PHARMACEUTICAL COMPOSITIONS AND METHODS FOR THE TREATMENT OF METABOLIC AND LIVER DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/565,442 filed March 14, 2024, which is incorporated herein by reference in its entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled VIKNG_027WO.xml created on March 12, 2025, which is 39,401 bytes in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Field

[0003] The present disclosure relates generally to the fields of chemistry and medicine. More specifically, the present disclosure relates to solid oral pharmaceutical compositions for the treatment of metabolic disorders and fatty liver diseases.

Description of the Related Art

[0004] The thyroid hormones (THs) play a critical role in growth, development, metabolism, and homeostasis. They are produced by the thyroid gland as thyroxine (T4) and 3,5,3′-triiodo-L-thyronine (T3). T4 is the major secreted form in humans and is enzymatically deiodinated by deiodinases to the more active form, T3, in peripheral tissues. THs exert their action by interacting with thyroid hormone receptors (TRs), which belong to the nuclear hormone receptor superfamily, and regulate the transcription of target genes. TH's form part of the thyroid axis, also known as the Hypothalmic-Pituitary-Thyroid, or HPT axis, which comprises a complex endocrine and paracrine feedback loop linking tissues of the brain and endocrine system in order to assert global control over issues such as overall metabolic rate, lipid secretion, cardiac function, muