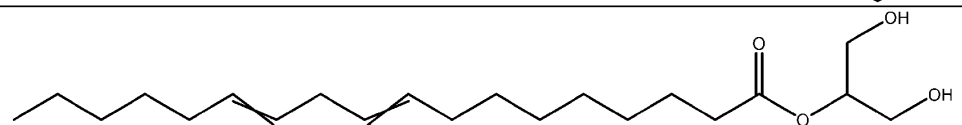
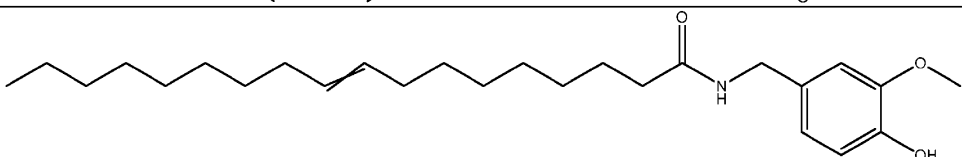
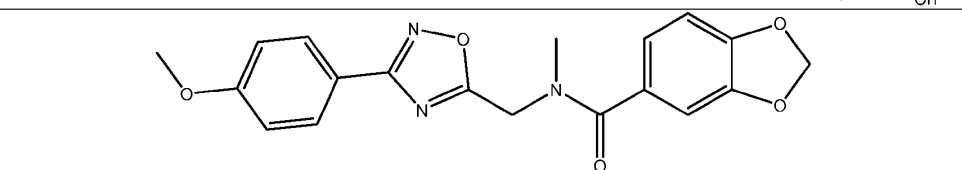
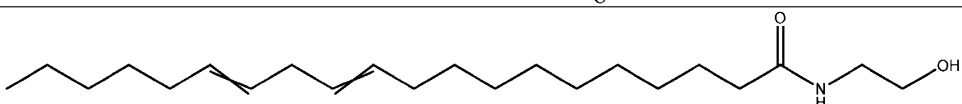
Table 2

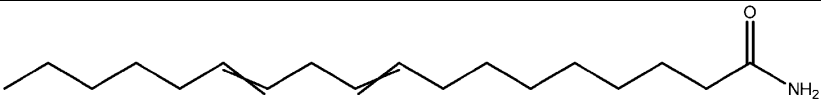
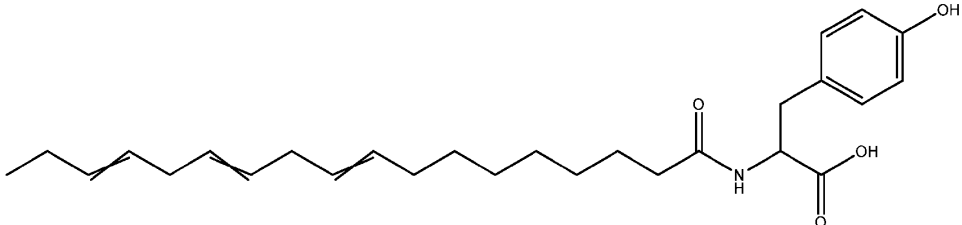
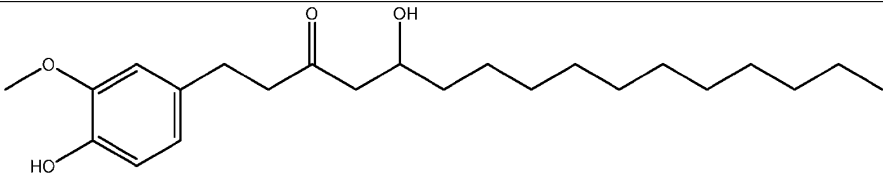
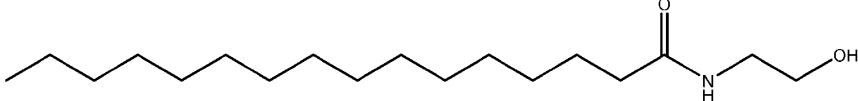
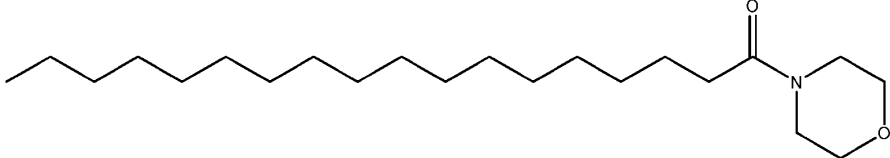
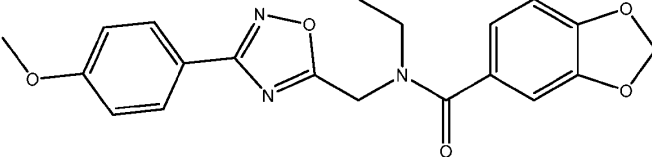
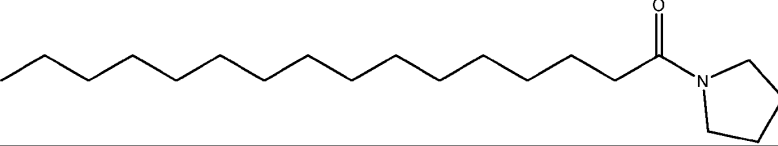
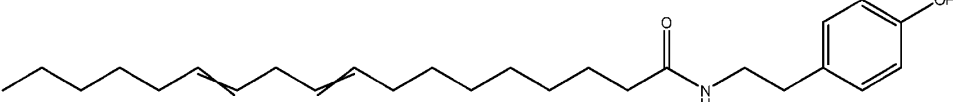
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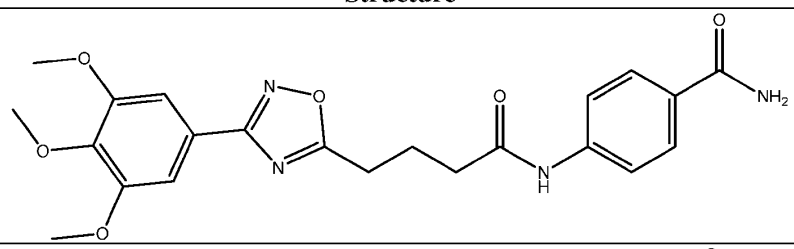
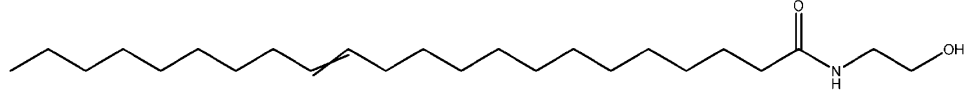
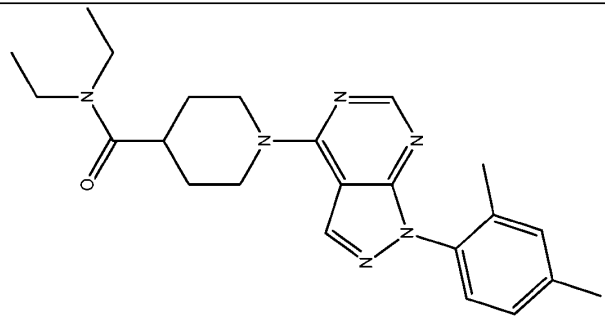
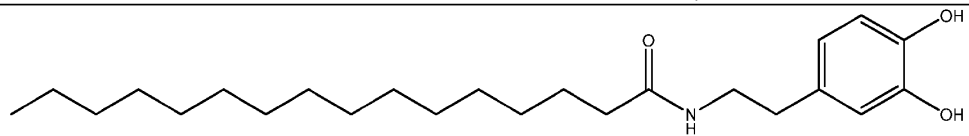
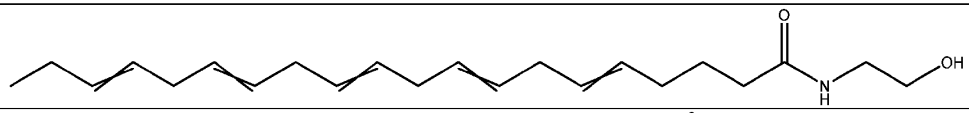
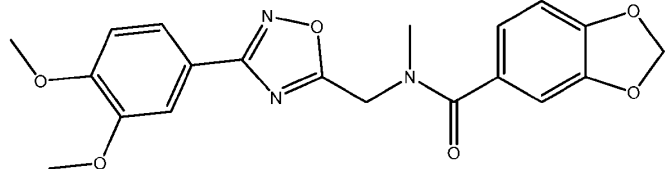
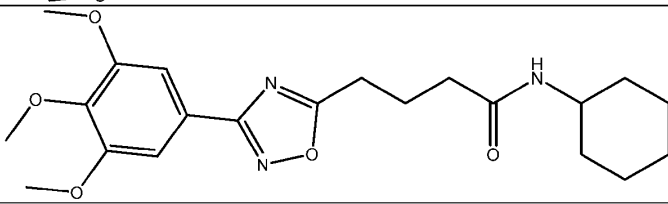
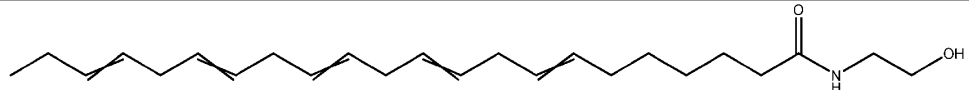
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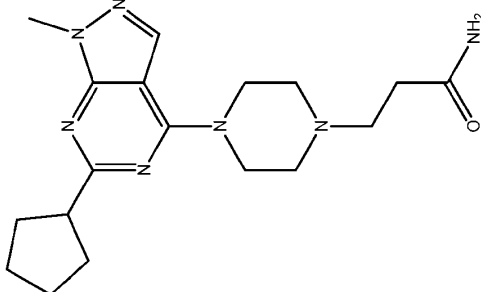
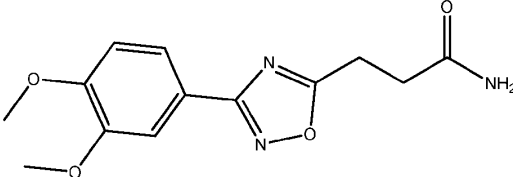
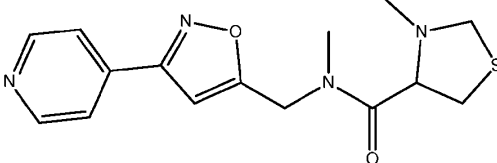
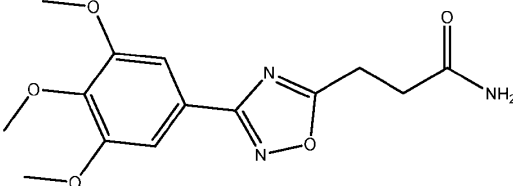
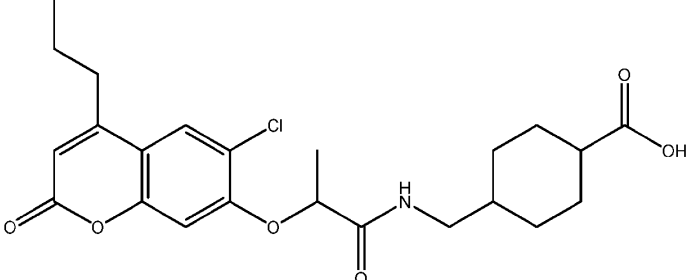
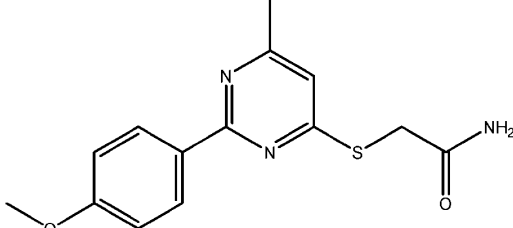
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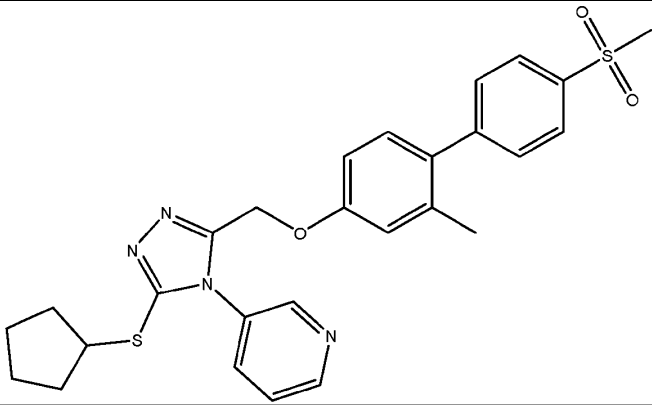
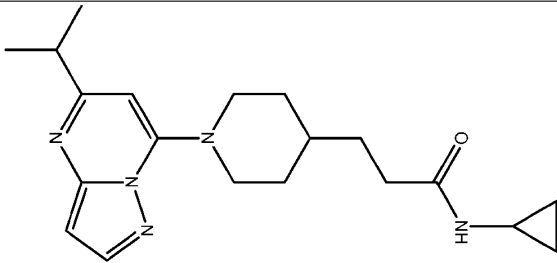
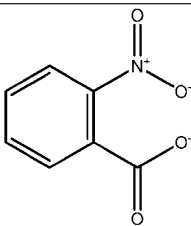
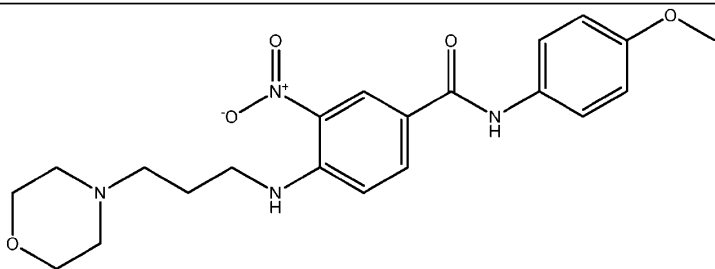
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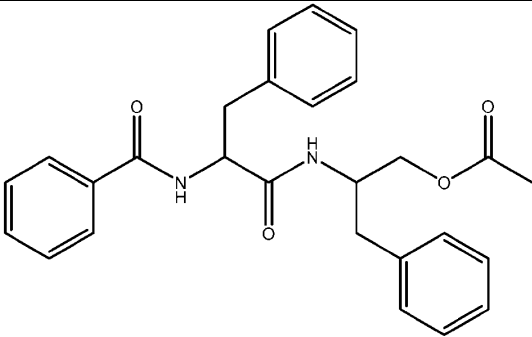
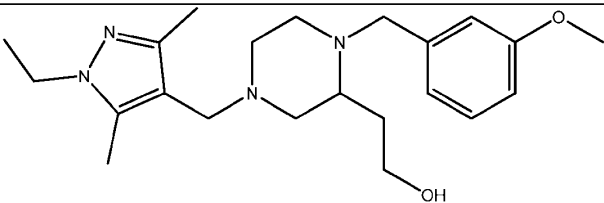
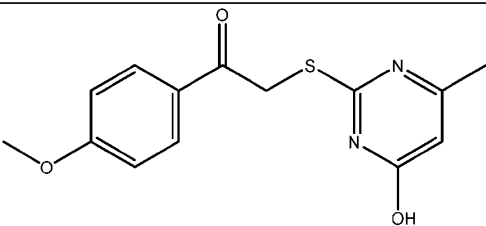
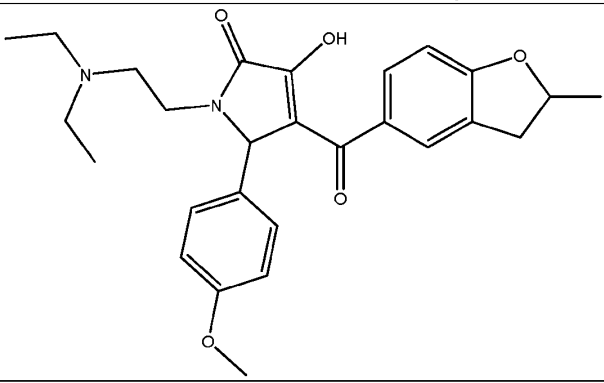
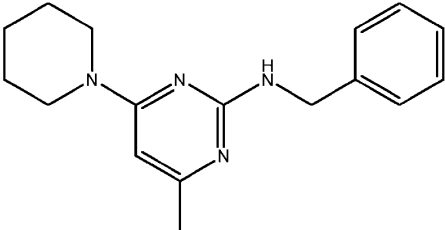
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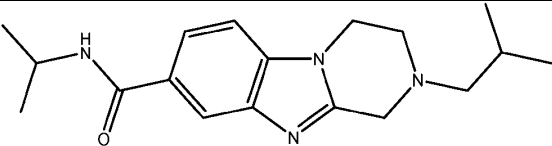
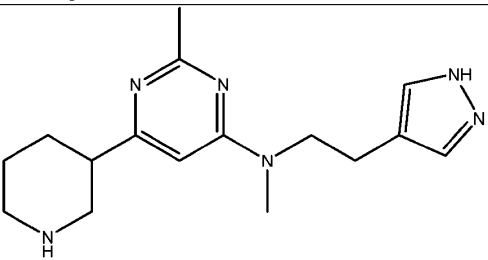
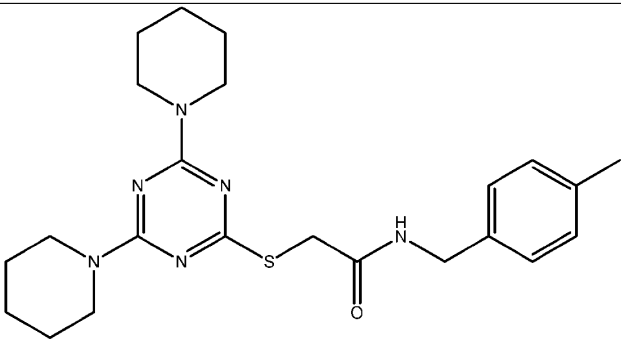
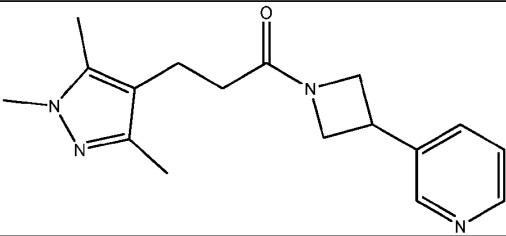
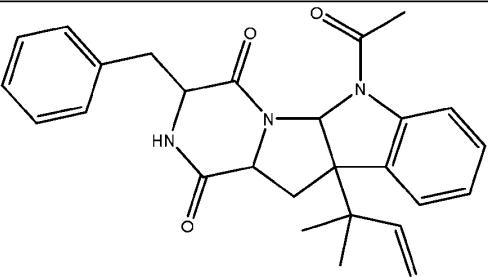
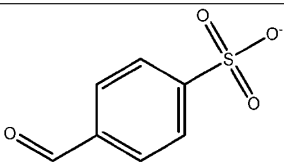
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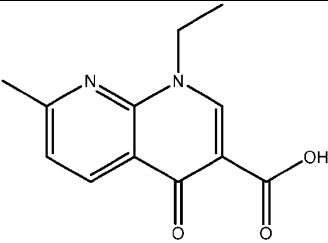
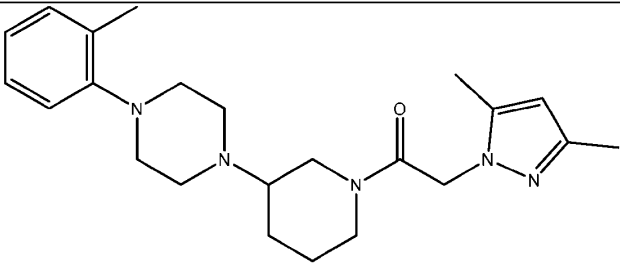
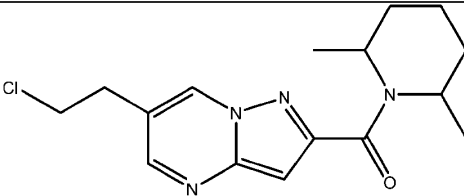
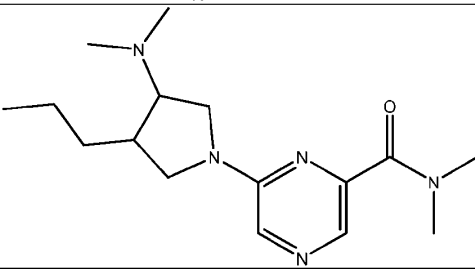
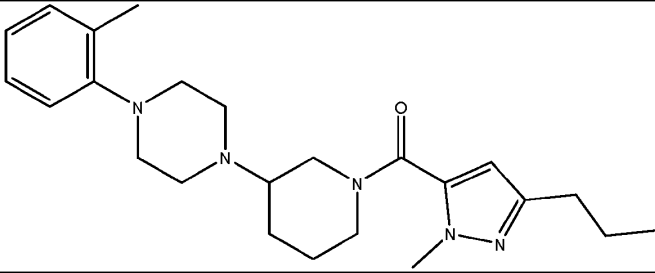
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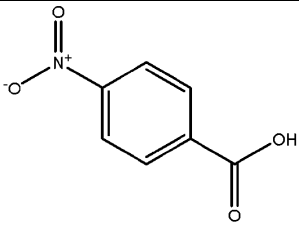
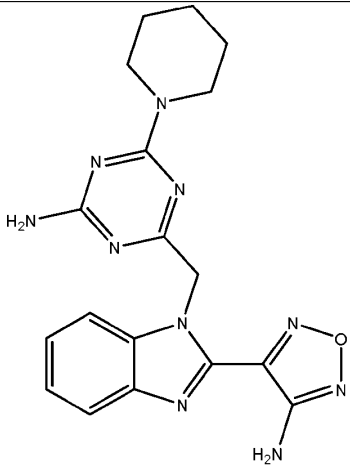
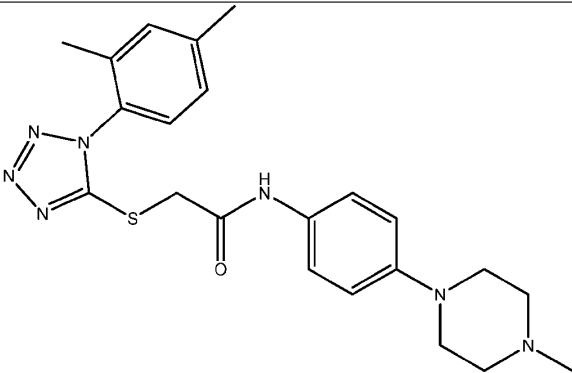
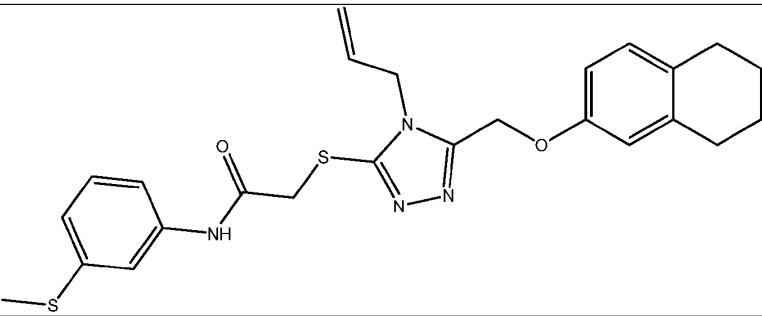
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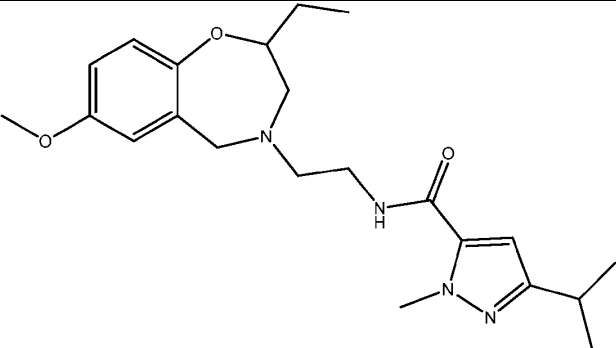
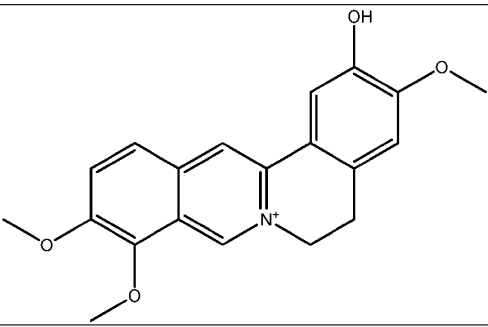
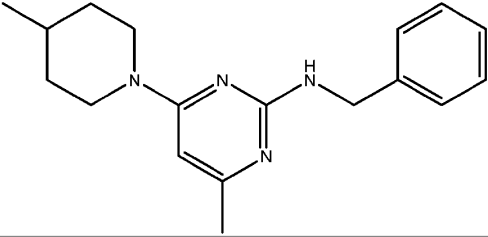
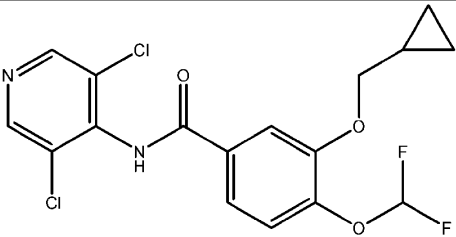
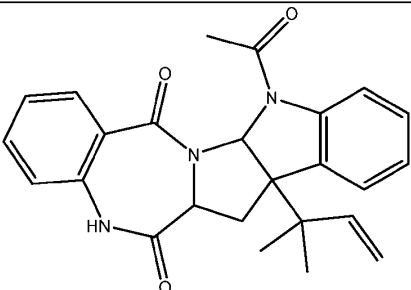
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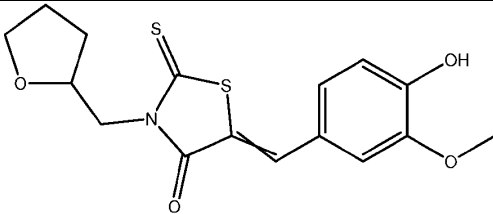
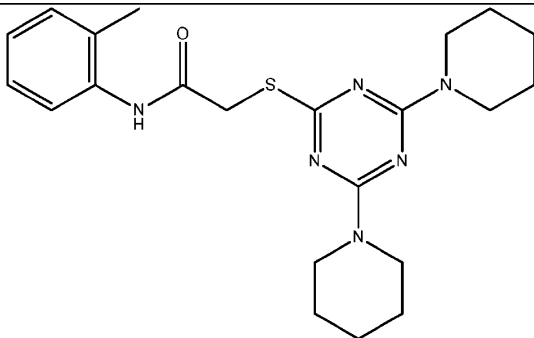
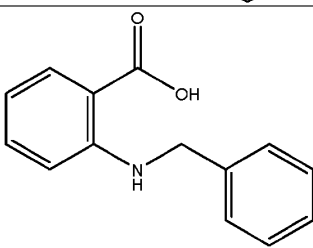
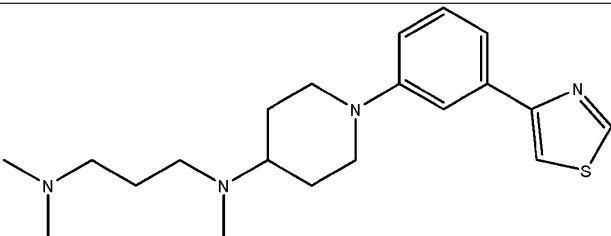
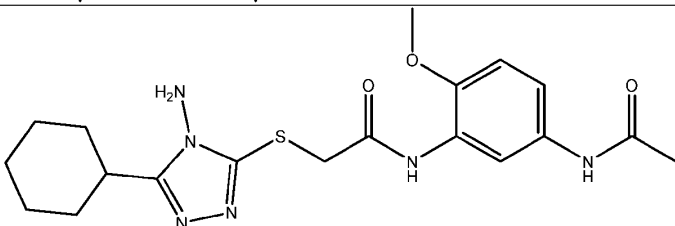
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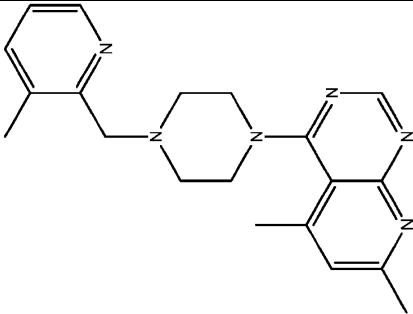
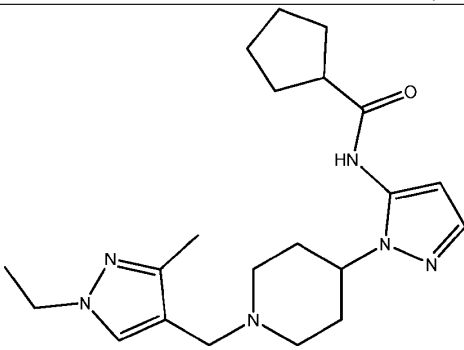
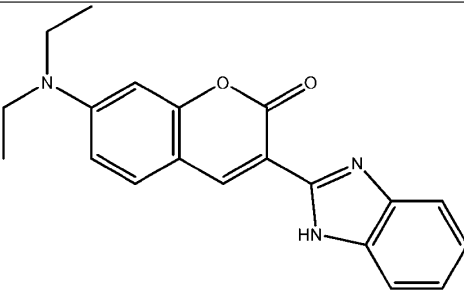
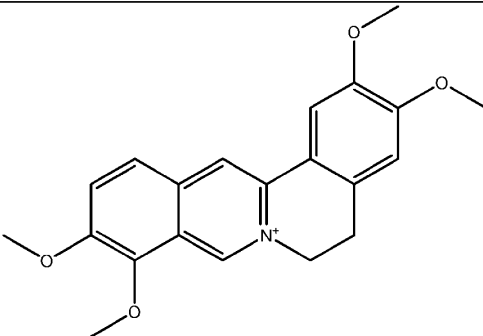
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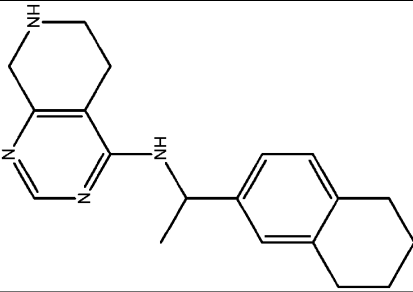
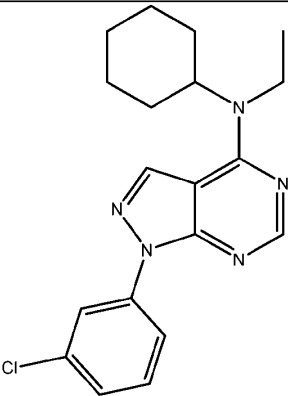
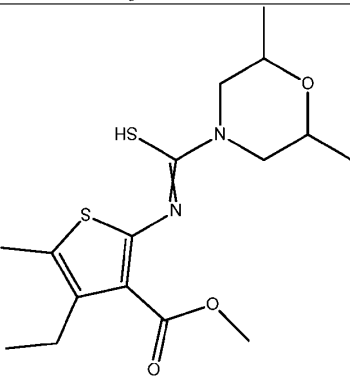
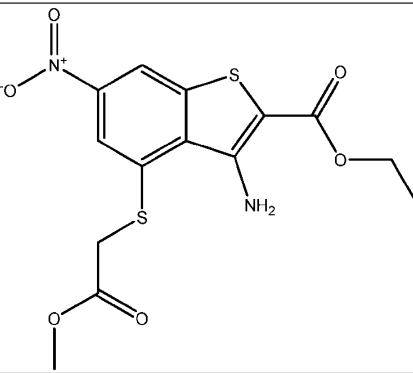
ID	Structure
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587	 <chem>CC1=CC=C(C=C1)N2CCN(CC2)N3CCCCN3C(=O)Cn4cc(C)c(C)n4</chem>
588	 <chem>ClCCc1nc2nc3c(nc12)C(=O)N3C4CCCC(C)C4</chem>
589	 <chem>CCN(C)C(=O)c1nc2c(nc1)N(C2)C3CCCC(C)N3</chem>
590	 <chem>CC1=CC=C(C=C1)N2CCN(CC2)N3CCCCN3C(=O)C4=CC=C(C4)N(C)C5CCCC5</chem>

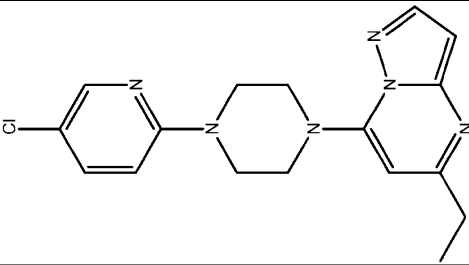
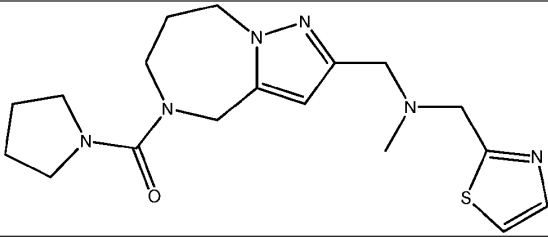
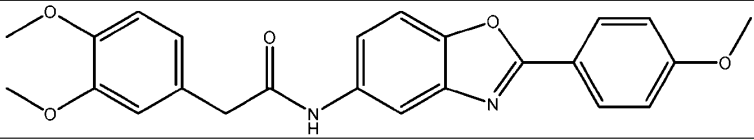
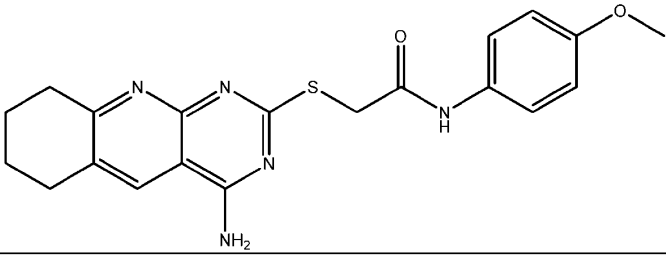
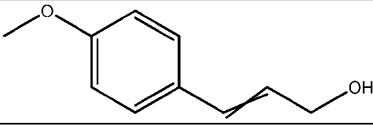
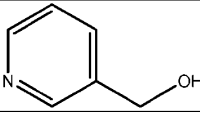
ID	Structure
591	 Chemical structure of 4-nitrobenzoic acid, showing a benzene ring with a carboxylic acid group (-COOH) and a nitro group (-NO₂) in the para position.
592	 Chemical structure of a complex heterocyclic compound. It features a central benzimidazole core. The benzimidazole ring is substituted with a 4-aminophenyl group (H₂N) and a 1,2,4-oxadiazol-5-yl group (H₂N). The benzimidazole ring is also substituted with a piperidine ring.
593	 Chemical structure of a complex heterocyclic compound. It features a central benzimidazole core. The benzimidazole ring is substituted with a 4-methylphenyl group (CH₃) and a 1,2,4-oxadiazol-5-yl group (H₂N). The benzimidazole ring is also substituted with a piperidine ring.
594	 Chemical structure of a complex heterocyclic compound. It features a central benzimidazole core. The benzimidazole ring is substituted with a 4-methylphenyl group (CH₃) and a 1,2,4-oxadiazol-5-yl group (H₂N). The benzimidazole ring is also substituted with a piperidine ring.

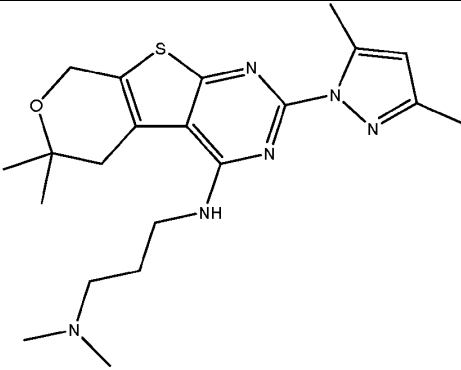
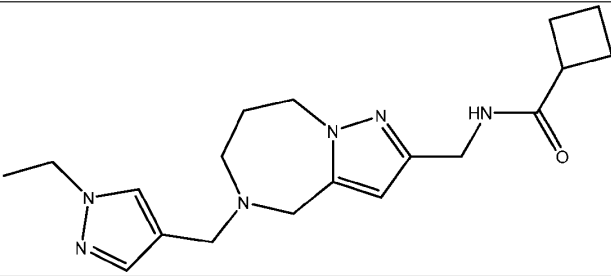
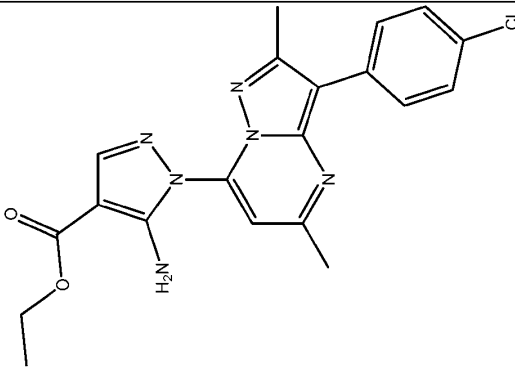
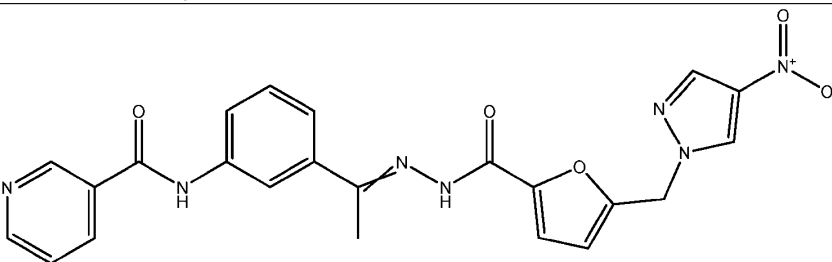
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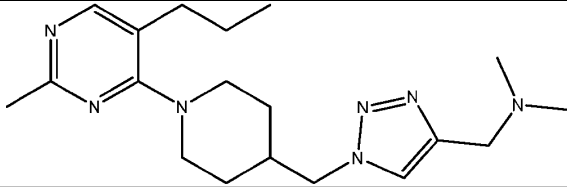
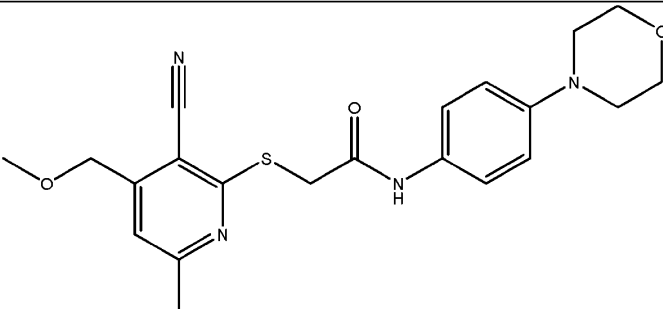
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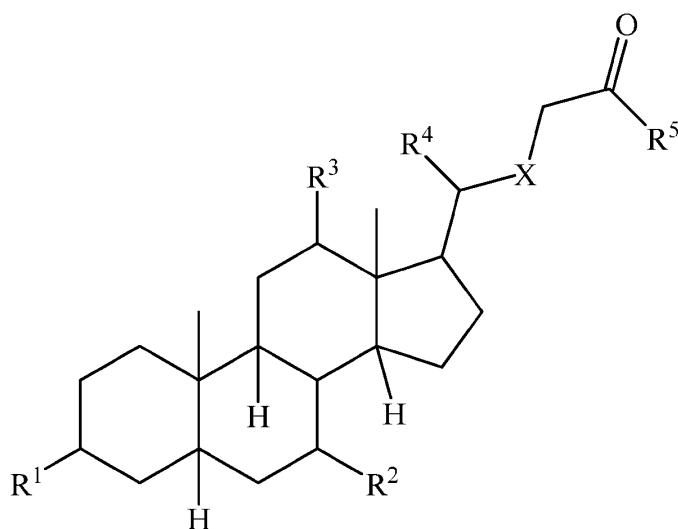
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[0039] In some embodiments, a composition is provided comprising one or more compounds capable of being useful as agonists of TGR5. TGR5, also known as G protein-coupled bile acid receptor 1 (GPBAR1) and “Takeda G protein-coupled receptor 5”, is a G protein-coupled receptor believed to play a role in glucose metabolism through its activation by bile acids. In some embodiments, the one or more compounds is a TGR5 ligand. A “TGR5 ligand” refers to a composition (e.g., compound, amino acid, peptide, polypeptide, antibody, nucleic acid, polynucleotide) which selectively binds to TGR5. A TGR5 ligand may be a “natural product TGR5 agonist”. The term “natural product TGR5 agonist” refers to physiological ligands of TGR5 which bind to and activate TGR5. The term encompasses TGR5 ligands such as bile acids (e.g., CA, LCA, DCA, CDCA, and UDCA) as well as derivatives of bile acids which are naturally synthesized by a host organism. In some embodiments, the composition is an oral composition.

[0040] In some embodiments, a compound of the disclosure is represented by a compound of Formula (III):



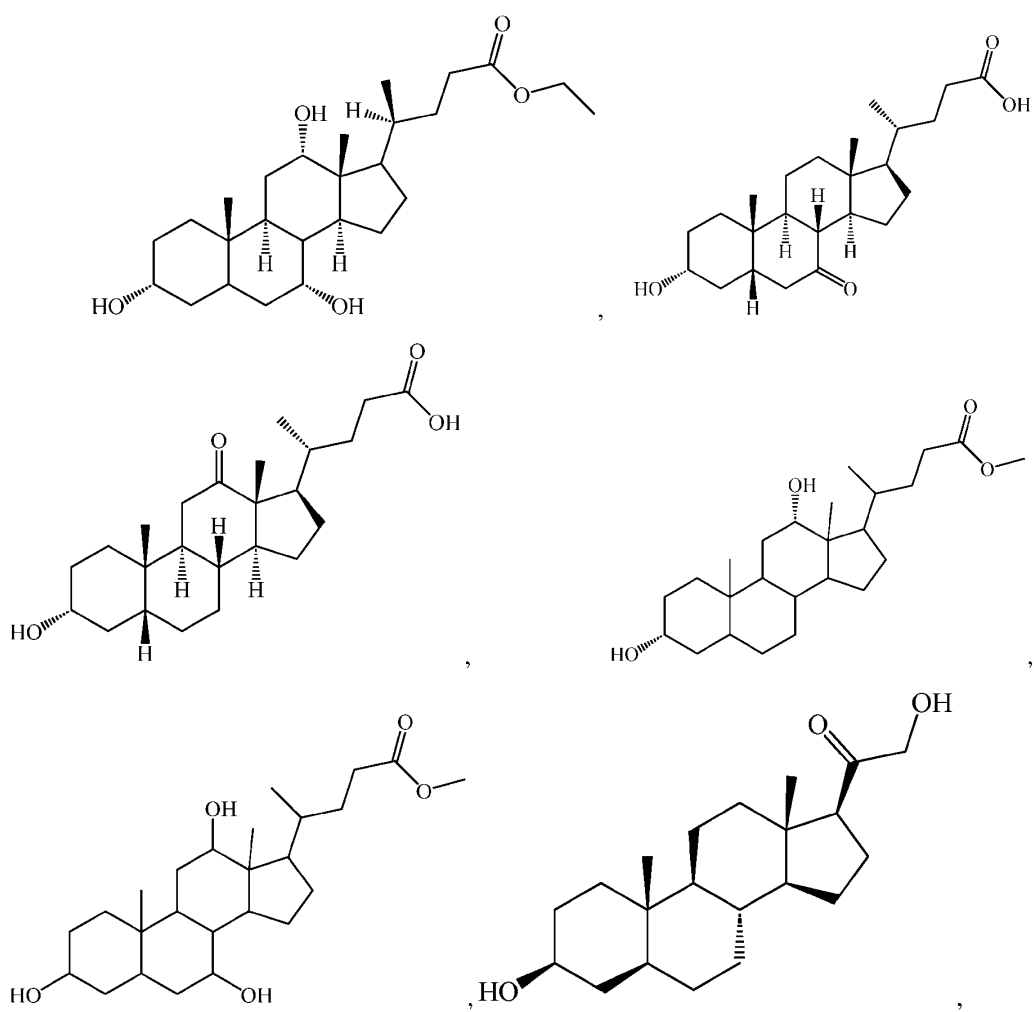
(III).

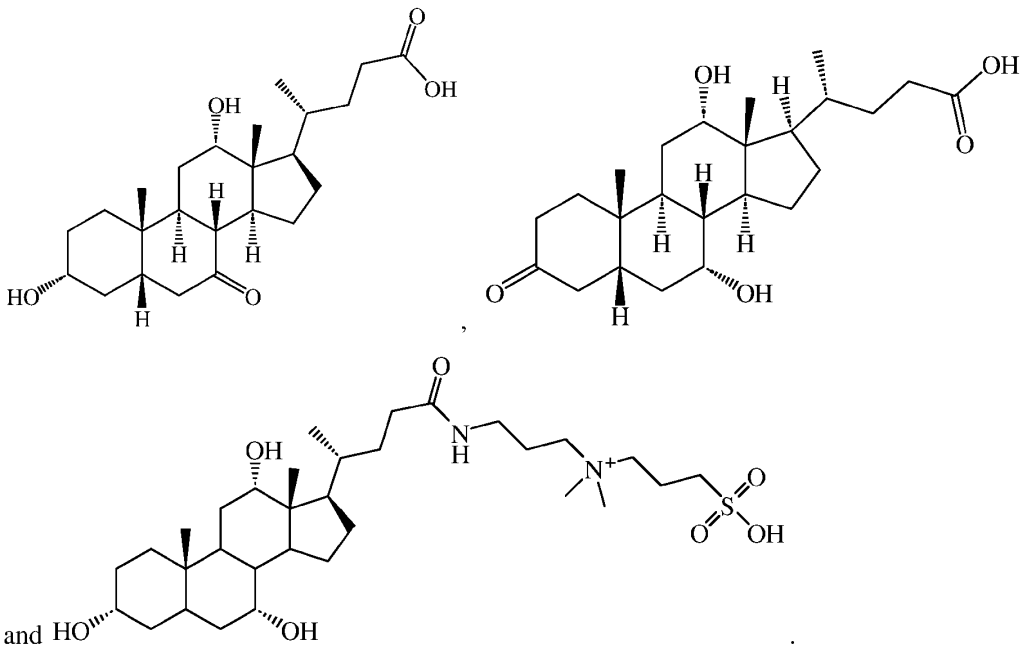
[0041] In some embodiments, the compound of Formula (III) is a pharmaceutically acceptable salt as described herein.

[0042] In some embodiments of the compounds of Formula (III), R¹, R², R³, R⁴, and R⁵ may each be independently selected from hydrogen, deuterium, hydroxyl, keto, halogen, optionally substituted amino, optionally substituted C-amido, optionally substituted ester, optionally substituted C₁ to C₆ alkyl, optionally substituted C₁ to C₆ alkoxy, optionally substituted C₃ to C₈ cycloalkyl, optionally substituted C₆ to C₁₀ aryl, optionally substituted C₃ to C₈ heterocyclyl, and optionally substituted C₃ to C₈ heterocyclylalkyl. In some embodiments, R¹ is hydroxyl. In some embodiments, R² is hydroxyl or keto. In some embodiments, R³ is hydroxyl or keto. In some embodiments, R⁴ is hydrogen, keto, or optionally substituted C₁ to C₆ alkyl. In some embodiments, R⁵ is hydroxyl, optionally substituted C₁ to C₆ alkyl, and optionally substituted C₃ to C₈ heterocyclyl.

[0043] In some embodiments of the compounds of Formula (III), X is a bond, –CH₂–, –CH₂CH₂–, and –NH–. In some embodiments, X is absent. In some embodiments, X is a bond or –CH₂–.

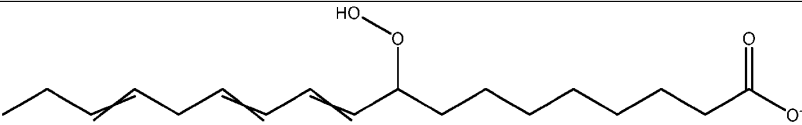
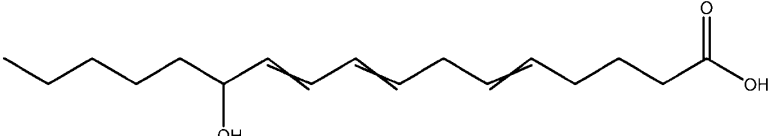
[0044] In some embodiments, a compound of Formula III may be selected from the following:

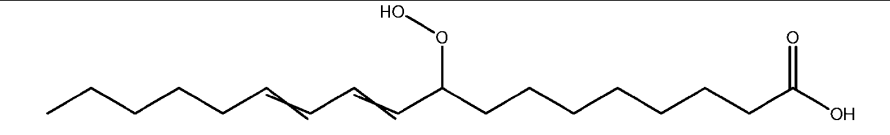
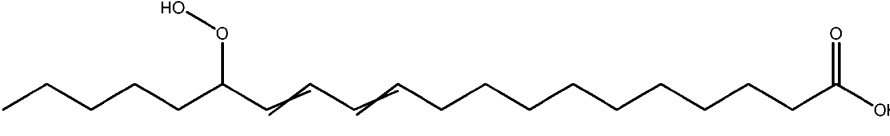
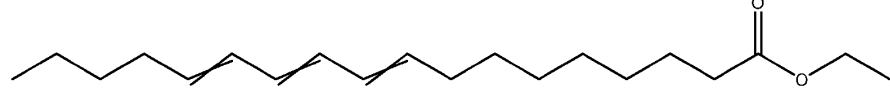
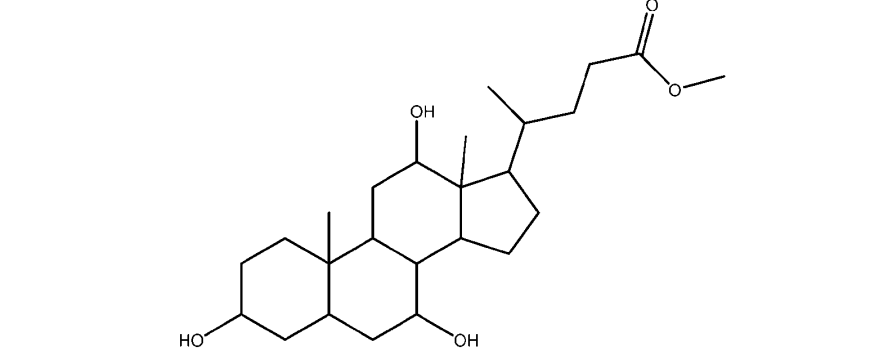
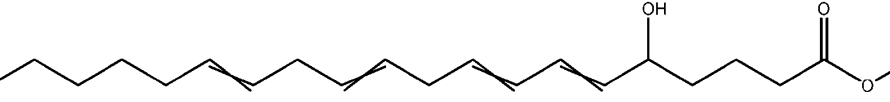
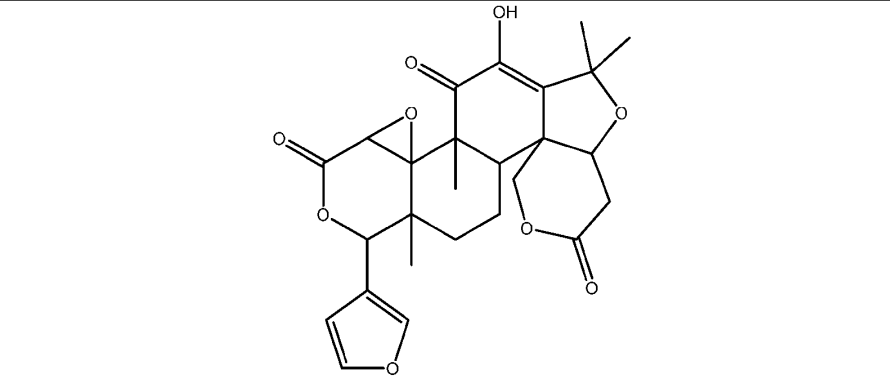


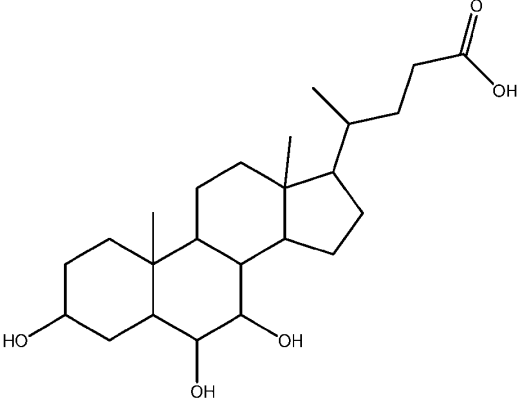
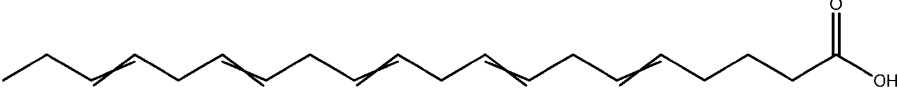
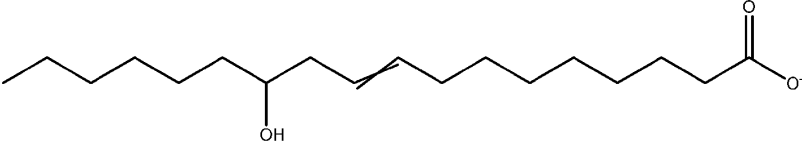
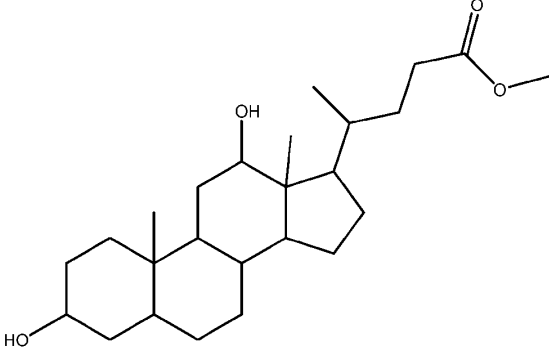
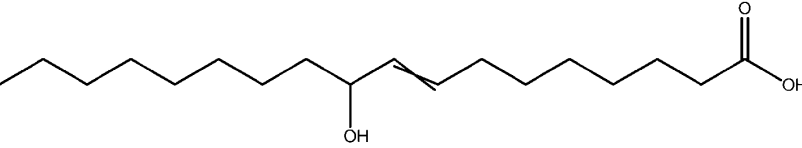


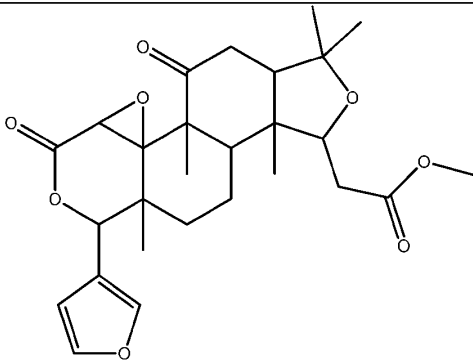
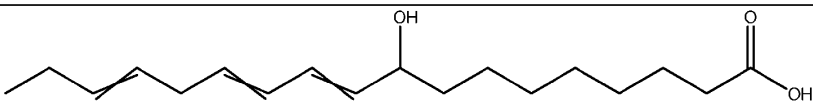
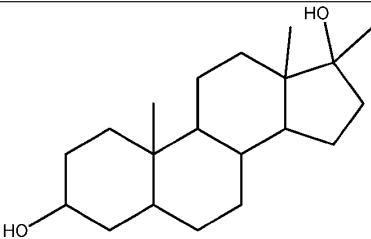
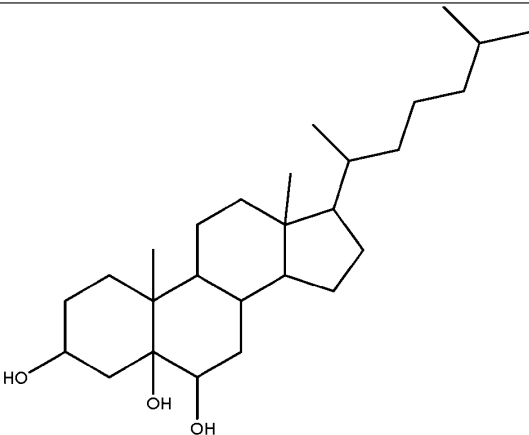
[0045] In some embodiments, a compound for Formula (III) is depicted in Table 3. In some embodiments, the composition comprises a compound according to Table 3. Table 3 depicts compounds according to the disclosure, and may include isomers and stereoisomers of the compounds portrayed. For example, compounds of Table 3 may simultaneously depict both *cis* and *trans* isomers by depicting a crossed double bond: . Such depiction may represent the compound in a mixture of both the *cis* and *trans* isomers, and may also represent either of the *cis* and *trans* isomers individually.

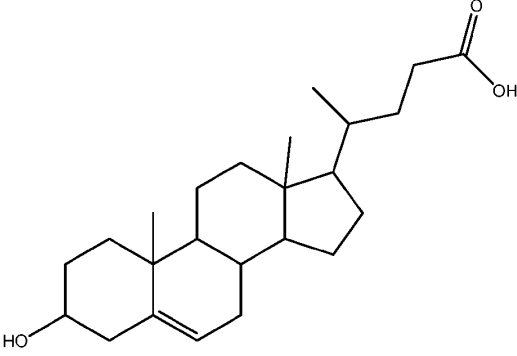
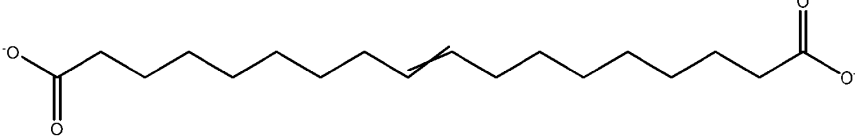
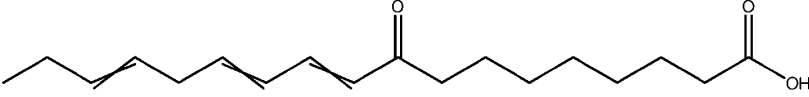
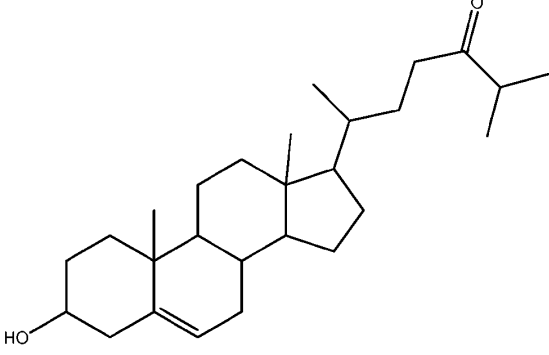
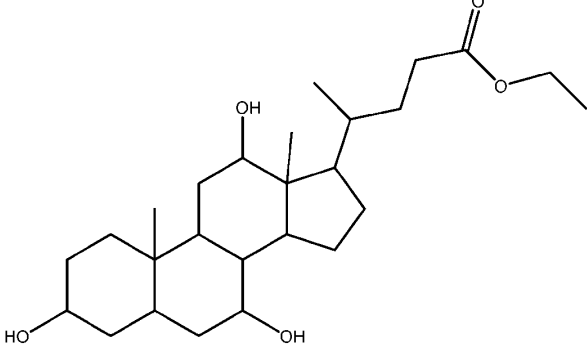
Table 3

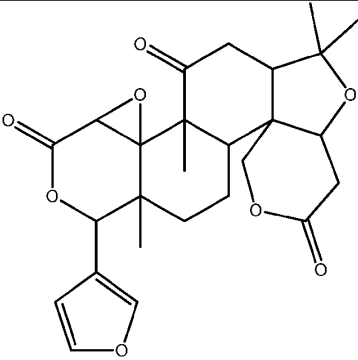
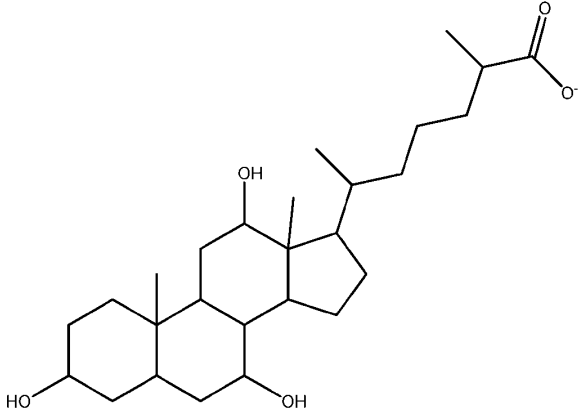
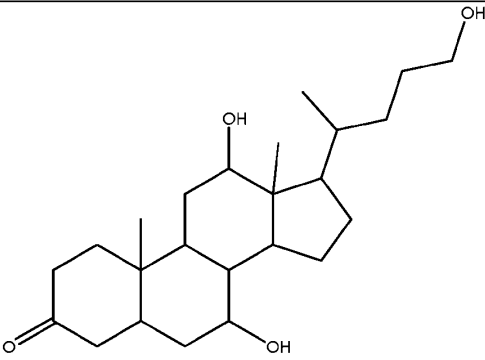
ID	Structure
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ID	Structure
702	 <chem>CCCCC/C=C/C(=O)OCCCCCCCC(=O)O</chem>
703	 <chem>CCCCC(=O)O/C=C/C(=O)OCCCCCCCC(=O)O</chem>
704	 <chem>CCCCC/C=C/C(=O)OCCCCCCCC(=O)OCC</chem>
705	 <chem>CCCC(C)(C)C(=O)O[C@H]1[C@@H](O)[C@H]2[C@@H](O)[C@H]3[C@@H](O)[C@H]1[C@@H]2[C@@H]3</chem>
706	 <chem>CCCCC/C=C/C(=O)OCCCCCCCC(=O)OCC</chem>
707	 <chem>CCCC(C)(C)C(=O)O[C@H]1[C@@H](O)[C@H]2[C@@H](O)[C@H]3[C@@H](O)[C@H]1[C@@H]2[C@@H]3</chem>

ID	Structure
708	 Chemical structure of a steroid derivative. The steroid nucleus is substituted with hydroxyl groups at C3, C14, and C15. A side chain at C17 consists of a 3-methylbutyl group attached to a carboxylic acid group.
709	 Chemical structure of a long-chain polyunsaturated fatty acid. It features a carboxylic acid group at one end and a long chain with five conjugated double bonds.
710	 Chemical structure of a long-chain monounsaturated fatty acid. It features a carboxylate group at one end and a long chain with one double bond and a hydroxyl group.
711	 Chemical structure of a steroid derivative. The steroid nucleus is substituted with hydroxyl groups at C3 and C14. A side chain at C17 consists of a 3-methylbutyl group attached to a methyl ester group.
712	 Chemical structure of a long-chain monounsaturated fatty acid. It features a carboxylic acid group at one end and a long chain with one double bond and a hydroxyl group.

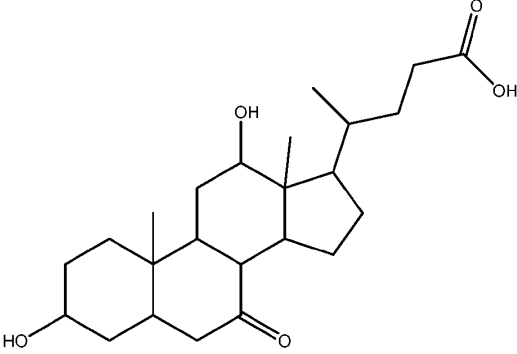
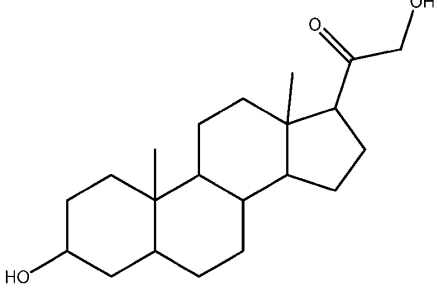
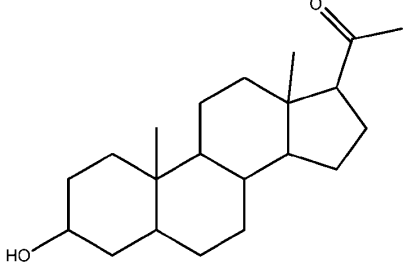
ID	Structure
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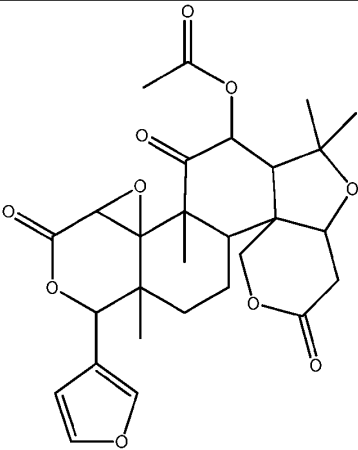
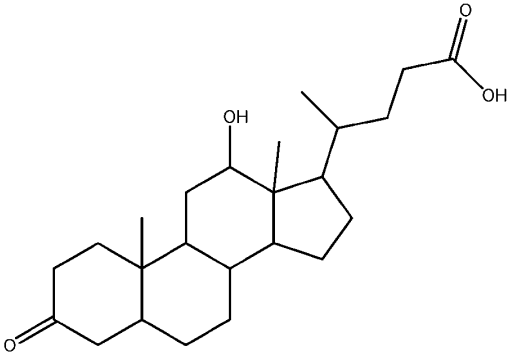
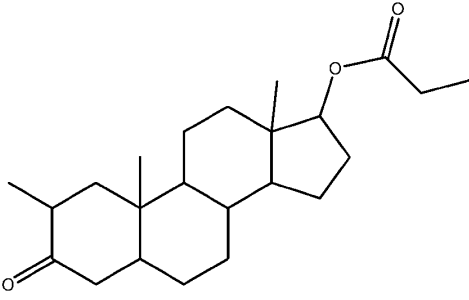
ID	Structure
717	 <chem>CC(C)CC(=O)O[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
718	 <chem>[O-]C(=O)CCCCC/C=C\CCCCCCCCCCCC(=O)[O-]</chem>
719	 <chem>CCCC/C=C\CC/C=C\CC/C=C\CC(=O)CCCCCCCC(=O)O</chem>
720	 <chem>CC(C)CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
721	 <chem>CCOC(=O)CC[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C[C@H]5[C@@H](C)CC(O)CC[C@@]54C</chem>

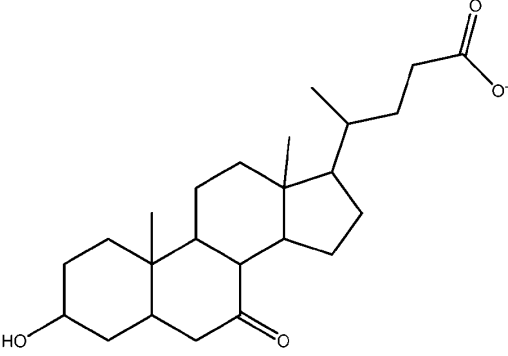
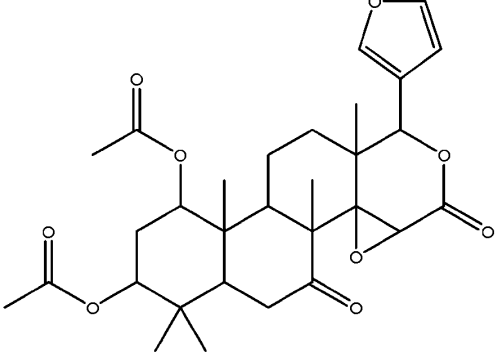
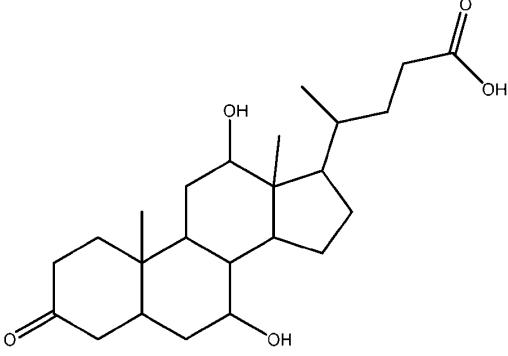
ID	Structure
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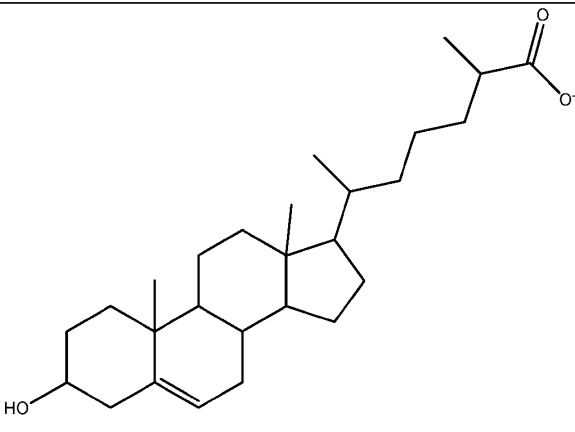
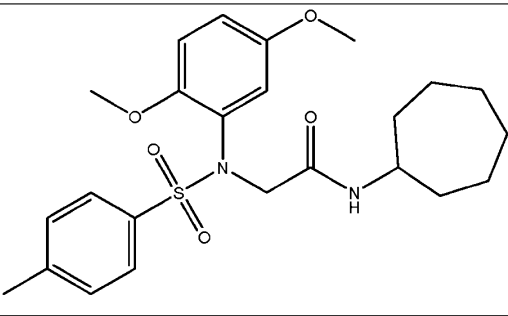
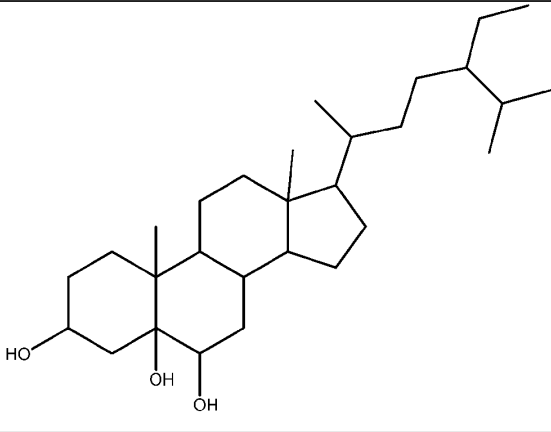
CC(C)CC(=O)O[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)CCC(C)CCCC(C)C1CCC2C3C(C1CC2)C(=O)C=C(C3C)C

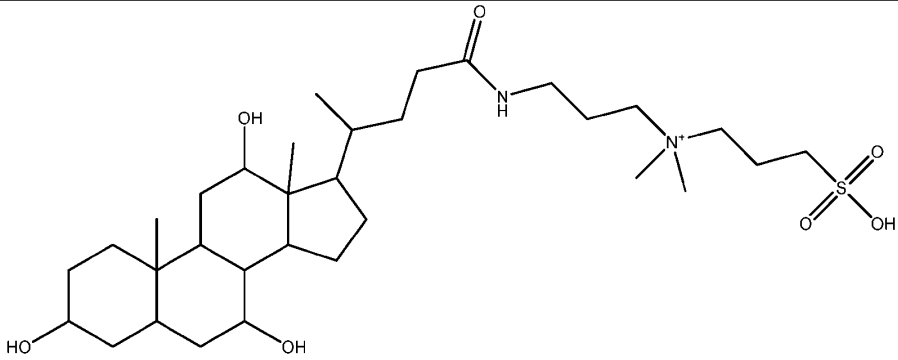
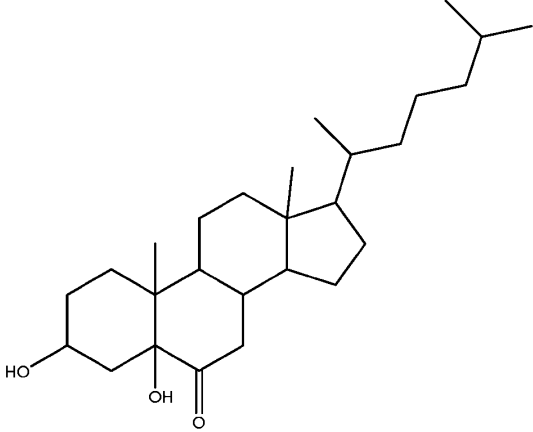
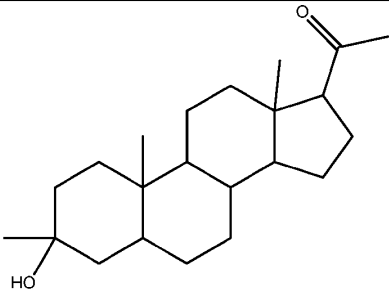
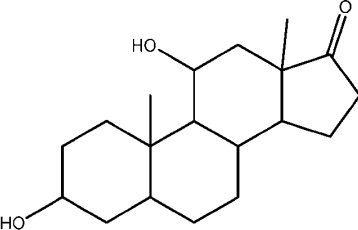
The chemical structure shows a complex polycyclic molecule, likely a steroid derivative. It features a fused ring system with a ketone group, an ester group, and a furan ring substituent.

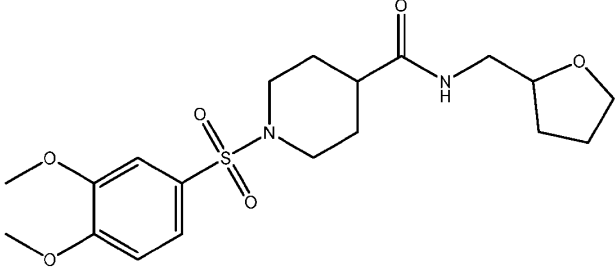
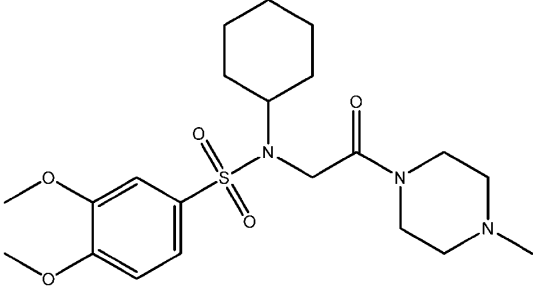
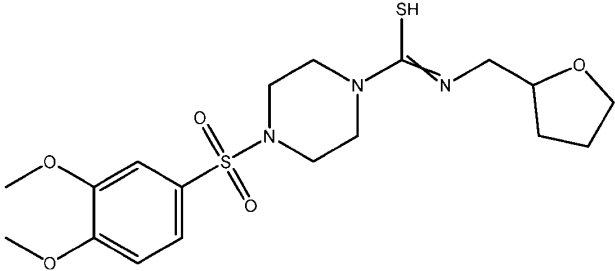
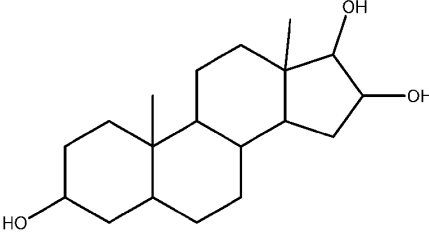
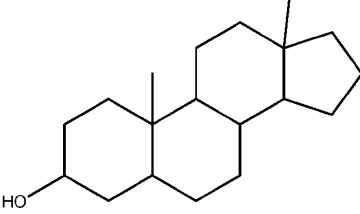
ID	Structure
728	 <chem>CC(CCCC(=O)O)C1CCC2C(C1CC3=C(C(=O)O)CCC4=C3C(=C(C=C4)C)C)C</chem>
729	 <chem>CCOC(=O)C1CCC2C(C1CC3=C(C(=O)O)CCC4=C3C(=C(C=C4)C)C)C</chem>
730	 <chem>CC(=O)C1CCC2C(C1CC3=C(C(=O)O)CCC4=C3C(=C(C=C4)C)C)C</chem>

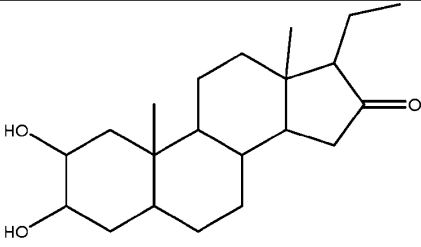
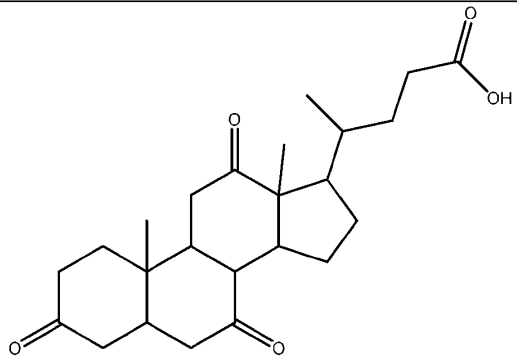
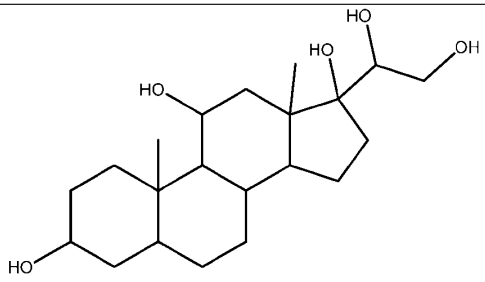
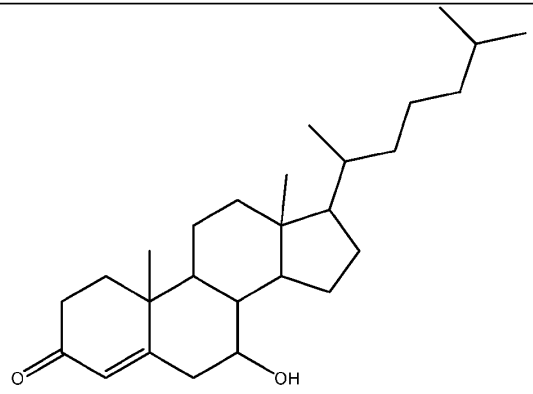
ID	Structure
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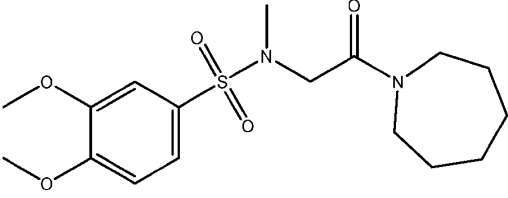
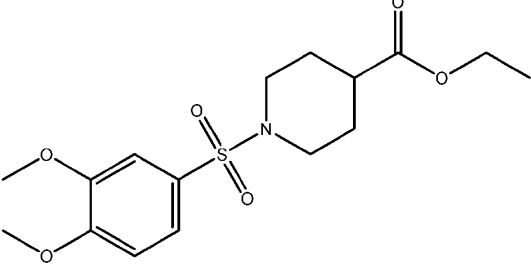
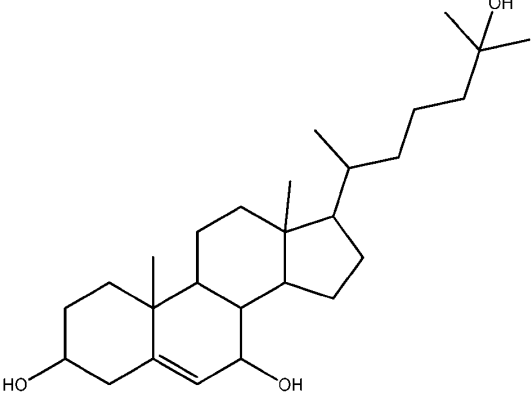
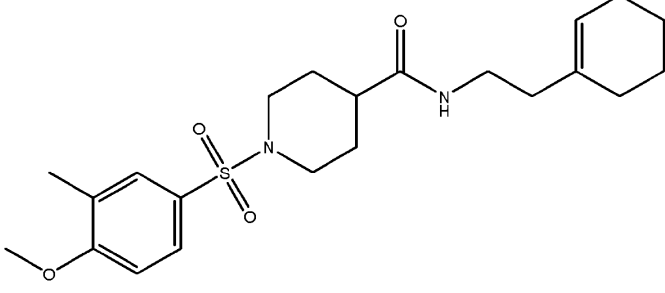
ID	Structure
734	 <chem>CC(C)CC(=O)O[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>
735	 <chem>CC(=O)OC[C@]12CC[C@@H]3[C@H]([C@@H]1CC[C@@H]2C(=O)OC)C[C@H]4[C@@]3(CC[C@@H](C4)OC(=O)c5ccoc5)C</chem>
736	 <chem>CC(C)CC(=O)O[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O)C)C</chem>

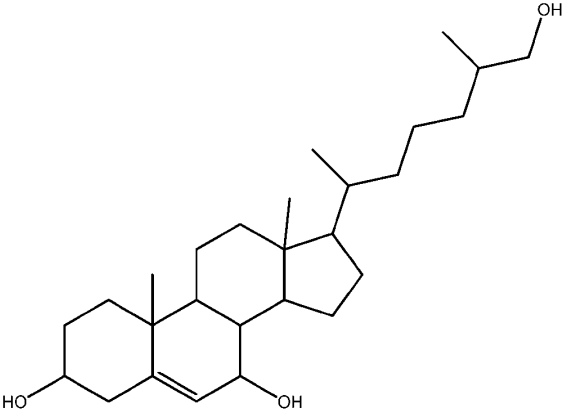
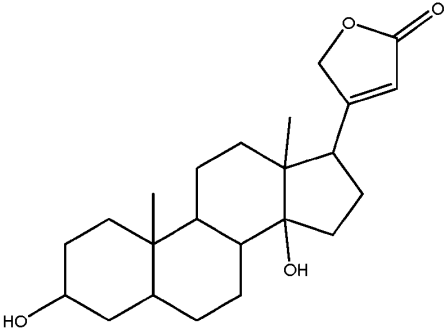
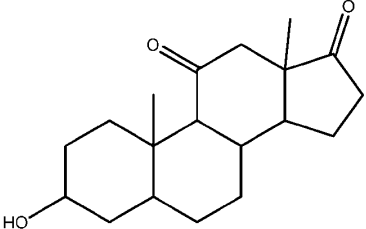
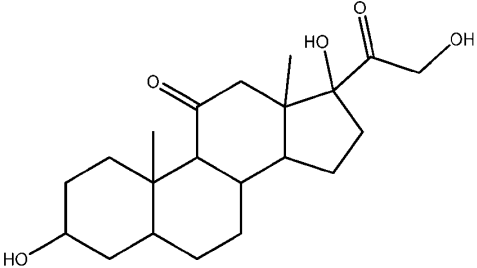
ID	Structure
737	 <chem>CC(C)CCCC(=O)[O-]C1CCC2C(C1CC3=C(C(=C(C=C3)O)CCC4C(C)CC5C(C4)CC6C(C)CC(C5)CC6)C)C</chem>
738	 <chem>COc1cc(OC)cc(NC(=O)CCNS(=O)(=O)c2ccc(C)cc2)c1</chem>
739	 <chem>CC(C)CCCC1CCC2C(C1CC3=C(C(=C(C=C3)O)CCC4C(C)CC5C(C4)CC6C(C)CC(C5)CC6)C)C</chem>

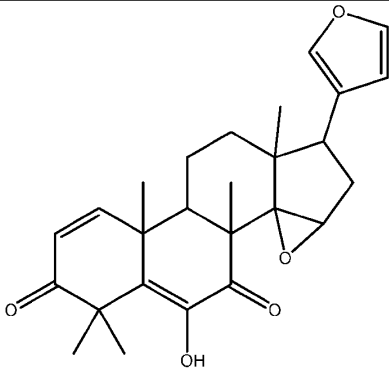
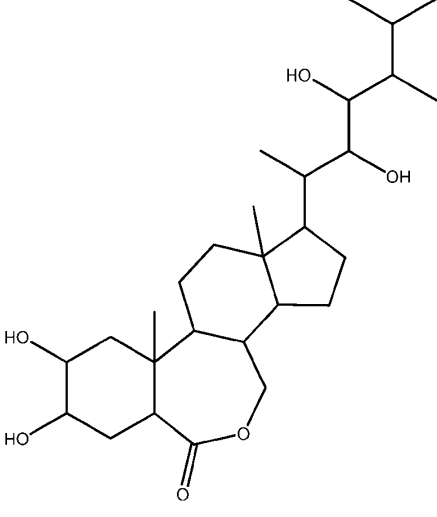
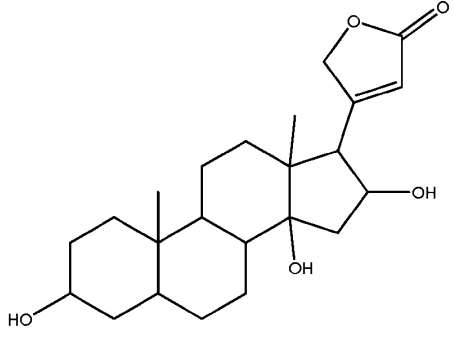
ID	Structure
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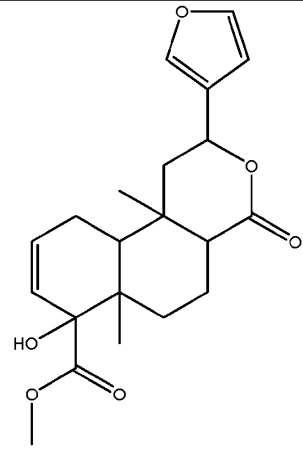
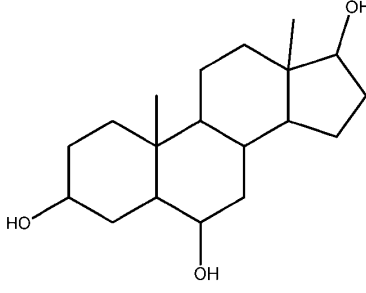
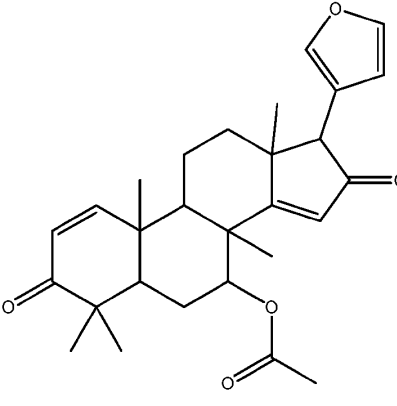
ID	Structure
744	 <chem>COc1ccc(OC)c(S(=O)(=O)N2CCCCC2C(=O)NCC3OCCO3)c1</chem>
745	 <chem>COc1ccc(OC)c(S(=O)(=O)N(C2CCCCC2)CC(=O)N3CCN(C)CC3)c1</chem>
746	 <chem>COc1ccc(OC)c(S(=O)(=O)N2CCCCC2N/C(S)=N/CC3OCCO3)c1</chem>
747	 <chem>CC12CCC3C(C1CC4CCCC(C4)O)CCC5C3(C)CC(O)C5O</chem>
748	 <chem>CC12CCC3C(C1CC4CCCC(C4)O)CCC5C3(C)CC(C)C5</chem>

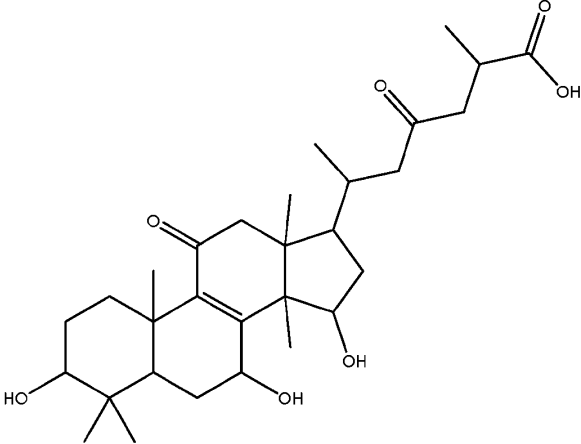
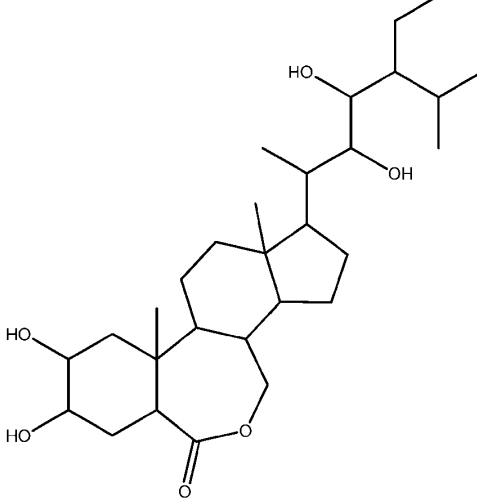
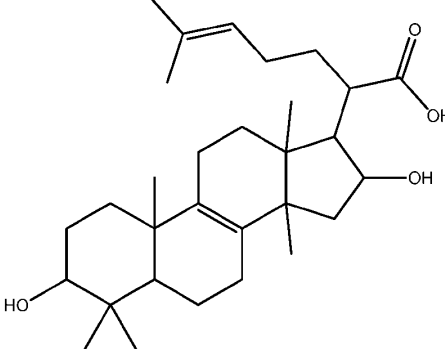
ID	Structure
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ID	Structure
753	 <chem>COc1ccc(cc1OC)S(=O)(=O)N(C)CC(=O)N1CCCCC1</chem>
754	 <chem>COc1ccc(cc1OC)S(=O)(=O)N1CCCC1C(=O)OCC</chem>
755	 <chem>CC(C)(O)C1CCC2C(C1)C(=C)C3C(C2)CC(O)CC3C</chem>
756	 <chem>COc1cc(C)ccc1S(=O)(=O)N1CCCC1C(=O)NCCc2ccccc2</chem>

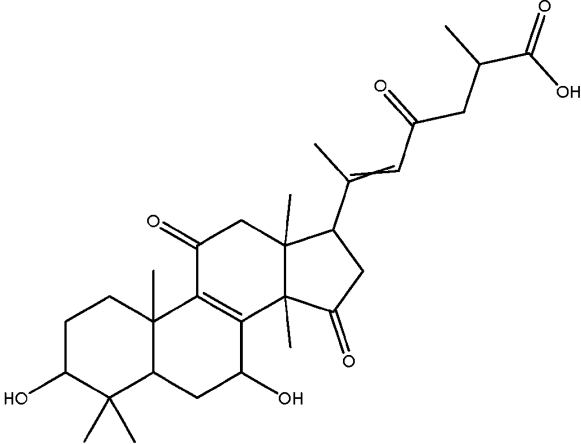
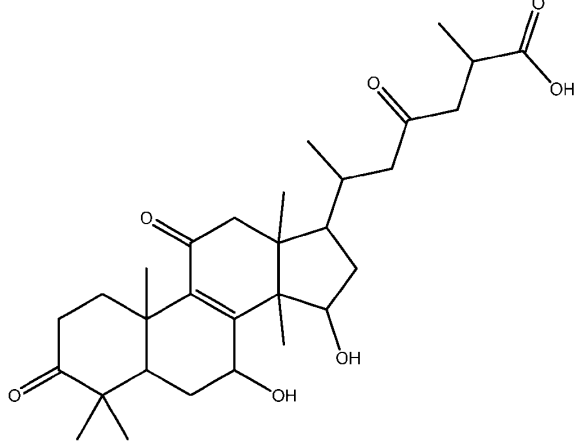
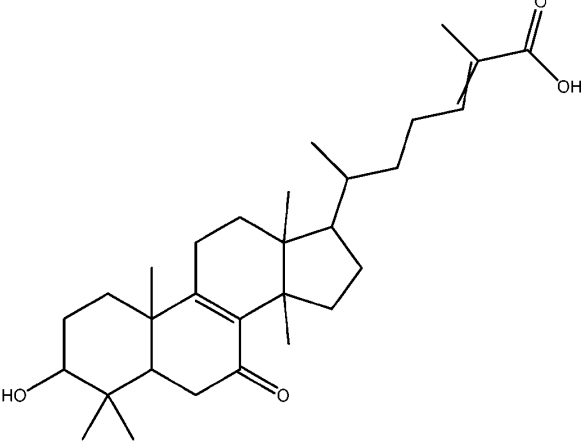
ID	Structure
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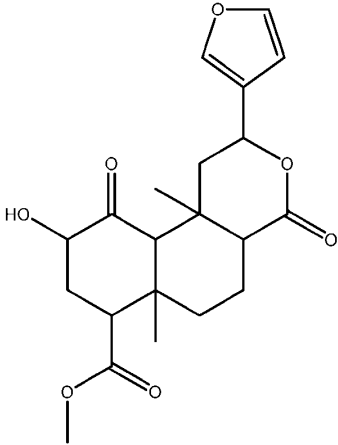
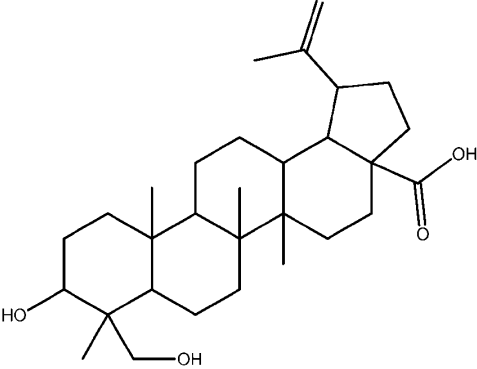
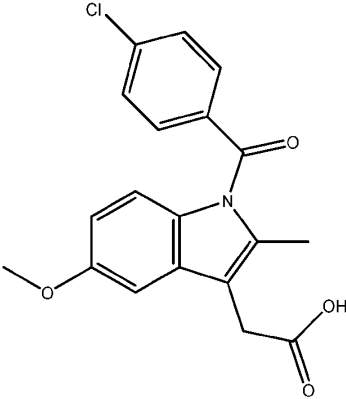
ID	Structure
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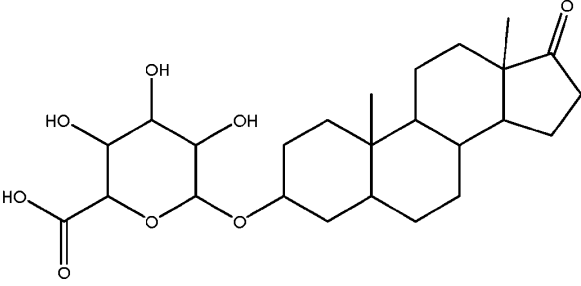
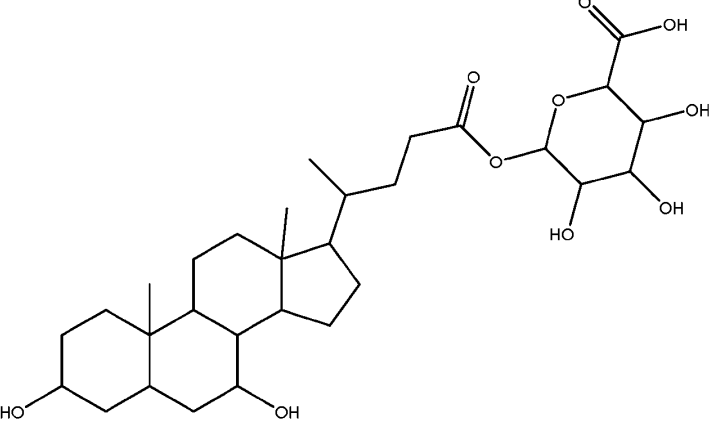
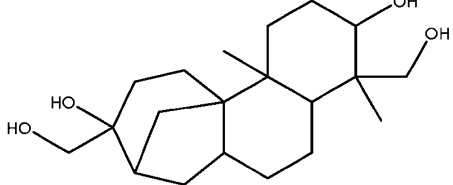
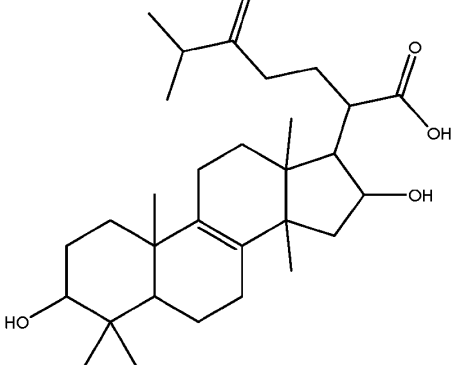
ID	Structure
767	 <chem>CCOC(=O)C1(C)C2=C(C1)C(=C)C(C2)C3(C)CC(C3)C(=O)OCC4=CC=CC=C4O</chem>
768	 <chem>OC1CCC2(C)C(C1)C3(C)CC(C2)C(C3)O</chem>
769	 <chem>CC(=O)OC1(C)C2=C(C1)C(=O)C(C2)C3(C)CC(C3)C(=O)OCC4=CC=CC=C4O</chem>

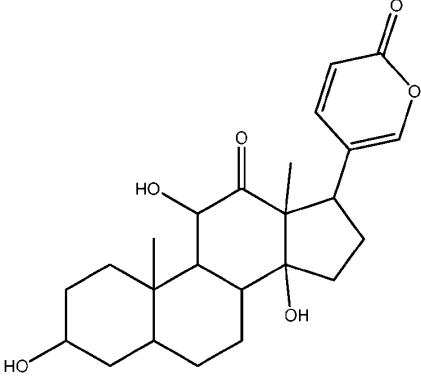
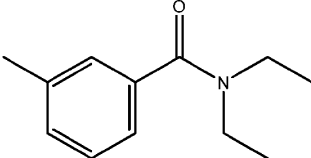
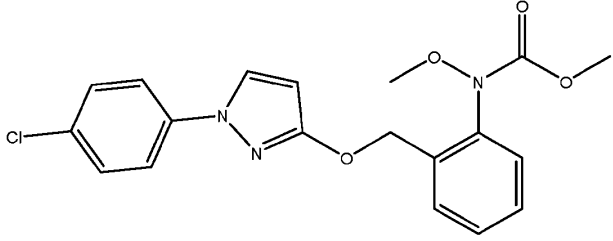
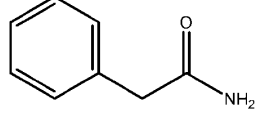
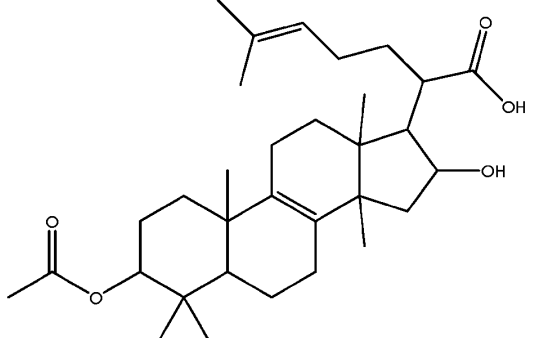
ID	Structure
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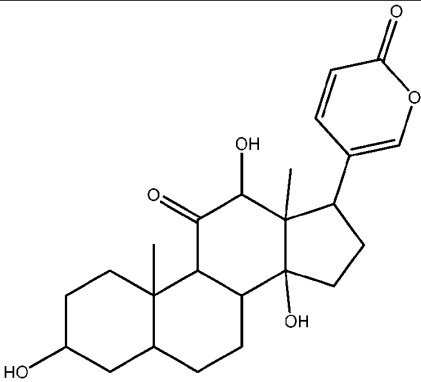
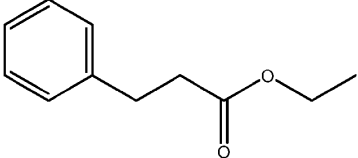
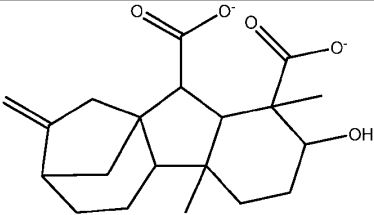
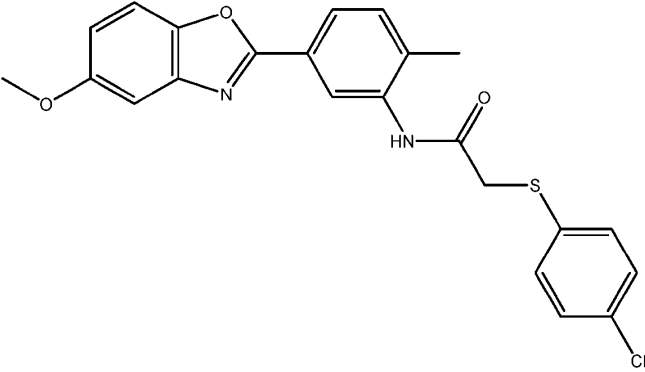
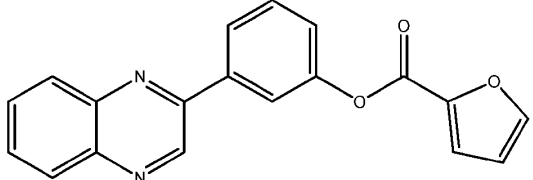
ID	Structure
773	 <chem>CC(C)CC(=O)CC(C)C1C(=O)CC2(C)C(=O)C3C2C(=O)C(C)(C)C(O)C3C1</chem>
774	 <chem>CCOC(=O)CC1C(=O)C2C(=O)C3C2C(=O)C(C)(C)C(O)C3C1</chem>
775	 <chem>CCOC(=O)CC1C(=O)C2C(=O)C3C2C(=O)C(C)(C)C(O)C3C1</chem>

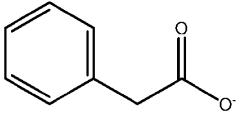
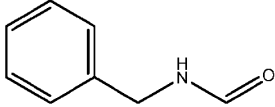
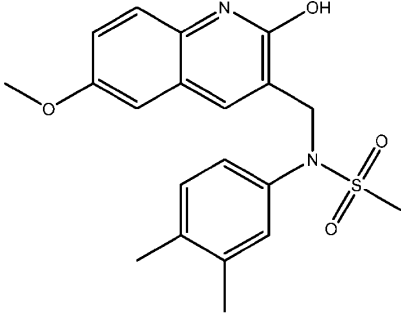
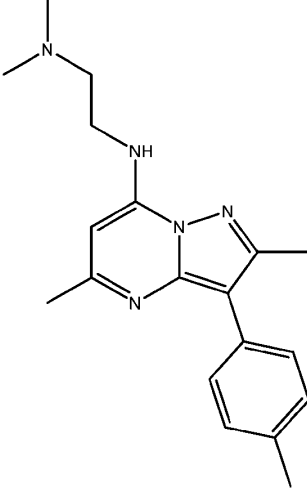
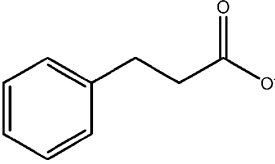
ID	Structure
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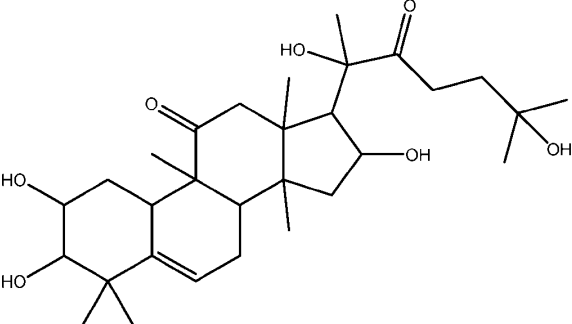
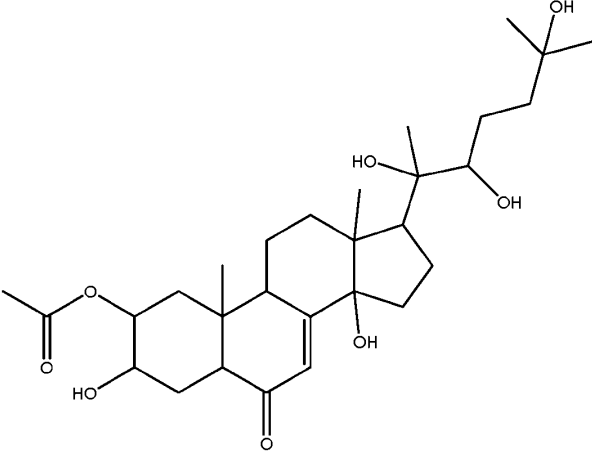
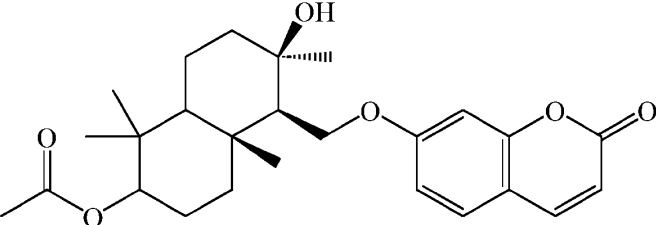
ID	Structure
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ID	Structure
782	 Chemical structure 782 is a complex polycyclic molecule. It features a steroid-like core with multiple hydroxyl groups and a carboxylic acid group. The structure is highly branched and includes several oxygen-containing functional groups.
783	 Chemical structure 783 is a complex polycyclic molecule. It features a steroid-like core with multiple hydroxyl groups and a carboxylic acid group. The structure is highly branched and includes several oxygen-containing functional groups.
784	 Chemical structure 784 is a complex polycyclic molecule. It features a steroid-like core with multiple hydroxyl groups and a carboxylic acid group. The structure is highly branched and includes several oxygen-containing functional groups.
785	 Chemical structure 785 is a complex polycyclic molecule. It features a steroid-like core with multiple hydroxyl groups and a carboxylic acid group. The structure is highly branched and includes several oxygen-containing functional groups.

ID	Structure
786	 <chem>CC12CCC3C(C1CC4C(C2)CC(C3)C(=O)C4(O)C5C(C)CC(C5)C6=CC(=O)OC6)O</chem>
787	 <chem>CCN(CC)C(=O)c1ccc(C)cc1</chem>
788	 <chem>COC(=O)N(OC)Cc1ccccc1COc2ncn(c2)c3ccc(Cl)cc3</chem>
789	 <chem>NC(=O)CCc1ccccc1</chem>
790	 <chem>CC(=O)OC12CCC3C(C1CC4C(C2)CC(C3)C(=O)C4(O)C5C(C)CC(C5)C(=O)O)C</chem>

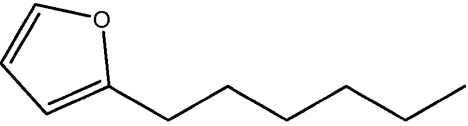
ID	Structure
791	 Chemical structure of a complex polycyclic molecule. It features a central polycyclic core with several hydroxyl groups (OH) and a furan ring attached to one of the rings.
792	 Chemical structure of ethyl 4-phenylbutanoate, showing a phenyl ring connected to a four-carbon chain, which is terminated by an ethyl ester group.
793	 Chemical structure of a complex polycyclic molecule. It features a central polycyclic core with several hydroxyl groups (OH) and a carboxylate group (COO⁻) attached to one of the rings.
794	 Chemical structure of a complex molecule. It features a benzimidazole core with a methoxy group (OCH₃) and a 4-chlorophenyl group attached to the imidazole ring.
795	 Chemical structure of a complex molecule. It features a quinoline core with a furan ring attached to the quinoline ring.

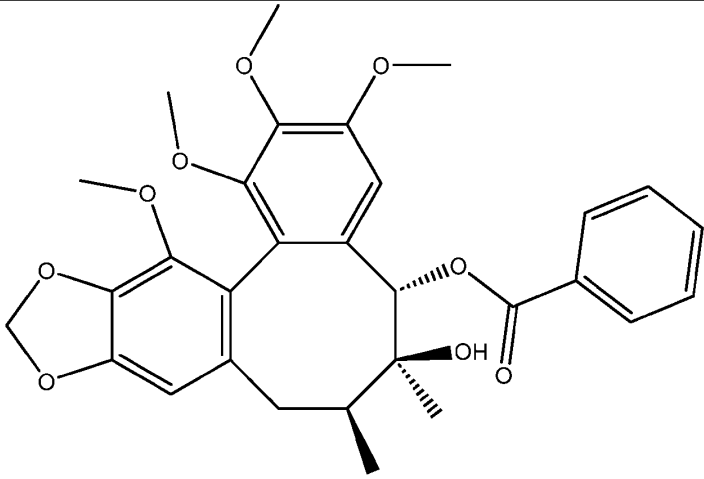
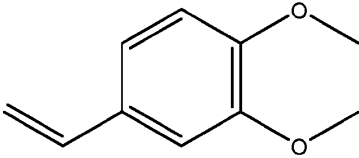
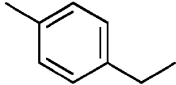
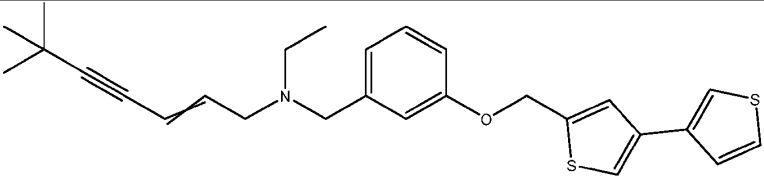
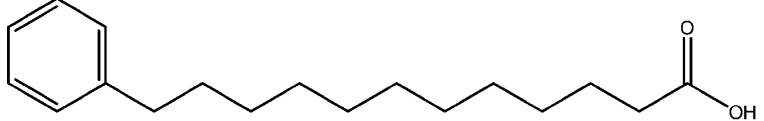
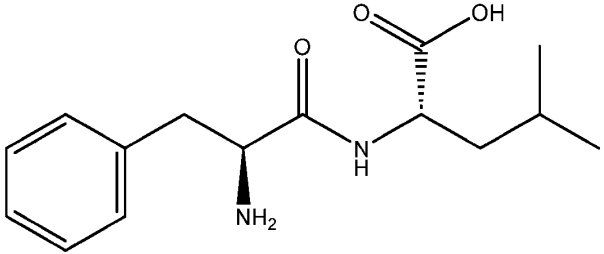
ID	Structure
796	 <chem>[O-]C(=O)CC1=CC=CC=C1</chem>
797	 <chem>O=CNC1=CC=CC=C1</chem>
798	 <chem>COc1ccc(cc1)CN(C2=CC=C(C)N=C3C=C(C=C2)O)C3</chem>
799	 <chem>CN(C)CCNC1=NC2=C(N1)N=CN2C3=CC=C(C)C=C3</chem>
800	 <chem>[O-]C(=O)CCC1=CC=CC=C1</chem>

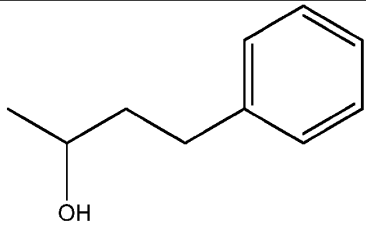
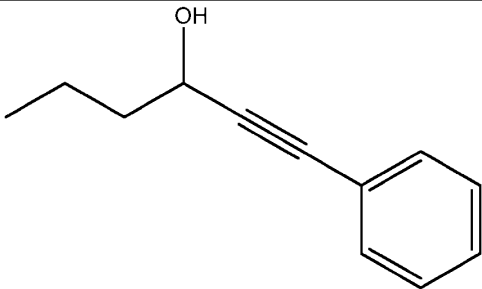
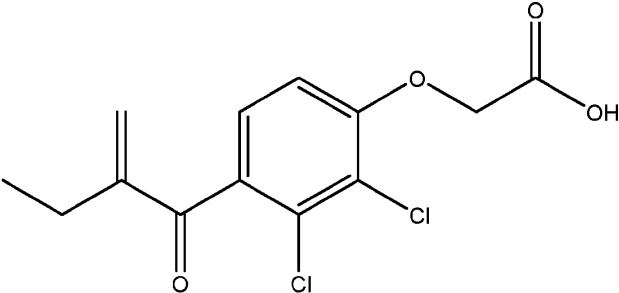
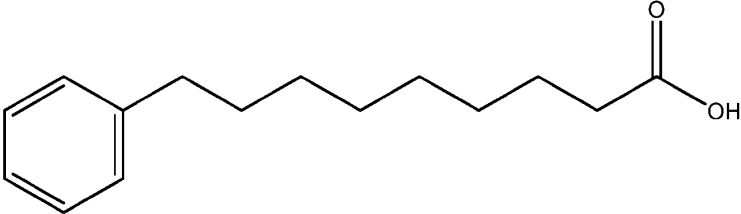
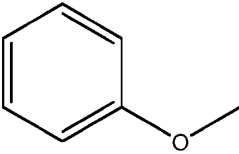
ID	Structure
809	
810	
811	

[0046] In some embodiments, the composition comprises one or more compounds according to Table 4.

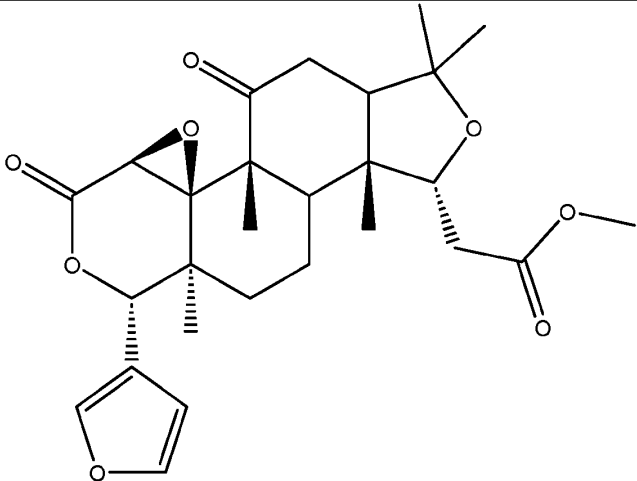
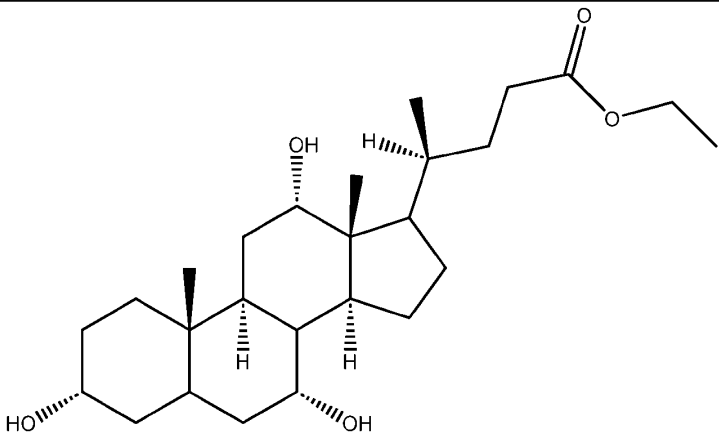
Table 4

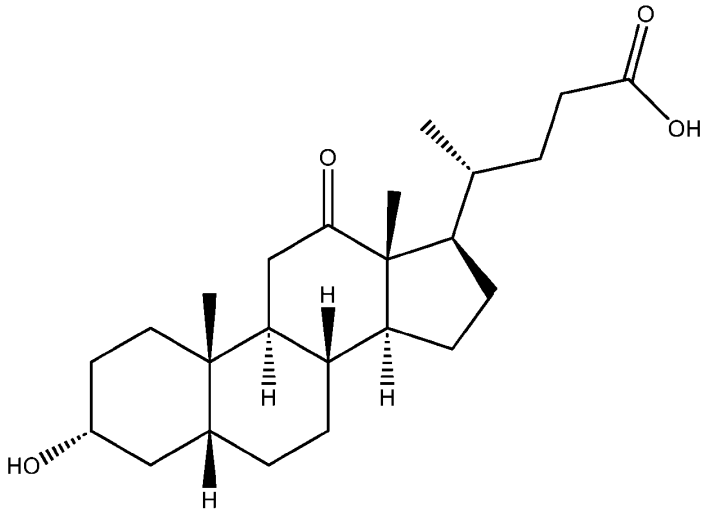
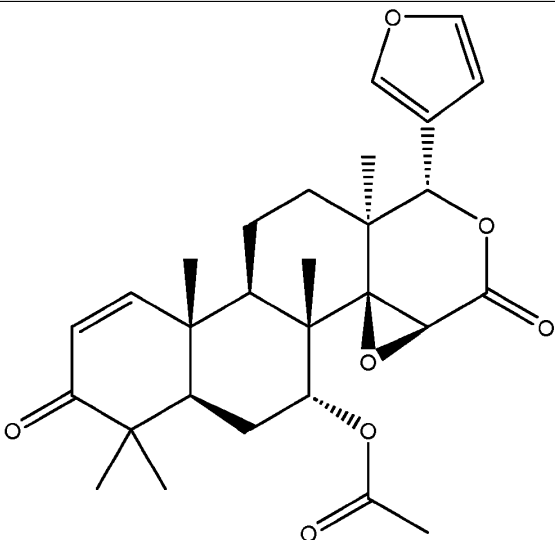
ID	Target	Structure
3	GPR40	

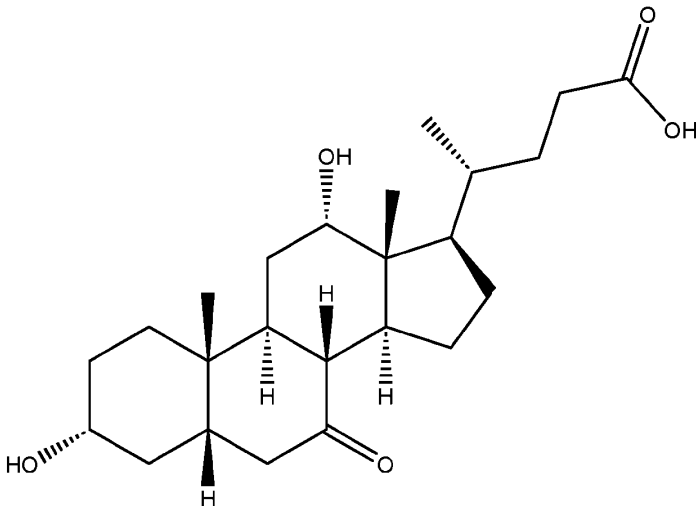
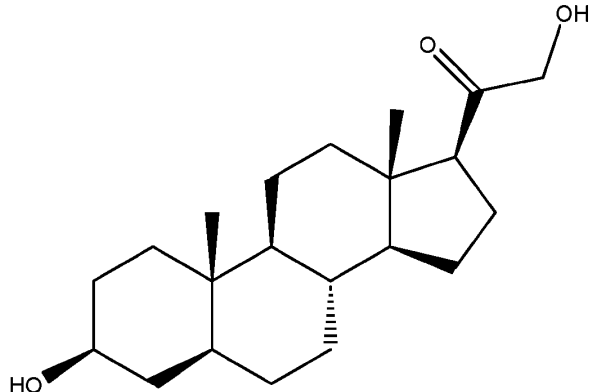
ID	Target	Structure
19	GPR40	
34	GPR40	
54	GPR40	
56	GPR40	
180	GPR40	
200	GPR40	

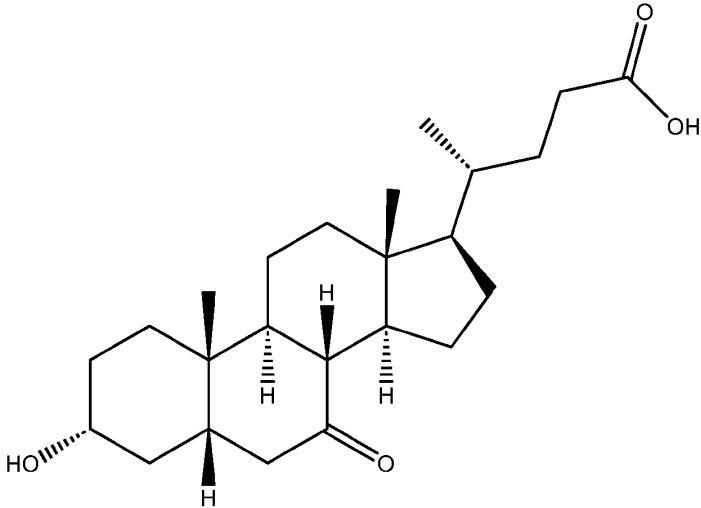
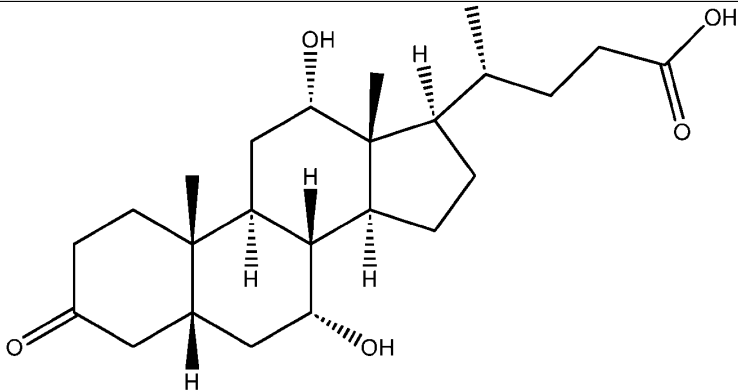
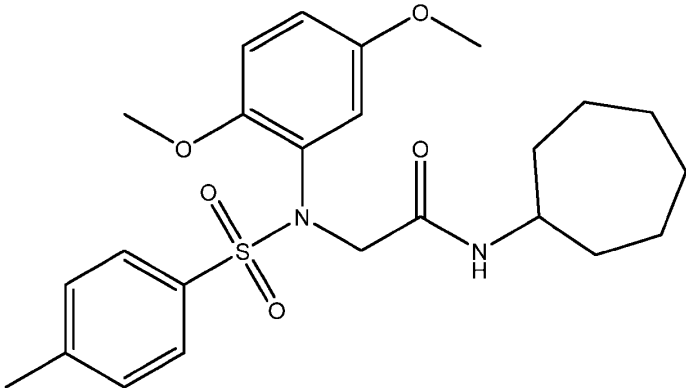
ID	Target	Structure
204	GPR40	 <chem>CC(O)CCC1=CC=CC=C1</chem>
206	GPR40	 <chem>CCCC(O)C#CC1=CC=CC=C1</chem>
235	GPR40	 <chem>CC(=C)CC(=O)c1cc(OC(=O)CC)cc(Cl)c1Cl</chem>
366	GPR40	 <chem>CCCCCCCCCCCC(=O)Oc1ccccc1</chem>
452	GPR40	 <chem>COC1=CC=CC=C1</chem>

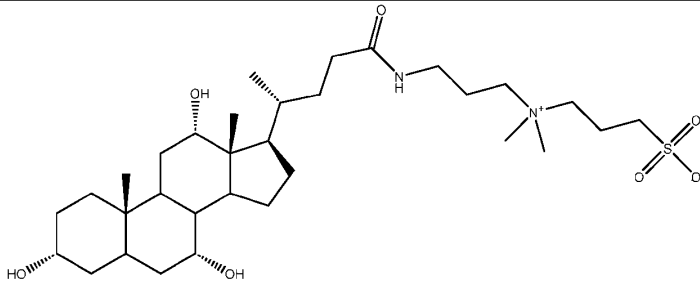
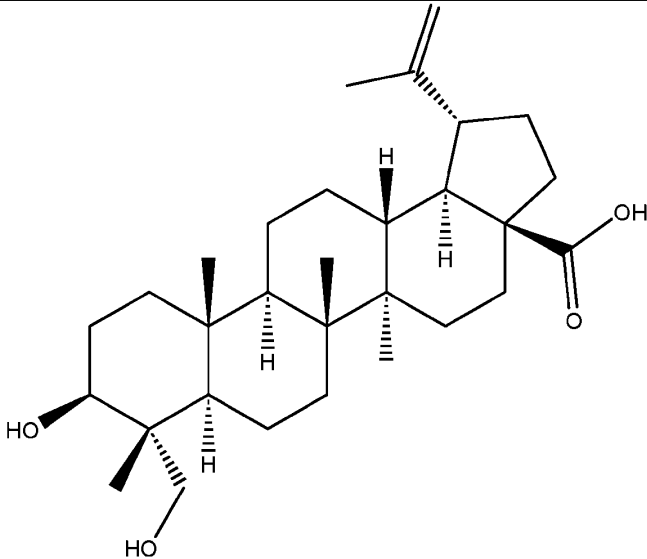
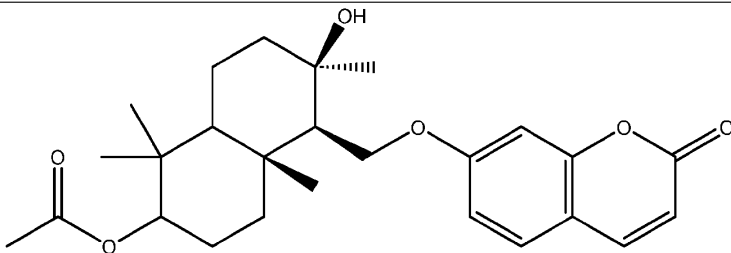
ID	Target	Structure
705	TGR5	Chemical structure of compound 705, a steroid derivative. It features a four-ring steroid nucleus with a methyl ester side chain at C-17 and two hydroxyl groups at C-3 and C-14. The structure is shown in a skeletal representation.
711	TGR5	Chemical structure of compound 711, a steroid derivative. It features a four-ring steroid nucleus with a methyl ester side chain at C-17 and two hydroxyl groups at C-3 and C-14. The stereochemistry is indicated by dashed bonds for the hydroxyl groups at C-3 and C-14.

ID	Target	Structure
713	TGR5	
721	TGR5	

ID	Target	Structure
725	TGR5	 <chem>CC(=O)CCC[C@H]1[C@@H]2[C@H]3[C@H]([C@@H]1CC[C@@H]2C(=O)CC[C@]3(C)CC[C@@H]4[C@@]1(CC[C@H]3[C@H]2CC=C4[C@]1(CC[C@@H](C3)O)C)C</chem>
727	TGR5	 <chem>CC(=O)OC[C@]12CC[C@@H]3[C@H]([C@@H]1CC[C@@H]2C(=O)O[C@H]3C[C@H]4[C@@H](C)C(=O)C=C[C@]5(C)[C@H]4CC[C@@H]5C)C[C@H]6[C@H]([C@@H]([C@H]([C@H]6O)C)C)C</chem>

ID	Target	Structure
728	TGR5	 The chemical structure of compound 728 is a complex pentacyclic triterpene. It features four fused six-membered rings and one five-membered ring. Key functional groups include a hydroxyl group at C-3 (dashed bond), a ketone at C-14, and a long side chain at C-13 consisting of two methylene groups followed by a carboxylic acid group (-CH ₂ -CH ₂ -COOH). Stereochemistry is indicated with wedges and dashes at several chiral centers.
729	TGR5	 The chemical structure of compound 729 is another pentacyclic triterpene. It has a similar core skeleton to 728 but lacks the long side chain. Instead, it has a hydroxyl group at C-3 (wedged bond) and a hydroxyethyl ketone side chain at C-13 (-CH ₂ -CH ₂ -OH). The stereochemistry differs from 728, particularly at the C-13 position where the side chain is attached with a wedge.

ID	Target	Structure
734	TGR5	 A steroid molecule with a carboxylic acid side chain. The side chain is attached to the D-ring and consists of a 4-carbon chain ending in a carboxylic acid group. The molecule has several stereocenters indicated by wedges and dashes, and a ketone group at C-3.
736	TGR5	 A steroid molecule with a carboxylic acid side chain and multiple hydroxyl groups. The side chain is attached to the D-ring and consists of a 4-carbon chain ending in a carboxylic acid group. The molecule has several stereocenters indicated by wedges and dashes, and a ketone group at C-3.
738	TGR5	 A sulfonamide molecule with a cyclooctyl group. The molecule consists of a benzene ring with a methyl group at the para position, a sulfonamide group (-SO ₂ NH-) at the other para position, and a methoxy group at the ortho position. The sulfonamide group is further substituted with a cyclooctyl group.

ID	Target	Structure
740	TGR5	
780	TGR5	
811	TGR5	

[0047] In some aspects, the disclosure provides for a composition comprising a plant extract and a carrier. In some embodiments, the composition is an oral composition. As used herein, an “extract” refers to a composition containing a desired compound of interest which is separated from other substances present in the natural source material from which the oral composition was obtained. In some embodiments, the plant extract comprises one or more

compounds of Table 1, Table 2, Table 3, and Table 4. Plant extracts can be obtained from any plant tissue including a whole plant; plant part such as shoot vegetative organs/structures (for example, leaves, stems and tubers), roots, flowers and floral organs/structures (for example, bracts, sepals, petals, stamens, carpels, anthers and ovules), seed (including embryo, endosperm, and seed coat) and fruit (the mature ovary); plant tissue (for example, vascular tissue, ground tissue, and the like); or cell (for example, guard cells, egg cells, and the like), and progeny and cultures or cell lines of the same. In some embodiments, the extract is generally recognized as safe for human consumption. Accordingly, in certain embodiments the extract is from an edible source. In this respect, the extract is an edible extract. Extracts can be prepared by freezing, grinding, macerating, pulverizing and/or fermenting the source material of interest, subjecting the source material to solvent extraction, and separating the insoluble material from soluble material. In this respect, an “extract” of the disclosure can be crude, fractionated, sub-fractionated, separated, isolated, enriched or purified, without being limited thereto.

[0048] In some embodiments, the plant extract may be a crude extract. As used herein, “crude” refers to compounds or molecules that have not been entirely separated from the components of the original composition in which it was present. In embodiments pertaining to fractions or sub- fractions, a molecule in crude extract may be subjected to partial separation to provide a less crude extract containing other substances. By comparison, the term “isolated” means that a compound or molecule is substantially enriched or purified with respect to the complex cellular milieu in which it naturally occurs, such as in a crude extract. When an isolated molecule is enriched or purified, the absolute level of purity may not be particularly significant and those skilled in the art can readily determine appropriate levels of purity according to the use to which the material is to be put. In some circumstances, the isolated molecule forms part of a composition (for example a more or less crude extract containing many other substances), which may for example contain other components. In other circumstances, the isolated molecule may be purified to essential homogeneity, for example as determined spectrophotometrically, by NMR or by chromatography (for example LC-MS).

[0049] A substantially pure compound as described herein can be combined with a carrier and provided in any suitable form for consumption by or administration to a subject. As used herein, “substantially pure” refers to a state where one or more of the desired active

compound or compounds have been isolated and/or concentrated to a high degree, with minimal undesired impurities present. In some embodiments, the compound or extract is added as an exogenous ingredient or additive to the consumable. Suitable consumable forms include, but are not limited to, a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition. In some embodiments, the compound or extract is provided in either a liquid or powder form. In some embodiments, the compound is plant derived and may be concentrated in the plant source without necessarily extracting the compound entirely or in part from the plant.

[0050] Suitable solvents for preparing an extract include, e.g., n-pentane, hexane, butane, chloroform, dichloromethane, di-ethyl ether, acetonitrile, water, butanol, isopropanol, ethanol, methanol, glacial acetic acid, acetone, norflurane (HFA134a), ethyl acetate, dimethyl sulfoxide, heptafluoropropane (HFA227), and subcritical or supercritical fluids such as liquid carbon dioxide and water, or a combination thereof in any proportion. When solvents such as those listed above are used, the resultant extract typically contains non-specific lipid-soluble material. This can be removed by a variety of processes including “winterization”, which involves chilling to a specified temperature, typically -20° C followed by filtration or centrifugation to remove waxy ballast, extraction with subcritical or supercritical carbon dioxide or non-polar solvents (e.g., hexane) and by distillation.

[0051] In some embodiments, the oral composition includes an extract from one or more plant source. In some embodiments, the oral composition includes an extract from two or more plant sources. In some embodiments, the oral composition includes an extract from three or more plant sources.

[0052] In some embodiments, the extract as described herein includes juices, infusions, and fermentation residues. The products fermentation plant-derived extracts or processed fractions thereof find use in consumable compositions such as health-promoting compositions or tonics for human and animals.

[0053] In some embodiments, the oral composition includes a salt form of a compound as described herein. A salt of a compound of this disclosure refers to a compound that possesses the desired pharmacological activity of the parent compound and includes: (1) an acid addition salt, formed with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with an organic acid

such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, camphorsulfonic acid, 4-toluenesulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) a salt formed when an acidic proton present in the parent compound is replaced.

[0054] In some embodiments, the oral composition includes a pharmaceutically acceptable salt form a compound as described herein. The term “pharmaceutically acceptable salt” as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In some embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (*e.g.*, hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid, and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic acid, acetic acid (AcOH), propionic acid, glycolic acid, pyruvic acid, malonic acid, maleic acid, fumaric acid, trifluoroacetic acid (TFA), benzoic acid, cinnamic acid, mandelic acid, succinic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, nicotinic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, muconic acid, butyric acid, phenylacetic acid, phenylbutyric acid, valproic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a lithium, sodium or a potassium salt, an alkaline earth metal salt, such as a calcium, magnesium or aluminum salt, a salt of organic bases such as dicyclohexylamine, N-

methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, dicyclohexylamine, triethanolamine, ethylenediamine, ethanolamine, diethanolamine, triethanolamine, tromethamine, and salts with amino acids such as arginine and lysine; or a salt of an inorganic base, such as aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, sodium hydroxide, or the like.

[0055] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, or may be stereoisomeric mixtures, and include all diastereomeric, and enantiomeric forms. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. Stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. Likewise, it is understood that, in any compound described, all tautomeric forms are also intended to be included.

[0056] It is understood that the compounds described herein can be labeled isotopically or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium), hydrogen-2 (deuterium), and hydrogen-3 (tritium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0057] It is understood that the compounds described herein can be labeled isotopically or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels. Substitution with

isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased *in vivo* half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium), hydrogen-2 (deuterium), and hydrogen-3 (tritium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0058] It is understood that the oral compositions, formulations, and methods described herein include the use of crystalline forms, amorphous phases, and/or pharmaceutically acceptable salts, solvates, hydrates, and conformers of compounds of some embodiments, as well as metabolites and active metabolites of these compounds having the same type of activity. A conformer is a structure that is a conformational isomer. Conformational isomerism is the phenomenon of molecules with the same structural formula but different conformations (conformers) of atoms about a rotating bond. In specific embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein. Other forms in which the compounds of some embodiments can be provided include amorphous forms, milled forms and nano-particulate forms.

[0059] Likewise, it is understood that the compounds described herein, such as compounds of some embodiments, include the compound in any of the forms described herein (*e.g.*, pharmaceutically acceptable salts, prodrugs, crystalline forms, amorphous form, solvated forms, enantiomeric forms, tautomeric forms, and the like).

[0060] In some aspects, the disclosure provided herein provides for a composition comprising a compound as described herein and a carrier. In some embodiments, the compound is a substantially pure compound. In some embodiments, the composition is an oral composition. The term “carrier” as used herein means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (*e.g.*, lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier should be compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials that can serve as carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate, and hydroxyl propyl methyl cellulose; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) lipids and/or phospholipids; and (23) other nontoxic compatible substances employed in conventional formulations.

[0061] In some embodiments, the oral composition may further include a preservative. In some embodiments, the preservative may be in an amount from about 0.01%, 0.05%, 0.1%, 0.15%, 0.20%, 0.25%, 0.50%, 0.75%, 1.0%, 1.25%, 1.50%, 1.75%, 2.0%, 2.25%, 2.50%, 2.75%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0% w/w, or ranges including and/or spanning the aforementioned values. In some embodiments, the preservative may be, but not limited to, the group selected from sodium benzoate, methyl parabens, propyl parabens, sodium nitrite, sulfur dioxide, sodium sorbate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate, (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as a disodium EDTA).

[0062] In some embodiments, the oral composition may further include a sweetener. In some embodiments, the sweetener may be in an amount from about 1.0%, 1.25%, 1.50%, 1.75%, 2.0%, 2.25%, 2.50%, 2.75%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 6.0%, 7.0%, 8.0%, 9.0%, 10.0% w/w, or ranges including and/or spanning the aforementioned values. In some embodiments, the sweetener may include a natural sweetener. In some embodiments, the sweetener may include a synthetic sweetener. Non-limiting examples of sweeteners include sucrose, dextrose, maltose, dextrin, dried invert sugar, fructose, high fructose corn syrup, levulose, galactose, corn syrup solids, tagatose, polyols (e.g., sorbitol, mannitol, xylitol, lactitol, erythritol, and maltitol), hydrogenated starch hydrolysates, isomalt, trehalose, and mixtures thereof.

[0063] In some embodiments, the oral composition may further include a flavoring agent. In some embodiments, the flavoring agent may be in an amount from about 1.0%, 1.25%, 1.50%, 1.75%, 2.0%, 2.25%, 2.50%, 2.75%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 6.0%, 7.0%, 8.0%, 9.0%, 10.0% w/w, or ranges including and/or spanning the aforementioned values. In some embodiments, the flavoring agent may include natural or artificial flavors. In a particular embodiment, the flavoring agent comprises an essential oil, such as an oil derived from a plant or a fruit, peppermint oil, spearmint oil, other mint oils, clove oil, cinnamon oil, oil of wintergreen, bay, thyme, cedar leaf, nutmeg, allspice, sage, mace, and almonds. In another particular embodiment, the flavoring agent comprises a plant extract or a fruit essence such as apple, banana, watermelon, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot, and mixtures thereof. In still another particular embodiment, the flavoring agent comprises a citrus flavor, such as an extract, essence, or oil of lemon, lime, orange, tangerine, grapefruit, citron, or kumquat.

[0064] In some embodiments, the oral composition may further include a coloring agent. In some embodiments, the coloring agent may be in an amount from about 1.0%, 1.25%, 1.50%, 1.75%, 2.0%, 2.25%, 2.50%, 2.75%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%, 4.75%, 5.0%, 6.0%, 7.0%, 8.0%, 9.0%, 10.0% w/w, or ranges including and/or spanning the aforementioned values.

[0065] In some embodiments, the oral composition may further include at least one additive. In some embodiments, the additive may be in an amount from about 1.0%, 1.25%, 1.50%, 1.75%, 2.0%, 2.25%, 2.50%, 2.75%, 3.0%, 3.25%, 3.5%, 3.75%, 4.0%, 4.25%, 4.5%,

4.75%, 5.0%, 6.0%, 7.0%, 8.0%, 9.0%, 10.0% w/w, or ranges including and/or spanning the aforementioned values. In some embodiments, the at least one additive may be an emulsifier. In some embodiments, the additive may include one or more vitamin. In some embodiments, the additive may include one or more minerals. In some embodiments, the additive may include a stabilizer.

[0066] In some embodiments, the oral composition consists essentially of an agonist of a G-protein coupled receptor. In some embodiments, the agonist of a G-protein coupled receptor is a GPR30 agonist. In some embodiments, the agonist of a G-protein coupled receptor is a GPR40 agonist. In some embodiments, the agonist of a G-protein coupled receptor is a GPR119 agonist. In some embodiments, the agonist of a G-protein coupled receptor is a GPR120 agonist. the agonist of a G-protein coupled receptor is a TGR5 agonist. In some embodiments, the agonist of a G-protein coupled receptor includes one or more compounds selected from Table 1, 2, and 3. In some embodiments, the one or more compounds is selected from Formula (I) or Formula (II). In some embodiments, the oral composition consists essentially of an agonist G-protein coupled receptor unbound to a lignocellulose material. In some embodiments, the oral composition consists essentially of antagonist of a G-protein coupled receptor. In some embodiments, the antagonist of a G-protein coupled receptor includes one or more compounds selected from Table 1, 2, and 3. In some embodiments, the oral composition consists essentially of an antagonist G-protein coupled receptor unbound to a lignocellulose material. Lignocellulosic material refers to a composite material composed primarily of lignin, cellulose, and hemicellulose. These are naturally occurring polymers found in the cell walls of plants. Lignocellulosic materials are characterized by their rigid structure, high strength, and resistance to decomposition. This material is commonly derived from wood, grasses, and the inedible parts of plants. In some embodiments, the composition does not include lignin, cellulose, and/or pectin. In some embodiments, the composition does not include an extract from a natural source.

Formulations

[0067] A composition comprising a plant extract or a compound, or a salt thereof, of this disclosure can be combined with a carrier and provided in any suitable form for consumption by or administration to a subject. In this respect, the plant extract or compound

is added as an exogenous ingredient or additive to the consumable. Suitable consumable forms include, but are not limited to, a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition. In some embodiments, the plant extract or compound is provided in either a liquid or powder form.

[0068] A food ingredient or additive is an edible substance intended to result, directly or indirectly, in becoming a component of or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food). A food product, in particular a functional food, is a food fortified or enriched during processing to include additional complementary nutrients and/or beneficial ingredients. A food product according to this disclosure can, *e.g.*, be in the form of butter, margarine, sweet or savory spreads, condiment, biscuits, health bar, bread, cake, cereal, candy, confectionery, soup, milk, yogurt or a fermented milk product, cheese, juice-based and vegetable-based beverages, fermented beverages, shakes, flavored waters, tea, oil, or any other suitable food. In some embodiments, the food product is a whole-food product in which the concentration of the compound has been enriched through particular post-harvest and food production processing methods to levels that provide an efficacious amount of the compound.

[0069] A dietary supplement is a product taken by mouth that contains a compound or extract of the disclosure and is intended to supplement the diet. A nutraceutical is a product derived from a food source that provides extra health benefits, in addition to the basic nutritional value found in the food. A pharmaceutical composition is defined as any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of humans or other animals. Dietary supplements, nutraceuticals and pharmaceutical compositions can be found in many capsules, forms such as tablets, coated tablets, pills, capsules, pellets, gummy, granules, softgels, gelcaps, liquids, powders, emulsions, suspensions, elixirs, syrup, and any other form suitable for use.

[0070] The pharmaceutical compositions disclosed herein may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes. Additionally, the active ingredients are contained in an amount effective to achieve its intended

purpose. Many of the compounds used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically compatible counterions.

[0071] Multiple techniques of administering a compound, salt and/or composition exist in the art including, but not limited to, oral, rectal, pulmonary, topical, aerosol, injection, infusion and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal and intraocular injections. In some embodiments, a compound described herein, including a compound as described herein, or a pharmaceutically acceptable salt thereof, can be administered orally.

[0072] One may also administer the compound, salt and/or composition in a local rather than systemic manner, for example, via injection or implantation of the compound directly into the affected area, often in a depot or sustained release formulation. Furthermore, one may administer the compound in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes will be targeted to and taken up selectively by the organ. For example, intranasal or pulmonary delivery to target a respiratory disease or condition may be desirable.

[0073] The oral compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions that can include a compound and/or salt described herein formulated in a compatible pharmaceutical excipient may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0074] A composition comprising a plant extract or a compound of this disclosure can be combined with a carrier and provided in any suitable form for consumption by or administration to a subject. In this respect, the plant extract or compound is added as an

exogenous ingredient or additive to the consumable. Suitable consumable forms include, but are not limited to, a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition. In some embodiments, the plant extract or compound is provided in either a liquid or powder form.

[0075] A “food ingredient” or “food additive” as referred to herein includes an edible substance intended to result, directly or indirectly, in becoming a component of or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food). A food product, in particular a functional food, is a food fortified or enriched during processing to include additional complementary nutrients and/or beneficial ingredients. A food product according to this disclosure can, *e.g.*, be in the form of butter, margarine, sweet or savory spreads, condiment, biscuits, health bar, bread, cake, cereal, candy, confectionery, soup, milk, yogurt or a fermented milk product, cheese, juice-based and vegetable-based beverages, fermented beverages, shakes, flavored waters, tea, oil, or any other suitable food. In some embodiments, the food product is a whole-food product in which the concentration of the compound has been enriched through particular post-harvest and food production processing methods to levels that provide an efficacious amount of the compound. In some embodiments, the food product includes one or more compounds as described herein and a fiber source. In some embodiments, the food product includes one or more compounds as described herein. In some embodiments, the food product is a food bar. In some embodiments, the food bar comprises from about 0.01% to about 20% (w/w) of one or more compounds as described herein. In some embodiments, the food bar comprises from about 0.1% to about 10% (w/w) of one or more compounds as described herein. In some embodiments, the food product is a crisp. In some embodiments, the food crisp comprises from about 0.01% to about 20% (w/w) of one or more compounds as described herein. In some embodiments, the food crisp comprises from about 0.1% to about 10% (w/w) of one or more compounds as described herein.

[0076] The compounds, compositions and extracts of the present disclosure can be prepared as nutritional formulations such as foods, including medical or functional foods. A “medical or functional food” is defined as being consumed as part of a usual diet but which has been demonstrated to have physiological benefits and/or to reduce the risk of a disease or

condition such as a chronic disease, beyond basic nutritional functions. By way of example, but not limitation, medical foods and functional foods may include one or more of the following ingredients: a compound described herein, a composition described herein, an extract described herein, vitamins, minerals, herbs, botanicals, amino acids, dietary substances intended to supplement the diet by increasing total dietary intake, concentrates, metabolites, constituents, extracts or combinations of any of the foregoing. Dietary supplements may also be incorporated into food stuffs, such as functional foods designed to promote health or to prevent disease or disorders. If administered as a medicinal preparation, the composition can be administered, either as a prophylaxis or treatment, to a patient in any of a number of methods. In some embodiments, the compositions described herein may be administered alone or in combination with other additives or pharmaceutical agents and can be combined with a physiologically acceptable carrier thereof. The effective amount and method of administration and aim of the particular formulation can vary based on the individual subject, the stage of the disease or condition, and other factors evident to one skilled in the art. In the case of a pharmaceutical formulation as well as a nutraceutical formulation, during the course of the treatment, the concentration of the subject compositions may be monitored (for example, blood plasma levels may be monitored) to ensure that the desired level is maintained.

[0077] In some embodiments, food product includes a carbohydrate. A variety of carbohydrates are used in food products, such as various sugars and starches. Carbohydrates are an important source of energy for the body, including complex carbohydrates (like whole grains and vegetables) and simple carbohydrates (like sugar and refined grains). There are several common carbohydrates that are used in food products, including: starch, sugar, fructose, maltodextrin, dextrose, corn syrup, oligosaccharides, cellulose, complex carbohydrates, such as inulin that may be added as a prebiotic fiber in processed foods. According to the disclosure, the concentration of carbohydrates may vary depending on the intended use of a product. In some embodiments, carbohydrates may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, carbohydrates may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, a food product may comprise carbohydrates in a range with high and low values independently selected from about 1%, 3%, 5%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%,

45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or ranges including, between, and/or spanning the aforementioned values.

[0078] In some embodiments, the food product may include a sugar. Sugars, such as high fructose corn syrup, sucrose, glucose syrup, dextrose, and other sweeteners are often added to processed foods to make them more palatable. Additionally, sugar alcohols or maltodextrins, may be added to food products to reduce caloric content and/or to enhance nutritional profile of the product. In some embodiments, a food product may comprise one or a plurality of saccharides that are slowly or incompletely digested by humans, if not totally indigestible. These sugars can include isomaltose, panose and branched oligomers having a degree of polymerization of four or greater. Additional non-limiting examples of sugars include sucrose, HFCS, fructose, brown sugar (which can be either partially or fully refined), powdered sugar (also known as confectioner's sugar), high fructose corn syrup, honey, molasses, maple syrup, agave nectar, coconut sugar, date sugar, fruit juice concentrates, maltodextrin, dextrose, glucose syrup, maple syrup, molasses, and lactose. According to the disclosure, the concentration of sugars may vary depending on the intended use of a product. In some embodiments, sugar may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, the sugar(s) component comprises from about 2% to about 10% by weight of the composition. In some embodiments, sugars may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, a food product may comprise sugars in a range with high and low values independently selected from about 1%, 3%, 5%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or ranges including, between, and/or spanning the aforementioned values.

[0079] In some embodiments, the food product includes a fiber source. In some embodiments, the food product includes from about 5% to about 30% (w/w) fiber. In some embodiments, the food product includes at least 10% fiber. In some embodiments, the food product includes at least 15% fiber. In some embodiments, the food product includes at least 20% fiber. In some embodiments, the food product includes at least 30% fiber. In some embodiments, the fiber may be selected from psyllium husk, inulin, beta-glucans, acacia fiber, pectin, wheat dextrin, cellulose, fructooligosaccharides, guar gum, fruit fiber, or a combination thereof. In some embodiments, the fiber is a soluble dietary fiber.

[0080] In some embodiments, the food product may include a protein. Proteins may be included in a range of concentrations depending on the product. Protein sources can include soy protein, soy flour, soy protein isolate, whey protein isolate, casein, gelatin, legume protein isolates, soy protein concentrate, egg albumin or egg white, wheat protein concentrate, legume protein concentrates and mixtures thereof. In some embodiments, meat products like beef jerky, sausages, or meatballs, may include proteins as a primary ingredient. Proteins may be included at concentrations ranging from about 10% to about 25% of the total ingredients. In dairy products like cheese, yogurt, or milk, proteins like casein or whey may be the primary ingredient. Proteins may be included at concentrations ranging from about 3% to about 15% of the total ingredients. In plant-based products like tofu, tempeh, or seitan, proteins from soy, peas, legumes, or wheat may be primary ingredients. Proteins may be included at concentrations ranging from about 10% to about 25% of the total ingredients. In energy bars and protein bars, proteins like whey or soy, or any protein according to the disclosure may be added to provide a source of protein. Proteins may be included at concentrations ranging from about 10% to about 25% of the total ingredients. According to the disclosure, the concentration of proteins may vary depending on the intended use of a product. In some embodiments, proteins may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, proteins may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, a food product may comprise proteins in a range with high and low values independently selected from about 1%, 3%, 5%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or ranges including, between, and/or spanning the aforementioned values.

[0081] In some embodiments, the food product may include a starch. In some embodiments, food products may additionally comprise a starch ingredient(s) in amounts sufficient to provide about 5% to 45%, or about 10%-30%, or about 15%-25 starch in the food products. Starchy components may include not only pure added cereal flours or other granulations but also any starchy fraction provided by other ingredients such as oat bran or soy protein. In some embodiments, a starch may comprise any conventionally employed starch or cereal flour ingredient, for use in a ready-to-eat cereal. Exemplary suitable starchy cereals include cereal flours from major cereal grains including wheat, rice, corn (maize), oats, barley, rye, or starch fractions isolated from the cereal flowers including, for example cornstarch,

wheat starch, rice starch, and various treated starches including pre-gelatinized starches and/or modified starches.

[0082] In some embodiments, the food product may include a flour. Several types of flour may be used according to the disclosure. For example, common types of flour used in food products, include all-purpose flour (which like most other flour may include protein content), Whole wheat flour, Bread flour, Cake flour, pastry flour, self-rising flour, and gluten-free flour. According to the disclosure, the concentration of flour may vary depending on the intended use of a product. For example, in baked goods like bread, cakes, and cookies, flour is typically a main ingredient and may be included at concentrations ranging from 50% to 100% of the total dry ingredients. In soups and sauces, flour is often used as a thickener and may be included at concentrations ranging from 1% to 5% of the total ingredients. Batter and breading: In fried foods like chicken or fish, flour is often used as part of the batter or breading and may be included at concentrations ranging from 20% to 50% of the total dry ingredients. In snack foods, like crackers and chips, flour may be included at concentrations ranging from 30% to 70% of the total ingredients. In some embodiments, flour may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, flours may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, a food product may comprise flour in a range with high and low values independently selected from about 1%, 3%, 5%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or ranges including, between, and/or spanning the aforementioned values.

[0083] In some embodiments, the food product may include a fat. In some embodiments, the food product may include an oil. In some embodiments, the food product may include one or more fats or oils. Several types of fats may be used according to the disclosure. For example, common types of fats include butter, margarine, vegetable oils, shortening, and lard. According to the disclosure, the concentration of fats may vary depending on the intended use of a product. In baked goods like cakes, cookies, and pastries, fats like butter, shortening, or oil are often used to provide moisture, flavor, and texture. In some embodiments, Fats may be included at concentrations ranging from 10% to 30% of the total ingredients. In some embodiments, like in sauces and dressings, fats like olive oil or mayonnaise are often used to provide flavor and texture. In some embodiments, Fats may be

included at concentrations ranging from 10% to 30% of the total ingredients. In fried foods like chicken or French fries, fats like vegetable oil or lard are used for frying and may be included at concentrations ranging from 30% to 60% of the total ingredients. In snack foods like chips and crackers, fats like vegetable oil or palm oil are often used to provide flavor and texture. In some embodiments, Fats may be included at concentrations ranging from 10% to 30% of the total ingredients. In some embodiments, fats may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, fats may comprise from about 1% by weight to about 95% by weight of a food product. In some embodiments, a food product may comprise fat in a range with high and low values independently selected from about 1%, 3%, 5%, 8%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or ranges including, between, and/or spanning the aforementioned values.

[0084] In some embodiments, the food product may include one or more additional ingredients. If desired, the disclosed food products may additionally include a variety of materials designed to improve their aesthetic or nutritional qualities. These adjuvant materials can include vitamin and/or mineral fortification, colors, flavors, sweetener(s), and mixtures thereof. The precise ingredient concentration may vary. Generally, however, such materials can each include about 0.01% to about 5%, or about 0.1% to 2% dry weight of a food product. One especially useful material is common salt. In some embodiments, salt comprises about 0.1 to 5%, or about 0.5 to 4.0% of the food products.

[0085] In some embodiments, the food product is derived from a plant. In some embodiments, the food product is derived from hemp hulls. In some embodiments, the food product is a solid food. In some embodiments, the food product is a semi-solid food. In some embodiments, the food product is a puffed product, a bakery product, a pressed cake, a cooked product, a food bar, a cereal, a crisp, or a spread.

[0086] A dietary supplement is a product taken by mouth that contains a compound or extract of the disclosure and is intended to supplement the diet. A nutraceutical is a product derived from a food source that provides extra health benefits, in addition to the basic nutritional value found in the food. A pharmaceutical composition is defined as any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any

function of the body of humans or other animals. Dietary supplements, nutraceuticals and pharmaceutical compositions can be found in many capsules, forms such as tablets, coated tablets, pills, capsules, pellets, granules, softgels, gelcaps, liquids, powders, emulsions, suspensions, elixirs, syrup, and any other form suitable for use. In some embodiments, the composition as described herein is provided as a dietary supplement. In some embodiments, the dietary supplement is provided as a capsule, tablet, powder, or in a liquid form. In some embodiments, the composition as described herein is provided as a nutritional supplement. In some embodiments, the nutritional supplement is provided as a capsule, tablet, powder, or in a liquid form. In some embodiments, the composition as described herein is provided as a pharmaceutical. In some embodiments, the pharmaceutical is provided as a capsule, tablet, powder, or in a liquid form.

[0087] The compounds, salt and/or pharmaceutical composition can be provided to an administering physician or other health care professional in the form of a kit. The kit is a package which houses a container which contains the compound(s) in a suitable pharmaceutical composition, and instructions for administering the pharmaceutical composition to a subject. The kit can optionally also contain one or more additional therapeutic agents. The kit can also contain separate doses of a compound(s) or pharmaceutical composition for serial or sequential administration. The kit can optionally contain one or more diagnostic tools and instructions for use. The kit can contain suitable delivery devices, for example, syringes, and the like, along with instructions for administering the compound(s) and any other therapeutic agent. The kit can optionally contain instructions for storage, reconstitution (if applicable), and administration of any or all therapeutic agents included. The kits can include a plurality of containers reflecting the number of administrations to be given to a subject.

Methods and Uses

[0088] Aspects of the disclosure relate to providing or administering to a subject in need thereof a compound or composition of the disclosure. In some embodiments, the compound or composition may be provided or administered to treat, prevent, reduce, or ameliorate a disease or condition. In some embodiments, the disease or condition is associated with G-protein coupled receptors. In some embodiments, the compounds of the present

disclosure are potent agonists of G-protein coupled receptors. The compounds, and salts thereof, may be efficacious in the treatment of diseases capable of treating a disease or condition by modulating a GPCR. In some embodiments, the compositions as described herein may be efficacious in the treatment of diseases that are modulated by GPR40 ligands, which are generally agonists. In some embodiments, the composition as described herein may be efficacious in the treatment of diseases that are modulated by GPR119 ligands. In some embodiments, the composition as described herein may be efficacious in the treatment of diseases that are modulated by TGR5 ligands.

[0089] One or more of these diseases may be treated by the administration of a therapeutically effective amount of a compound or composition of the present disclosure, or a salt thereof, to a subject in need of thereof. Also, the compounds or composition of the present disclosure may be used for the manufacture of a medicament which may be useful for treating one or more of these diseases: (1) non-insulin dependent diabetes mellitus (Type 2 diabetes); (2) hyperglycemia; (3) insulin resistance; (4) metabolic syndrome; (5) obesity; (6) hypercholesterolemia; (7) hypertriglyceridemia (elevated levels of triglyceride-rich-lipoproteins); (8) mixed or diabetic dyslipidemia; (9) low HDL cholesterol; (10) high LDL cholesterol; (11) hyperapo-B lipoproteinemia; and (12) atherosclerosis. The term “subject” as used herein refers to an animal, preferably a mammal. In some embodiments, the subject is a veterinary, companion, farm, laboratory or zoological animal. In other embodiments, the subject is a human.

[0090] As used herein, the terms “treating”, “treatment”, “treat” and the like mean affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing, or reducing the severity of, a disease or associated symptom, and/or may be therapeutic in terms of a partial or complete cure of a disease.

[0091] By “effective amount” it is meant an amount sufficient that when administered to the patient an amount of the drug is provided to achieve an effect. Therefore, the “effective amount” may be a “therapeutically effective amount”. By “therapeutically effective amount” it is meant an amount sufficient that when administered to the subject an amount of drug is provided to treat the disease or a symptom of the disease.

[0092] The terms “administration of” and or “administering a” compound should be understood to mean providing a compound of the disclosure or a prodrug of a compound of the disclosure to a human or other mammal in need of treatment.

[0093] The term “patient” should be understood to mean a human or other mammal in need of treatment.

[0094] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating a disease or condition associated with GPR30 in a subject in need thereof by providing or administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, providing the one or more compounds or composition to the subject stimulates insulin secretion in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates blood glucose levels in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves glucose tolerance in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves insulin sensitivity in the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates the release of incretins in the subject. In some embodiments, the incretins released are glucagon-like peptide-1 (GLP-1). In some embodiments, the incretins are hormones that enhance insulin secretion in response to food intake. In some embodiments, providing the one or more compounds or composition to the subject promotes insulin release in response to food intake by the subject. In some embodiments, providing the one or more compounds or composition to the subject improves energy homeostatic in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates appetite in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats type-2 diabetes in the subject. In some embodiments, the metabolic disorder is Type-2 diabetes. In some embodiments, the metabolic disorder is obesity. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2. In some embodiments, the compound is a compound of Formula (I) or Formula (II).

[0095] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating a disease or condition associated with a GPR40 in a subject in

need thereof include providing or administering one or more compounds or a composition as described herein to the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates insulin secretion in the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates glucose metabolism in the subject. In some embodiments, providing the one or more compounds or composition to the subject provides glucose homeostasis in the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates the release of incretins in the subject. In some embodiments, the incretins released are glucagon-like peptide-1 (GLP-1). In some embodiments, the incretins are hormones that enhance insulin secretion in response to food intake. In some embodiments, providing the one or more compounds or composition to the subject promotes insulin release in response to food intake by the subject. In some embodiments, providing the one or more compounds or composition to the subject improves energy homeostatic in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates appetite in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats type-2 diabetes in the subject. In some embodiments, providing the one or more compounds or composition to the subject promotes lipid metabolism in the subject. In some embodiments, providing the one or more compounds or composition to the subject promote or inhibits inflammation in the subject. In some embodiments, the one or more compounds is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound of Formula (I) or Formula (II). In some embodiments, the compound is compound 180, 366, or 426.

[0096] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating a disease or condition associated with GPR119 in a subject in need thereof by providing or administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, providing the one or more compounds or composition to the subject stimulates insulin secretion in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates blood glucose levels in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves glucose tolerance in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves insulin sensitivity in the subject. In some embodiments, providing the one or more compounds or

composition to the subject modulates the release of incretins in the subject. In some embodiments, the incretins released are glucagon-like peptide-1 (GLP-1). In some embodiments, the incretins are hormones that enhance insulin secretion in response to food intake. In some embodiments, providing the one or more compounds or composition to the subject promotes insulin release in response to food intake by the subject. In some embodiments, providing the one or more compounds or composition to the subject improves energy homeostatic in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates appetite in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats type-2 diabetes in the subject. In some embodiments, the metabolic disorder is Type-2 diabetes. In some embodiments, the metabolic disorder is obesity. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2. In some embodiments, the compound is a compound of Formula (I) or Formula (II).

[0097] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating a disease or condition associated with GPR120 in a subject in need thereof by providing or administering a therapeutically effective amount of a compound or composition as described herein. In some embodiments, providing the one or more compounds or composition to the subject stimulates insulin secretion in the subject. In some embodiments, providing the one or more compounds or composition to the subject regulates blood glucose levels in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves glucose tolerance in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves insulin sensitivity in the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates the release of incretins in the subject. In some embodiments, the incretins released are glucagon-like peptide-1 (GLP-1). In some embodiments, the incretins are hormones that enhance insulin secretion in response to food intake. In some embodiments, providing the one or more compounds or composition to the subject promotes insulin release in response to food intake by the subject. In some embodiments, providing the one or more compounds or composition to the subject improves energy homeostatic in the subject. In some embodiments, providing the one or more

compounds or composition to the subject regulates appetite in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats type-2 diabetes in the subject. In some embodiments, the metabolic disorder is Type-2 diabetes. In some embodiments, the metabolic disorder is obesity. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2. In some embodiments, the compound is a compound of Formula (I) or Formula (II).

[0098] In some embodiments, methods and uses to modulate insulin in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2.

[0099] In some embodiments, methods and uses to produce favorable glucose homeostasis in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2.

[0100] In some embodiments, methods and uses to induce β -cell preservation in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, or 3. In some embodiments, the compound is a compound from Table 2.

[0101] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating a disease or condition associated with TGR5 in a subject in need thereof by providing or administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, providing the one or more compounds or composition to the subject activates bile acids in the subject. In some embodiments, providing the one or more compounds or composition to the subject improves insulin sensitivity in the subject. In some embodiments, providing the one or more compounds or composition to the subject modulates the release of incretins in the subject. In some embodiments, the incretins released are glucagon-like peptide-1 (GLP-1). In some embodiments, the incretins are hormones that enhance insulin secretion in response to food intake. In some embodiments, providing the one or more compounds or composition to the

subject promotes insulin release in response to food intake by the subject. In some embodiments, providing the one or more compounds or composition to the subject induces thermogenesis in the subject. In some embodiments, , providing the one or more compounds or composition to the subject increases in the conversion of thyroxine (T4) to the more active triiodothyronine (T3) in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats, reduces, prevents, or ameliorates a metabolic disorder in the subject. In some embodiments, providing the one or more compounds or composition to the subject treats, prevents, reduces, or ameliorates inflammation in the subject. In some embodiments, the metabolic disorder is Type-2 diabetes. In some embodiments, the metabolic disorder is obesity. In some embodiments, the compound is a compound from Table 1, 2, 3, or 4. In some embodiments, the compound is a compound from Table 3. In some embodiments, the compound is selected from Formula (I) or Formula (II).

[0102] In some embodiments, methods and uses for regulating TGR5 include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, or 4. In some embodiments, the compound is a compound from Table 3 or 4. In some embodiments, regulating TGR5 includes regulating one or more signaling pathways. In some embodiments, the one or more signaling pathways is selected from the group consisting of nuclear factor κ B (NF- κ B), AKT, and extracellular signal-regulated kinases (ERK).

[0103] In some embodiments, methods and uses for treating cancer in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. As used herein, the term “cancer” refers to all types of cancer, neoplasm, or malignant or benign tumors found in mammals, including leukemia, carcinomas and sarcomas. Exemplary cancers include acute myeloid leukemia (“AML”), chronic myelogenous leukemia (“CML”), and cancer of the brain, breast, pancreas, colon, liver, kidney, lung, non-small cell lung, melanoma, ovary, sarcoma, and prostate. Additional examples include, cervix cancers, stomach cancers, head & neck cancers, uterus cancers, mesothelioma, metastatic bone cancer, Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulinoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions,

testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, and neoplasms of the endocrine and exocrine pancreas. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, the cancer may be selected from, but is not limited to, colorectal cancer, gastric cancer, liver cancer, ovarian cancer, or breast cancer.

[0104] In some embodiments, methods and uses for treating hypertension in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the hypertension may be arterial hypertension. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0105] In some embodiments, methods and uses for treating fibrinolysis in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0106] In some embodiments, methods and uses for treating endothelial dysfunction in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0107] In some embodiments, methods and uses for treating polycystic ovary syndrome in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. As used herein, the term “polycystic ovary syndrome” or “PCOS” refers to endocrine disorders and associated diseases thereof characterized by menstrual irregularity. Clinical manifestations of PCOS include, but are not limited to, hormonal imbalance, hyperandrogenism, amenorrhea, acanthosis nigricans, acne, obesity, hirsutism, alopecia, and female infertility. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, the compound is a compound from Table 3.

[0108] In some embodiments, methods and uses for treating cardiovascular disease in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. As used herein, “cardiovascular disease” refers

to diseases associated with the heart, blood vessels or both. Cardiovascular diseases include, but are not limited to, coronary heart disease, cardiomyopathy, hypertensive heart disease, heart failure, cardiac dysrhythmias, inflammatory heart disease, peripheral arterial disease, cerebrovascular disease and inflammatory heart disease. In some embodiments, methods and uses for treating coronary heart disease in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, methods and uses for treating atherosclerosis in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, methods and uses for treating myocardial infarction in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0109] In some embodiments, methods and uses for treating atherothrombosis in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0110] In some embodiments, methods and uses for treating fatty liver disease in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0111] In some embodiments, methods and uses for treating hyperglycemia in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, methods and uses for treating insulin resistance in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, methods and uses for treating hyperinsulinemia in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as

described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0112] In some embodiments, methods and uses for treating dyslipidemia in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof. In some embodiments, methods and uses for treating hypertriglyceridemia in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0113] In some embodiments, methods and uses for reducing blood pressure in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0114] In some embodiments, methods and uses for treating decreasing glycated hemoglobin (HbA1c) in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0115] In some embodiments, methods and uses for reducing liver weight in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0116] In some embodiments, methods and uses for reducing kidney weight in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0117] In some embodiments, methods and uses for treating liver disease in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0118] In some embodiments, methods and uses for regulating energy homeostasis in a subject in need thereof include administering a therapeutically effective amount or a

compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0119] In some embodiments, methods and uses for regulating glucose metabolism in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0120] In some embodiments, methods and uses for regulating an inflammatory response in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0121] In some embodiments, methods and uses for regulating liver regulation in a subject in need thereof include administering a therapeutically effective amount or a compound or composition as described herein. In some embodiments, the compound is a compound from Table 1, 2, 3, 4 or a combination thereof.

[0122] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating obesity in a subject includes administering a therapeutically effective amount of a compound or composition as described herein. The term “obesity” as used herein is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). “Obesity” refers to a condition whereby an otherwise healthy subject has a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 , or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to 27 kg/m^2 . An “obese subject” is an otherwise healthy subject with a Body Mass Index (BMI) greater than or equal to 30 kg/m^2 or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m^2 . An overweight subject is a subject at risk of obesity. A “subject at risk of obesity” is an otherwise healthy subject with a BMI of 25 kg/m^2 to less than 30 kg/m^2 or a subject with at least one co-morbidity with a BMI of 25 kg/m^2 to less than 27 kg/m^2 .

[0123] The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, “obesity” refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity, that requires weight reduction or that would be improved by weight reduction, has a BMI greater

than or equal to 25 kg/m². In Asian countries, including Japan, an “obese subject” refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with a BMI greater than or equal to 25 kg/m². In Asia-Pacific, a “subject at risk of obesity” is a subject with a BMI of greater than 23 kg/m² to less than 25 kg/m².

[0124] As used herein, the term “obesity” is meant to encompass all of the above definitions of obesity.

[0125] Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes mellitus, non-insulin dependent diabetes mellitus—type 2, diabetes associated with obesity, impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hypertension associated with obesity, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodysnia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, and other obesity-related conditions.

[0126] Treatment of obesity and obesity-related disorders refers to the administration of the compounds of the present invention to reduce or maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in patients in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the

reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from weight loss.

[0127] Prevention of obesity and obesity-related disorders refers to the administration of the compounds of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the administration of the compounds of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

[0128] The obesity-related disorders herein are associated with, caused by, or result from obesity. Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g., children with acute lymphoblastic leukemia. Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux,

respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricemia, lower back pain, gallbladder disease, gout, and kidney cancer. The compounds of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

[0129] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating metabolic syndrome in a subject includes administering a therapeutically effective amount of a compound or composition as described herein. The term “metabolic syndrome”, also known as syndrome X, is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670. E. S. Ford et al., JAMA, vol. 287 (3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the following disorders: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-III. Treatment of metabolic syndrome refers to the administration of the combinations of the present invention to a subject with metabolic syndrome. Prevention of metabolic syndrome refers to the administration of the combinations of the present invention to a subject with two of the disorders that define metabolic syndrome. A subject with two of the disorders that define metabolic syndrome is a subject that has developed two of the disorders that define metabolic syndrome, but has not yet developed three or more of the disorders that define metabolic syndrome.

[0130] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating hypercholesterolemia in a subject includes administering a therapeutically effective amount of a compound or composition as described herein.

[0131] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating type-2 diabetes in a subject includes administering a therapeutically effective amount of a compound or composition as described herein. The term “diabetes,” as used herein, includes both insulin-dependent diabetes mellitus (i.e., IDDM, also known as type 1 diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also

known as Type 2 diabetes). Type 1 diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type 2 diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type 2 diabetics are also obese. The compositions of the present invention may be useful for treating both Type 1 and Type 2 diabetes. The term “diabetes associated with obesity” refers to diabetes caused by obesity or resulting from obesity.

[0132] Diabetes is characterized by a fasting plasma glucose level of greater than or equal to 126 mg/dl. A diabetic subject has a fasting plasma glucose level of greater than or equal to 126 mg/dl. A pre diabetic subject is someone suffering from prediabetes. Prediabetes is characterized by an impaired fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl; or impaired glucose tolerance; or insulin resistance. A prediabetic subject is a subject with impaired fasting glucose (a fasting plasma glucose (FPG) level of greater than or equal to 110 mg/dl and less than 126 mg/dl); or impaired glucose tolerance (a 2 hour plasma glucose level of ≥ 140 mg/dl and < 200 mg/dl); or insulin resistance, resulting in an increased risk of developing diabetes.

[0133] Treatment of diabetes mellitus refers to the administration of a compound or combination of the present invention to treat a diabetic subject. One outcome of treatment may be decreasing the glucose level in a subject with elevated glucose levels. Another outcome of treatment may be decreasing insulin levels in a subject with elevated insulin levels. Another outcome of treatment may be decreasing plasma triglycerides in a subject with elevated plasma triglycerides. Another outcome of treatment is decreasing LDL cholesterol in a subject with high LDL cholesterol levels. Another outcome of treatment may be increasing HDL cholesterol in a subject with low HDL cholesterol levels. Another outcome of treatment is increasing insulin sensitivity. Another outcome of treatment may be enhancing glucose tolerance in a subject with glucose intolerance. Yet another outcome of treatment may be decreasing insulin resistance in a subject with increased insulin resistance or elevated levels of insulin. Prevention of diabetes mellitus, in particular diabetes associated with obesity, refers to the administration of a compound or combination of the present invention to prevent the onset of diabetes in a

subject in need thereof. A subject in need of preventing diabetes is a prediabetic subject that is overweight or obese.

[0134] The term “diabetes related disorders” should be understood to mean disorders that are associated with, caused by, or result from diabetes. Examples of diabetes related disorders include retinal damage, kidney disease, and nerve damage.

[0135] In some embodiments, the compound or composition of the disclosure may also have utility in improving or restoring β -cell function, so that they may be useful in treating type-1 diabetes or in delaying or preventing a patient with type-2 diabetes from needing insulin therapy. In some embodiments, the disclosure also includes compounds, including pharmaceutically acceptable salts of the compounds, or compositions as described herein useful in treating insulin resistance, type 2 diabetes, hyperglycemia, and dyslipidemia that is associated with type 2 diabetes and insulin resistance. In some embodiments, methods and uses for lowering glucose and lipids in diabetic patients and in non-diabetic patients who have impaired glucose tolerance and/or are in pre-diabetic condition. In some embodiments, the compounds or compositions of the disclosure may ameliorate hyperinsulinemia, which often occurs in diabetic or pre-diabetic patients, by modulating the swings in the level of serum glucose that often occurs in these patients. In some embodiments, the compounds and compositions of the disclosure may also be effective in treating or reducing insulin resistance. In some embodiments, the compounds and composition of the disclosure may be effective in treating or preventing gestational diabetes.

[0136] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating atherosclerosis in a subject includes administering a therapeutically effective amount of a compound or composition as described herein. The term “atherosclerosis” as used herein encompasses vascular diseases and conditions that are recognized and understood by physicians practicing in the relevant fields of medicine. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all clinical manifestations of atherosclerosis and are therefore encompassed by the terms “atherosclerosis” and “atherosclerotic disease.” The combination comprised of a therapeutically effective amount of a GPR40 agonist in combination with a therapeutically effective amount of an anti-hypertensive agent may be administered to prevent or reduce the

risk of occurrence, or recurrence where the potential exists, of a coronary heart disease event, a cerebrovascular event, or intermittent claudication. Coronary heart disease events are intended to include CHD death, myocardial infarction (i.e., a heart attack), and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease. The term “atherosclerotic disease event” as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that persons who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists. The term “atherosclerosis related disorders” should be understood to mean disorders associated with, caused by, or resulting from atherosclerosis.

[0137] In some embodiments, methods and uses for treating, preventing, reducing, modulating, or ameliorating hypertension in a subject includes administering a therapeutically effective amount of a compound or composition as described herein. The term “hypertension” as used herein includes essential, or primary, hypertension wherein the cause is not known or where hypertension is due to greater than one cause, such as changes in both the heart and blood vessels; and secondary hypertension wherein the cause is known. Causes of secondary hypertension include, but are not limited to obesity; kidney disease; hormonal disorders; use of certain drugs, such as oral contraceptives, corticosteroids, cyclosporin, and the like. The term “hypertension” encompasses high blood pressure, in which both the systolic and diastolic pressure levels are elevated (≥ 140 mmHg/ ≥ 90 mmHg), and isolated systolic hypertension, in which only the systolic pressure is elevated to greater than or equal to 140 mm Hg, while the diastolic pressure is less than 90 mm Hg. Normal blood pressure may be defined as less than 120 mmHg systolic and less than 80 mmHg diastolic. A hypertensive subject is a subject with hypertension. A pre-hypertensive subject is a subject with a blood pressure that is between 120 mmHg over 80 mmHg and 139 mmHg over 89 mmHg. One outcome of treatment is decreasing blood pressure in a subject with high blood pressure. Treatment of hypertension refers to the administration of the compounds and combinations of the present invention to treat hypertension in a hypertensive subject. Treatment of hypertension-related disorder refers to the administration of a compound or combination of the present invention to treat the

hypertension-related disorder. Prevention of hypertension, or a hypertension related disorder, refers to the administration of the combinations of the present invention to a pre-hypertensive subject to prevent the onset of hypertension or a hypertension related disorder. The hypertension-related disorders herein are associated with, caused by, or result from hypertension. Examples of hypertension-related disorders include, but are not limited to: heart disease, heart failure, heart attack, kidney failure, and stroke.

[0138] In some embodiments, methods and uses for treating or preventing lipid disorder in a subject include providing a therapeutically effective amount of a compound or composition as described herein. In some embodiments, methods and uses for treating or preventing dyslipidemias in a subject include providing a therapeutically effective amount of a compound or composition as described herein. Dyslipidemias and lipid disorders are disorders of lipid metabolism including various conditions characterized by abnormal concentrations of one or more lipids (i.e. cholesterol and triglycerides), and/or apolipoproteins (i.e., apolipoproteins A, B, C and E), and/or lipoproteins (i.e., the macromolecular complexes formed by the lipid and the apolipoprotein that allow lipids to circulate in blood, such as LDL, VLDL and IDL). Hyperlipidemia is associated with abnormally high levels of lipids, LDL and VLDL cholesterol, and/or triglycerides. Treatment of dyslipidemia refers to the administration of the combinations of the present invention to a dyslipidemic subject. Prevention of dyslipidemia refers to the administration of the combinations of the present invention to a pre-dyslipidemic subject. A pre-dyslipidemic subject is a subject with higher than normal lipid levels, that is not yet dyslipidemic. The terms “dyslipidemia related disorders” and “lipid disorder related disorders” should be understood to mean disorders associated with, caused by, or resulting from dyslipidemia or lipid disorders. Examples of dyslipidemia related disorder and lipid disorder related disorders include, but are not limited to: hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high density lipoprotein (HDL) levels, high plasma low density lipoprotein (LDL) levels, atherosclerosis and its sequelae, coronary artery or carotid artery disease, heart attack, and stroke.

Administration and Dose Ranges

[0139] Any suitable route of administration may be employed for providing a mammal, especially a human, with a therapeutically effective dose of a compound of the

present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of the present disclosure are administered orally.

[0140] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the patient undergoing therapy.

[0141] The compounds of this invention may be used in pharmaceutical compositions comprising (a) the compound(s) or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier. The compounds of this invention may be used in pharmaceutical compositions that include one or more other active pharmaceutical ingredients. The compounds of this invention may also be used in pharmaceutical compositions in which the compound of the present invention or a pharmaceutically acceptable salt thereof is the only active ingredient.

[0142] The term “composition,” as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

EXAMPLES

[0143] The following non-limiting examples are provided to further illustrate the present disclosure.

Example 1

[0144] An *in vitro* validation and screening data for GPR40 extracts and purified compounds was performed.

[0145] Without wishing to be bound by theory, it is believed that GPR40 agonism leads to beneficial metabolic outcomes via actions in the pancreas and the gut. Partial agonists (~50% receptor stimulation) do not trigger GLP-1 secretion but have beneficial glycemic outcomes by engaging the pancreas to boost glucose-dependent insulin secretion. Full agonists (~100% receptor stimulation) engage the pancreas but also trigger GLP-1 secretion. In contrast, TGR5 agonism leads to robust GLP-1 secretion but small molecule therapeutics are challenging so a safe bioactive approach would be desirable. As for GPR119, while its activation boosts the effects of other substances that induce GLP-1 secretion, it is considered to have a relatively weak effect when used alone.

[0146] An *in vitro* assay was conducted as described in FIG. 1. The assay involved cAMP and IP1 (HTRF). The assay showed no interference from the plant extract from the samples tested. In preliminary tests using a pilot plate, no positive signals were detected in the absence of cells. While beta-arrestin assays were also set up, this signaling pathway was ultimately deemed less relevant to the desired pharmacological effects. The process for these experiments is detailed in Figure 2, and the specific HTRF IP1 assay procedure is depicted in FIG 3. For all assays, the positive control was full GPR40 agonist (K-003/AM-5262; CAS No. 1222088-90-5), with additional reference assays for a partial GPR40 agonist (K-103/TAK-875; CAS No. 1000413-72-8). Each sample was tested in triplicate.

[0147] The compounds showing the most activity were chosen for further testing in a counter-screening plate. The criteria for plate controls were an assay window > 2-fold with a Z' > 0.5. An issue was identified because the positive control lacked an over-expressed receptor, leading to the inclusion of two plant extracts known for significant 'off-target' effects. The reduction in signal caused by the extract in this portion of the experiments was not as marked. The outcomes of this phase of the trials are illustrated in FIG. 4. Two pure compounds, 180 and 366, emerged as strong hits. The two hits were well optimized partial agonists and were above the 50% threshold of a typical partial agonist. These finding are shown in FIG. 5. A summary of the results is provided in Table 5.

Table 5

Pure Compound ID	% Activation	Standard Deviation
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	(Avg. of Triplicates)	
366	60.6	2.7
180	112.9	1.1

Example 2

[0148] An hGPR40 IP1 counter screen assay on plant extracts and pure compounds was performed. The plate controls were an assay window > 2-fold, $Z' > 0.5$, and K-003 did not show any signal in the parental CHO line. All samples with >50% activity were run in the counter screen. The results are described in FIG. 6. The pure compounds, 180 and 366, boxed in FIG. 7, are the hits found in the IP1 assay. Given the assay noise, they do not appear to show considerable off-target activity. The majority of plant extracts with high (>50%) hGPR40 activity also showed off-target activity. 78% (66/85 extracts run) have off-target activity >20%. Only four extracts with > 50% hGPR40 activity have interference $\leq 20\%$. The pure compounds, 180 and 366, did not show substantial signal interference as outlined in Table 6.

Table 6

Pure Compound ID	% Off-Target	% Activity
180	15.5	112.9
366	-41.5	60.6

[0149] Interference values for plant extracts run on two different days were generally reproducible.

Example 3

[0150] An *in vitro* assay was performed to screen TGR5 pure compounds. The percentage of activation values were calculated by normalizing samples' HTRF signals to 100% HTRF signal was equal to 100 nM K-155 (avg. of 14 tech. replicates) and 0% HTRF signal was equal to DMSO (avg. of 14 tech. replicates). The TGR5 controls of DMSO and K-155 to HTRF ratio are illustrated in FIG. 8. The cut off was set to >50% activity and 7/80 hits were found. All compounds were counter screened in TGR5 null cells. The activity is described in Table 7.

Table 7

Pure Compound ID	% Activation (Avg. of Triplicates)	Standard Deviation
705	82.2	1.1
711	96.9	1.0
721	75.6	2.5
725	89.8	0.8
727	79.6	2.2
734	61.9	2.7
738	66.1	1.3

[0151] Compounds were screened and positive controls were formed. FIG. 9 illustrates the results for the TGR5 pure compounds in cAMP screen. Compounds 711, 725, and 727 showed highest % max activity and μ M potency.

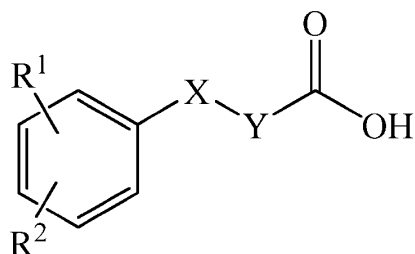
Example 4

[0152] This study focused on evaluating GPR40 pure compounds through dose-response tests, building on two initial hits discovered from the Example 1. GPR40 compounds qualified for further examination if they met either the following criteria in the previous IP1 assay: >50% hGPR40 activity or 1/3 technical replicates showing $\geq 20\%$ GPR40 activity. The results of the control screen are depicted in FIG. 10 where K-003 EC_{50} (full) = 0.5 nM, K-13 EC_{50} (partial) = 3.4 nM, the assay window = 2.5, and $Z' = 0.48$. The GPR 40 pure compounds, 180 and 366, were tested in dose response and were tested against the other hits. The results are described in the FIG. 11. The screen confirmed compound 180 had a high % max and ~ 1 μ M potency and compound 366 had a high % max and a ~ 5 μ M potency. It was also found that compound 19 had a low % max but dose response initiation.

[0153] Accordingly, some aspects described herein relate to the following numbered alternatives:

[0154] 1. An oral composition, the oral compositions comprising: a therapeutically effective amount of a compound, wherein the compound is an agonist of a G-protein coupled receptor, or a salt thereof; and one or more carriers or excipients, wherein, the agonist is capable of treating, reducing, modulating, or ameliorating a disease or condition mediated by the G-protein coupled receptor.

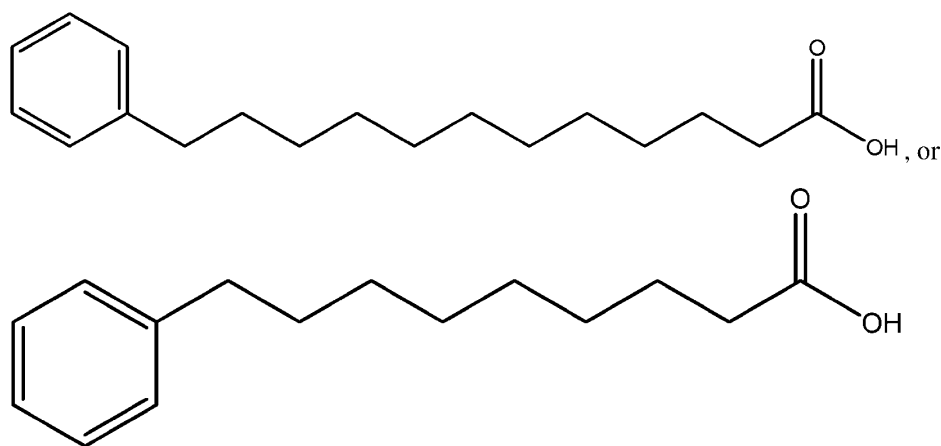
[0155] 2. The oral composition of alternative 1, wherein the compound is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein, R^1 and R^2 are each independently selected from hydrogen, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted amino, optionally substituted C_1 - C_6 -alkyl, and optionally substituted $-O$ - C_1 - C_6 -alkyl; X and Y are each independently selected from an optionally substituted C_1 - C_{18} alkyl, an optionally substituted C_1 - C_{18} alkenyl, and optionally substituted $-O$ - C_1 - C_{18} -alkyl.

[0156] 3. The oral composition of alternative 2, wherein the compound of Formula (I) is selected from



[0157] 4. The oral composition of any one of alternatives 1 to 3, wherein the compound is a GPR40 agonist.

[0158] 5. The oral composition of any one of alternatives 1 to 4, wherein the compound is a GPR119 agonist.

[0159] 6. The oral composition of any one of alternatives 1 to 5, wherein the compound is a TGR5 agonist.

[0160] 7. The oral composition of any one of alternatives 1 to 6, wherein the oral composition is formulated as a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition.

[0161] 8. The oral composition of any one of alternatives 1 to 7, wherein the oral composition is in a dosage form configured as one of a soft-gel capsule, a hard capsule, gummy, functional beverage, functional food, liquid, powder, and a tablet.

[0162] 9. The oral composition of any one of alternatives 1 to 8, wherein the oral composition comprises 1.0% to 99% w/w of a plant extract.

[0163] 10. The oral composition of any one of alternatives 1 to 9, wherein the oral composition further comprises a preservative.

[0164] 11. The oral composition of any one of alternatives 1 to 10, wherein the oral composition further comprises a sweetener.

[0165] 12. The oral composition of any one of alternatives 1 to 11, wherein the oral composition further comprises a coloring agent.

[0166] 13. The oral composition of any one of alternatives 1 to 12, wherein the oral composition further comprises an additive.

[0167] 14. The oral composition of any one of alternatives 1 to 13, wherein the oral composition further comprises a flavoring agent.

[0168] 15. The oral composition of any one of alternatives 1 to 14, wherein the compound is a compound of Table 1, Table 2, or Table 3.

[0169] 16. A method of treating, preventing, reducing, modulating, or ameliorating a disease or disorder associated with GPR40, GPR 119, or TGR5 in a subject in need thereof, the method comprising: administering a therapeutically effective amount of a composition comprising the oral composition of any one of alternatives 1 to 15.

[0170] 17. The method of alternative 16, wherein the composition activates GPR40.

[0171] 18. The method of alternative 16 or 17, wherein the composition is provided with food to induce activation of GPR40.

[0172] 19. The method of any one of alternatives 16 to 18, wherein activation of GPR40 controls appetite and glucose metabolism in the subject.

[0173] 20. A method of treating, preventing, reducing, modulating, or ameliorating obesity in a subject in need thereof, the method comprising administering a therapeutically effective amount of a composition comprising the oral composition of any one of alternatives 1 to 15.

[0174] 21. The method of alternative 20, wherein administering the composition to the subject provides sustained weight management.

[0175] 22. The method of alternative 20 or 21, wherein administering the composition to the subject provides fat loss.

[0176] 23. The method of any one of alternatives 20 to 22, wherein administering the composition to the subject provides glucose level normalization.

[0177] 24. The method of any one of alternatives 20 to 23, wherein the subject has pre-diabetes.

[0178] 25. The method of any one of alternatives 20 to 24, wherein administering the composition provides improvement in metabolic rate.

[0179] 26. The method of any one of alternatives 20 to 25, wherein administering the composition to the subject provides an improvement in a waist-to-hip ratio in the subject.

[0180] 27. The method of any one of alternatives 20 to 26, wherein administering the composition to the subject provides improvement in insulin sensitivity in the subject.

[0181] 28. The method of any one of alternatives 20 to 27, wherein administering the composition to the subject improves one or more biomarkers associated with inflammation and obesity.

[0182] 29. The method of any one of alternatives 20 to 28, wherein administering the composition provides a reduction in body fat mass.

[0183] 30. The method of any one of alternatives 20 to 29, wherein the body fat mass reduction is from at least 5% to about 15% from baseline measurements, as measured in kilograms (kg) or pounds (lbs).

[0184] 31. The method of any one of alternatives 20 to 29, further comprising maintaining fat loss within a range of $\pm 3\%$ to $\pm 10\%$ of the achieved reduction in body fat mass.

[0185] 32. A method of treating, preventing, reducing, modulating, or ameliorating diabetes in a subject in need thereof, the method comprising providing a therapeutically effective amount of a composition comprising the oral composition of any one of alternatives 1 to 15.

[0186] 33. The method of alternative 32, wherein the diabetes is type-2 diabetes.

[0187] 34. The method of alternative 32 or 33, wherein providing to the subject the composition provides glucose level normalization followed by fat loss benefits.

[0188] 35. The method of any one of alternative 32 to 34, wherein providing to the subject a normal blood glucose regulation followed by fat loss benefits.

[0189] 36. The method of any one of alternative 32 to 35, wherein providing the composition provides improvement in metabolic rate.

[0190] 37. The method of any one of alternative 32 to 36, wherein providing the composition to a subject provides an improvement in a waist-to-hip ratio in the subject.

[0191] 38. The method of any one of alternative 32 to 37, wherein providing the composition to the subject provides improvement in insulin sensitivity in the subject.

[0192] 39. The method of any one of alternative 32 to 38, wherein providing the composition to the subject improves one or more biomarkers associated with inflammation and obesity.

[0193] 40. The method of any one of alternative 32 to 39, wherein providing the composition improves insulin secretion and appetite regulation.

[0194] 41. A method of treating, preventing, reducing, modulating, or ameliorating metabolic syndrome in a subject in need thereof, the method comprising providing a therapeutically effective amount of a composition comprising the oral composition of any one of alternatives 1 to 15.

[0195] 42. The method of alternative 41, wherein metabolic syndrome is selected from obesity, insulin resistance, hyperlipidemia, cardiovascular disease, fatty liver, cholesterol, oxidative stress, and hypertension.

[0196] 43. The method of alternative 41 or 42, wherein providing the composition reduces body weight of the subject or alleviates weight gain.

[0197] 44. The method of any one of alternatives 41 to 43, wherein providing the composition enhances insulin secretion in the subject.

[0198] 45. The method of any one of alternatives 41 to 44, wherein providing the composition enhances glucose metabolism.

[0199] 46. A method of treating, preventing, reducing, modulating, or ameliorating a lipid disorder in a subject in need thereof, the method comprising providing a therapeutically effective amount of a composition comprising the oral composition of any one of alternatives 1 to 15.

[0200] 47. The method of alternative 46, wherein providing the composition enhances insulin secretion and improves fatty acid metabolism.

[0201] 48. The method of alternative 46 or 47, wherein providing the composition improves dyslipidemia the subject.

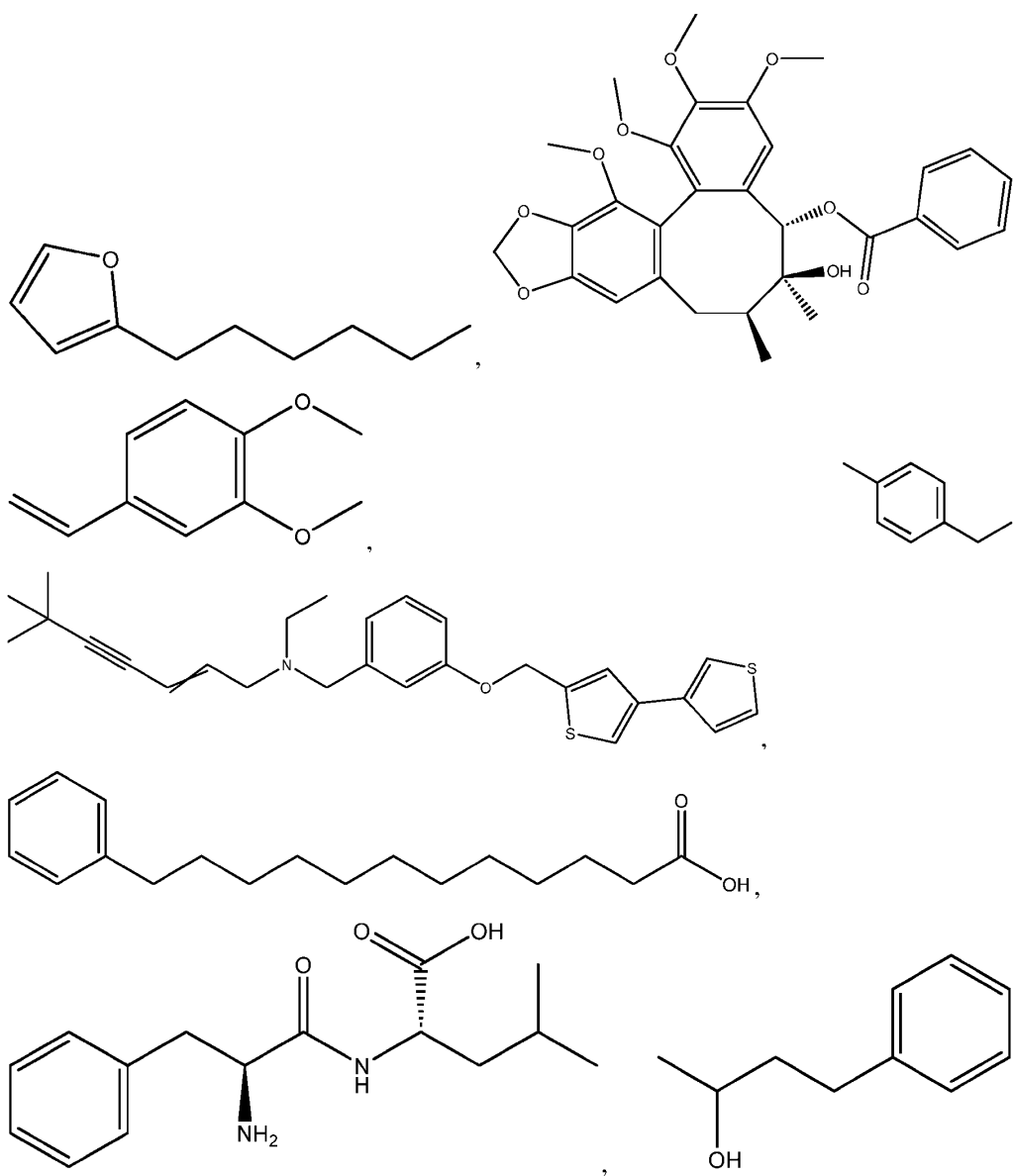
[0202] 49. The method of any one of alternatives 46 to 48, wherein providing the composition improves NAFLD in the subject.

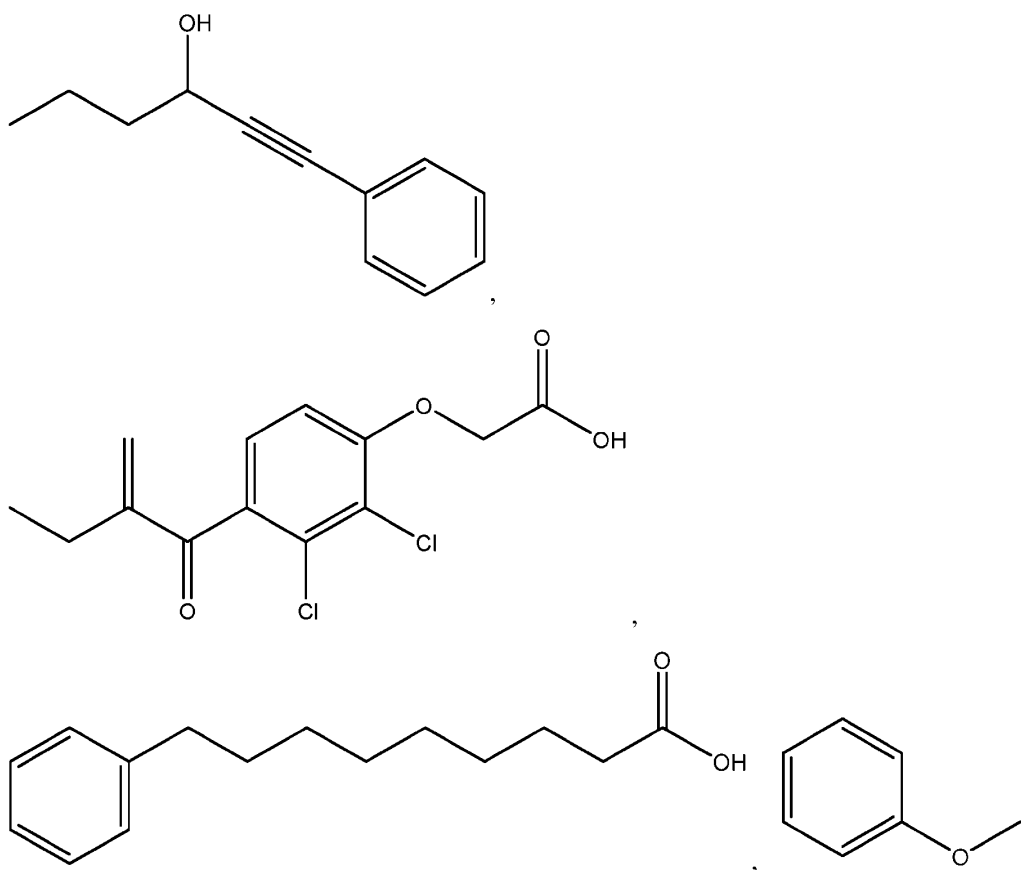
[0203] 50. A compound, wherein the compound is selected from Table 1, Table 2, Table 3, and Table 4.

[0204] 51. The compound of alternative 50, wherein the compound is substantially pure.

[0205] 52. The compound of alternative 50 or 51, wherein the compound is 90% pure, by weight, excluding solvent molecules.

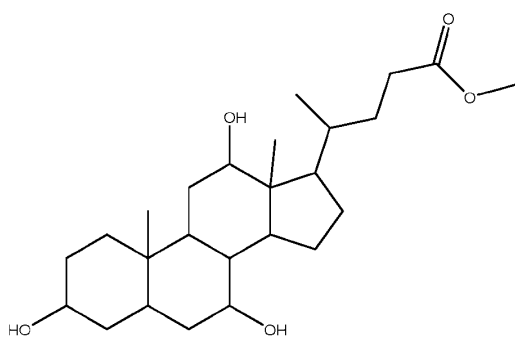
[0206] 53. Uses of a composition for treating, reducing, preventing, ameliorating, or modulating a disease or condition associated with GPR40, the composition comprising a compound comprising:



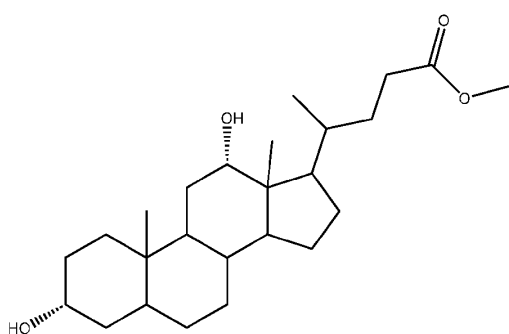


or a combination thereof.

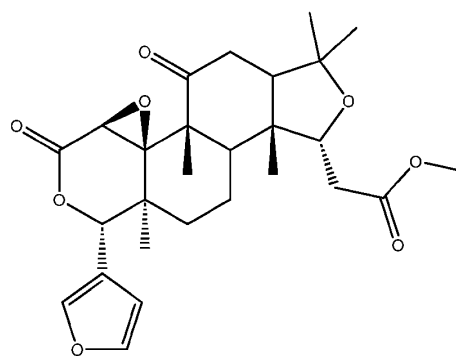
[0207] 54. Uses of a composition for treating, reducing, preventing, ameliorating, or modulating a disease or condition associated with TGR5, the composition comprising a compound comprising



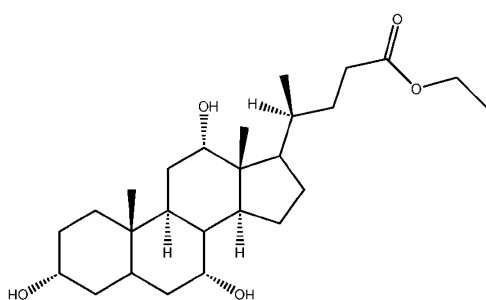
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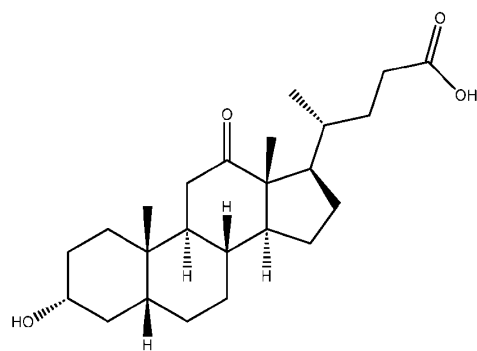
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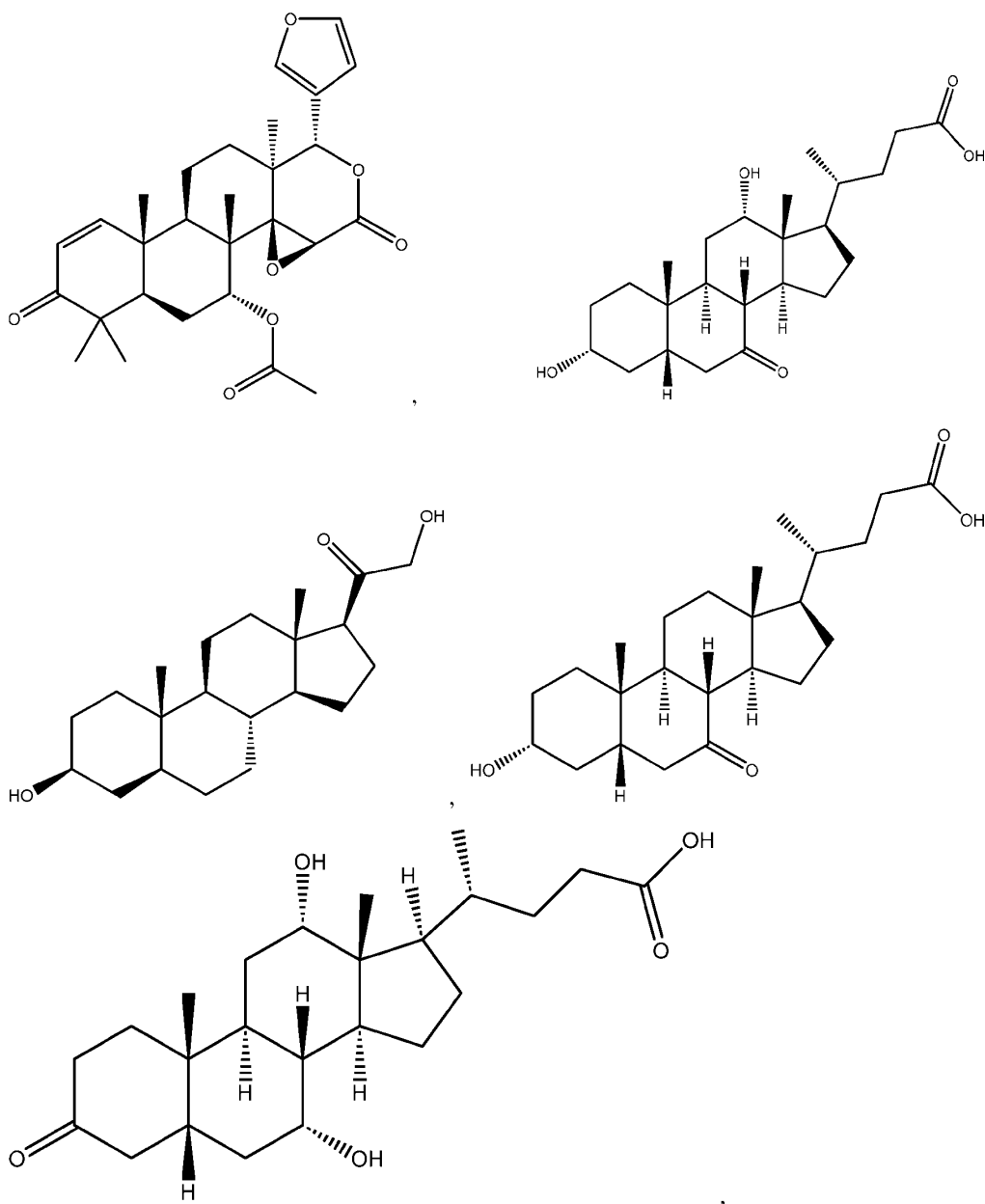
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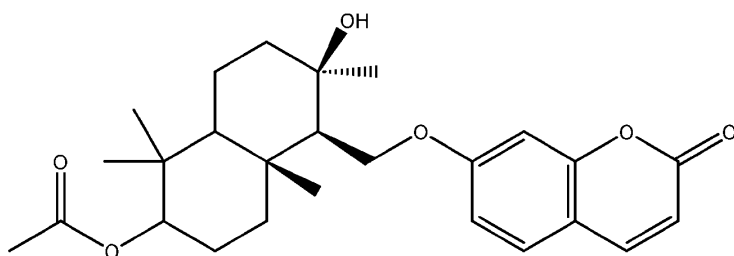
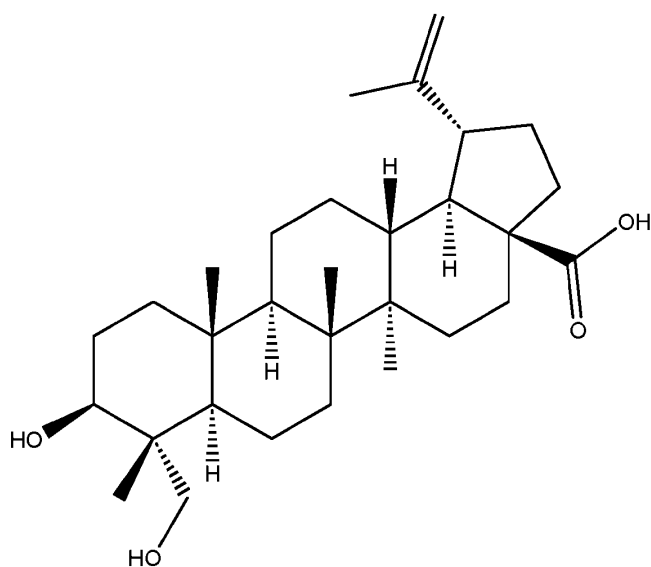
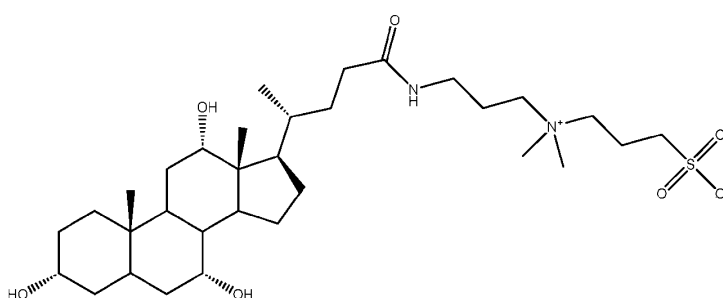
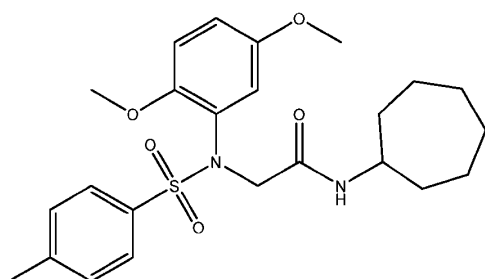


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, or a combination thereof.

[0208] The above description presents the best mode contemplated for carrying out the present invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use this invention. This invention is, however, susceptible to modifications and alternate constructions from that discussed above that are fully equivalent. Consequently, this invention is not limited to the particular embodiments disclosed. On the contrary, this invention covers all modifications and alternate constructions coming within the spirit and scope of the invention as generally expressed by the following claims, which particularly point out and distinctly claim the subject matter of the invention. While the disclosure has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive.

[0209] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0210] Unless otherwise defined, all terms (including technical and scientific terms) are to be given their ordinary and customary meaning to a person of ordinary skill in the art, and are not to be limited to a special or customized meaning unless expressly so defined herein. It should be noted that the use of particular terminology when describing certain features or aspects of the disclosure should not be taken to imply that the terminology is being re-defined herein to be restricted to include any specific characteristics of the features or aspects of the disclosure with which that terminology is associated. Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; adjectives such as 'known', 'normal', 'standard', and

terms of similar meaning should not be construed as limiting the item described to a given time period or to an item available as of a given time, but instead should be read to encompass known, normal, or standard technologies that may be available or known now or at any time in the future; and use of terms like ‘preferably,’ ‘preferred,’ ‘desired,’ or ‘desirable,’ and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the invention. Likewise, a group of items linked with the conjunction ‘and’ should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as ‘and/or’ unless expressly stated otherwise. Similarly, a group of items linked with the conjunction ‘or’ should not be read as requiring mutual exclusivity among that group, but rather should be read as ‘and/or’ unless expressly stated otherwise.

[0211] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0212] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article ‘a’ or ‘an’ does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0213] It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases ‘at least one’ and ‘one or more’ to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the

indefinite articles ‘a’ or ‘an’ limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases ‘one or more’ or ‘at least one’ and indefinite articles such as ‘a’ or ‘an’ (e.g., ‘a’ and/or ‘an’ should typically be interpreted to mean ‘at least one’ or ‘one or more’); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (e.g., the bare recitation of ‘two recitations,’ without other modifiers, typically means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to ‘at least one of A, B, and C, etc.’ is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., ‘a system having at least one of A, B, and C’ would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to ‘at least one of A, B, or C, etc.’ is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., ‘a system having at least one of A, B, or C’ would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase ‘A or B’ will be understood to include the possibilities of ‘A’ or ‘B’ or ‘A and B.’

[0214] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term ‘about.’ Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0215] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention to the specific embodiments and examples described herein, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

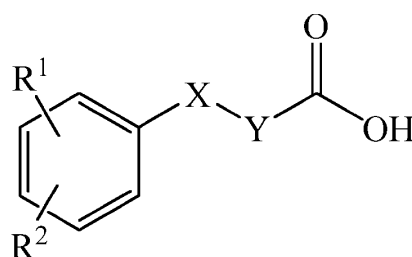
WHAT IS CLAIMED IS:

1. An oral composition, the oral compositions comprising:

a therapeutically effective amount of one or more compounds, or a salt thereof, wherein the one or more compounds is an agonist of a G-protein coupled receptor; and one or more carriers or excipients,

wherein, the agonist is capable of treating, reducing, modulating, or ameliorating a disease or condition mediated by the G-protein coupled receptor.

2. The oral composition of claim 1, wherein the one or more compounds is a compound of represented by Formula (I):



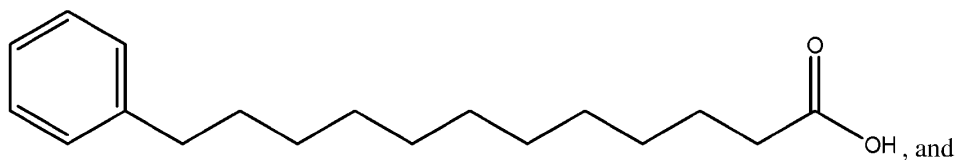
Formula (I)

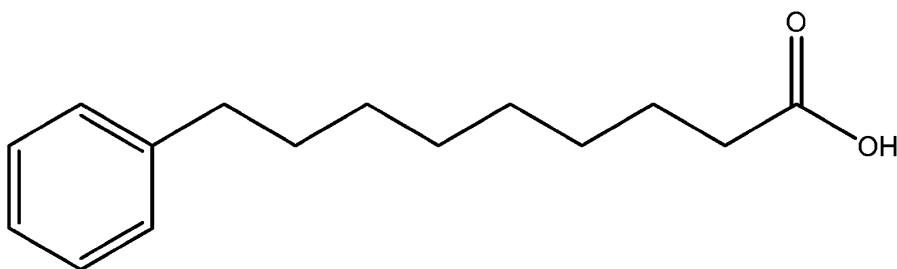
or a salt thereof, wherein,

R^1 and R^2 are each independently selected from hydrogen, deuterium, hydroxyl, halogen, cyano, nitro, optionally substituted amino, optionally substituted C_1 - C_6 -alkyl, and optionally substituted $-O$ - C_1 - C_6 -alkyl;

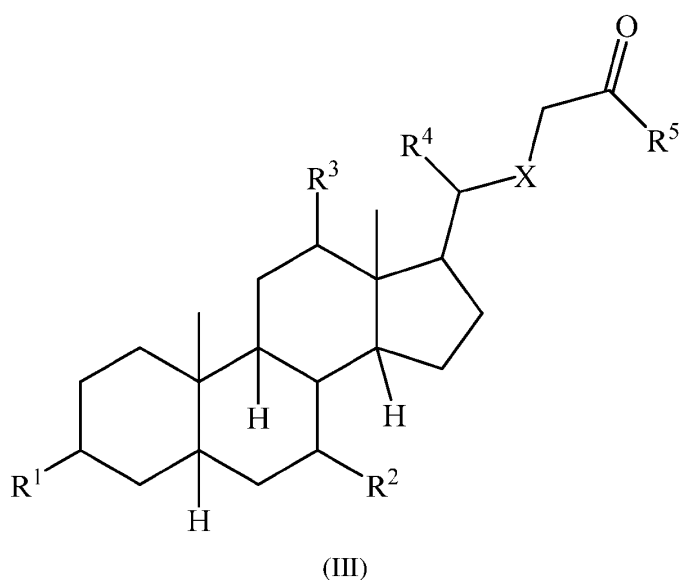
X and Y are each independently selected from an optionally substituted C_1 - C_{18} alkyl, an optionally substituted C_1 - C_{18} alkenyl, and optionally substituted $-O$ - C_1 - C_{18} -alkyl.

3. The oral composition of claim 2, wherein the one or more compounds of Formula (I) is selected from





4. The oral composition of claim 1, wherein the one or more compounds is a compound represented by Formula (III):



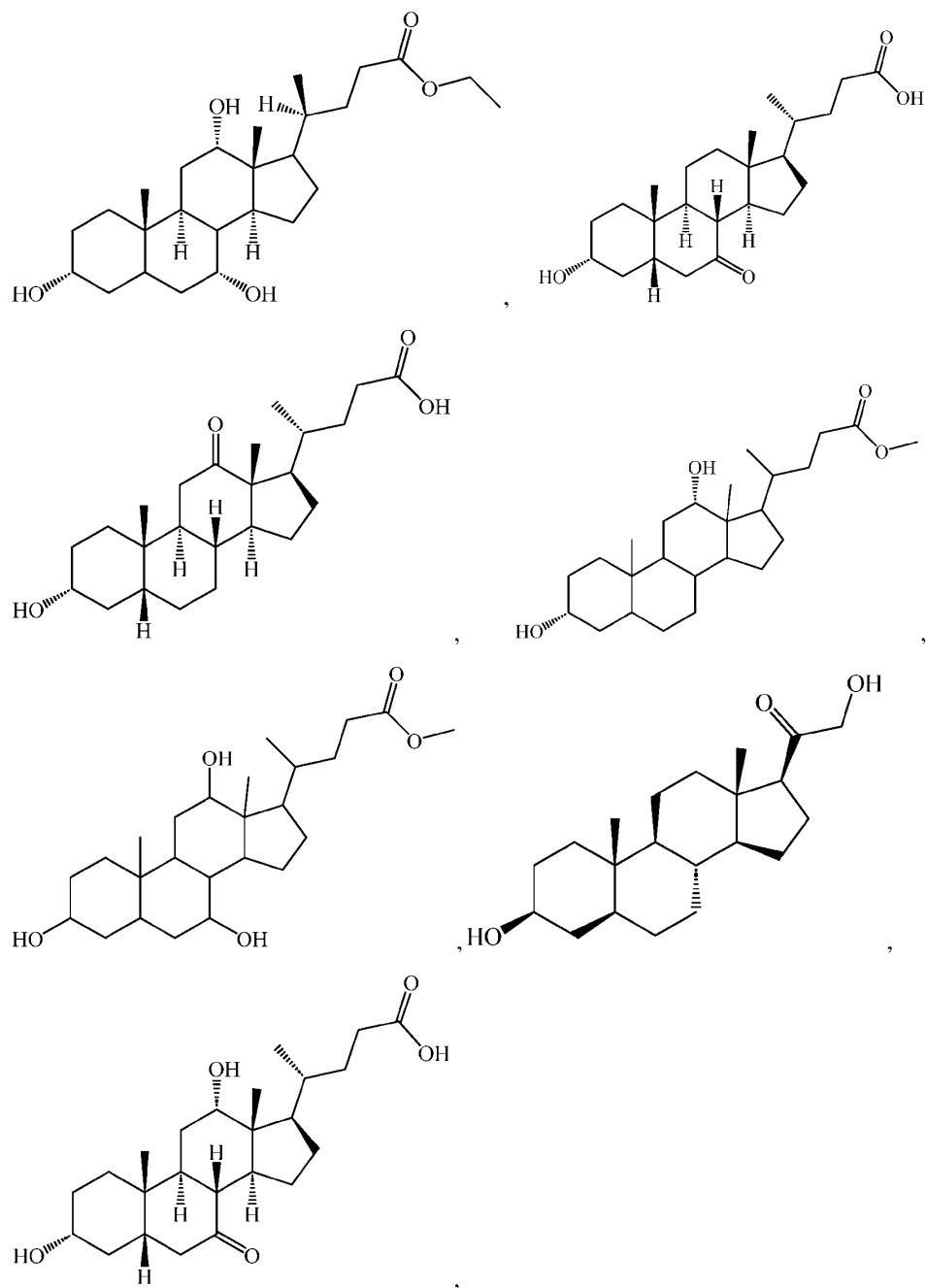
or a salt thereof,

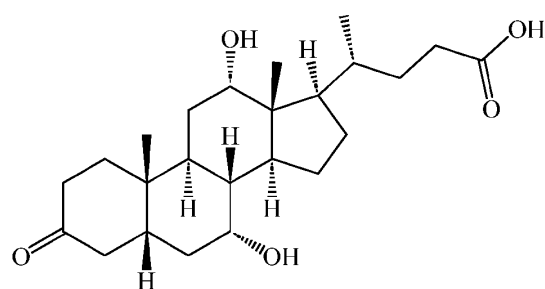
wherein,

R^1 , R^2 , R^3 , R^4 , and R^5 are each independently selected from hydrogen, deuterium, hydroxyl, keto, halogen, optionally substituted amino, optionally substituted C-amido, optionally substituted ester, optionally substituted C_1 to C_6 alkyl, optionally substituted C_1 to C_6 alkoxy, optionally substituted C_3 to C_8 cycloalkyl, optionally substituted C_6 to C_{10} aryl, optionally substituted C_3 to C_8 heterocyclyl, and optionally substituted C_3 to C_8 heterocyclylalkyl; and

X is a bond, $-CH_2-$, $-CH_2CH_2-$, and $-NH-$.

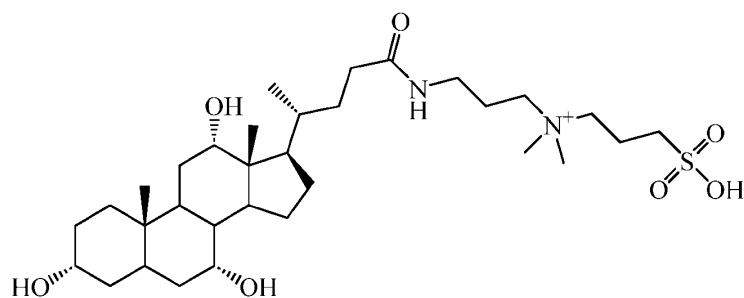
5. The oral composition of claim 4, wherein the compound of Formula III is selected from the following:





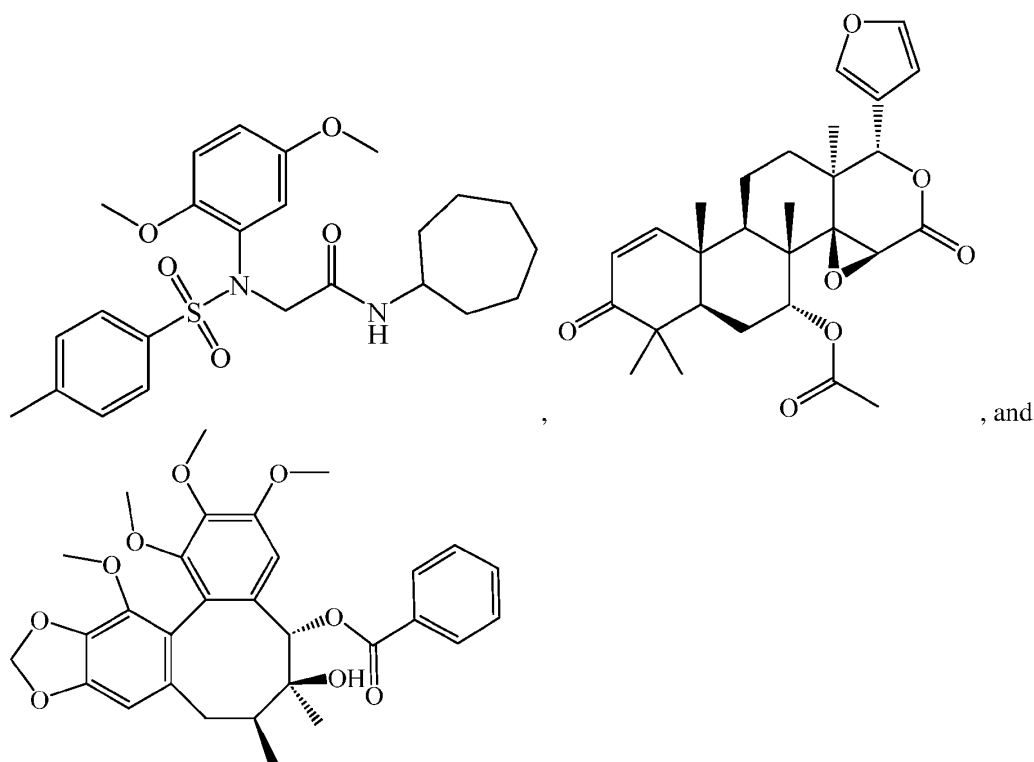
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and



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6. The oral composition of claim 1, wherein the one or more compounds is selected from the group consisting of:



7. The oral composition of claim 2, wherein the compound is a GPR40 agonist.

8. The oral composition of claim 2, wherein the compound is a GPR119 agonist.

9. The oral composition of claim 4, wherein the compound is a TGR5 agonist.

10. The oral composition of claim 2, wherein the oral composition is formulated as a dietary supplement, food ingredient or additive, a medical food, nutraceutical or pharmaceutical composition.

11. The oral composition of claim 2, wherein the oral composition is in a dosage form configured as one of a soft-gel capsule, a hard capsule, gummy, functional beverage, functional food, liquid, powder, and a tablet.

12. The oral composition of claim 1, wherein the oral composition comprises 1.0% to 99% w/w of a plant extract.

13. The oral composition of claim 2, wherein the oral composition further comprises a preservative.

14. The oral composition of claim 2, wherein the oral composition further comprises a sweetener.

15. The oral composition of claim 2, wherein the oral composition further comprises a coloring agent.

16. The oral composition of claim 2, wherein the oral composition further comprises an additive.

17. The oral composition of claim 2, wherein the oral composition further comprises a flavoring agent.

18. The oral composition of claim 1, wherein the compound is a compound of Table 1, Table 2, Table 3, and Table 4.

19. The oral composition of claim 18, wherein the compound is a compound of Table 4.

20. A method of treating, preventing, reducing, modulating, or ameliorating a disease or disorder associated with GPR40, GPR 119, or TGR5 in a subject in need thereof, the method comprising:

administering a therapeutically effective amount of a composition comprising the oral composition of any one of claims 1 to 19.

21. The method of claim 20, wherein the composition activates GPR40.

22. The method of claim 20, wherein the composition is provided with food to induce activation of GPR40.

23. The method of claim 20, wherein activation of GPR40 controls appetite and glucose metabolism in the subject.

24. A method of treating, preventing, reducing, modulating, or ameliorating obesity in a subject in need thereof, the method comprising:

administering a therapeutically effective amount of a composition comprising the oral composition of any one of claims 1 to 19.

25. The method of claim 24, wherein administering the composition to the subject provides sustained weight management.

26. The method of claim 24, wherein administering the composition to the subject provides fat loss.

27. The method of claim 24, wherein administering the composition to the subject provides glucose level normalization.

28. The method of claim 24, wherein the subject has pre-diabetes.

29. The method of claim 24, wherein administering the composition provides improvement in metabolic rate.

30. The method of claim 24, wherein administering the composition to the subject provides improvement in insulin sensitivity in the subject.

31. The method of claim 24, wherein administering the composition to the subject improves one or more biomarkers associated with inflammation and obesity.

32. The method of claim 24, wherein administering the composition provides a reduction in body fat mass.

33. The method of claim 32, wherein the body fat mass reduction is from at least 5% to about 15% from baseline measurements, as measured in kilograms (kg) or pounds (lbs).

34. The method of claim 33, further comprising maintaining fat loss within a range of $\pm 3\%$ to $\pm 10\%$ of the achieved reduction in body fat mass.

35. A method of treating, preventing, reducing, modulating, or ameliorating diabetes in a subject in need thereof, the method comprising:

providing a therapeutically effective amount of a composition comprising the oral composition of any one of claims 1 to 19.

36. The method of claim 35, wherein the diabetes is type-2 diabetes.

37. The method of claim 35, wherein providing to the subject the composition provides glucose level normalization followed by fat loss benefits.

38. The method of claim 35, wherein providing to the subject a normal blood glucose regulation followed by fat loss benefits.

39. The method of claim 35, wherein providing the composition provides improvement in metabolic rate.

40. The method of claim 35, wherein providing the composition to the subject provides improvement in insulin sensitivity in the subject.

41. The method of claim 35, wherein providing the composition improves insulin secretion and appetite regulation.

42. A method of treating, preventing, reducing, modulating, or ameliorating metabolic syndrome in a subject in need thereof, the method comprising:

providing a therapeutically effective amount of a composition comprising the oral composition of any one of claims 1 to 18.

43. The method of claim 42, wherein metabolic syndrome is selected from obesity, insulin resistance, hyperlipidemia, cardiovascular disease, fatty liver, cholesterol, oxidative stress, and hypertension.

44. The method of claim 42, wherein providing the composition reduces body weight of the subject or alleviates weight gain.

45. The method of claim 42, wherein providing the composition enhances inulin secretion in the subject.

46. The method of claim 42, wherein providing the composition enhances glucose metabolism.

47. A method of treating, preventing, reducing, modulating, or ameliorating a lipid disorder in a subject in need thereof, the method comprising:

providing a therapeutically effective amount of a composition comprising the oral composition of any one of claims 1 to 19.

48. The method of claim 47, wherein providing the composition enhances insulin secretion and improves fatty acid metabolism.

49. The method of claim 47, wherein providing the composition improves dyslipidemia the subject.

50. The method of claim 47, wherein providing the composition improves NAFLD in the subject.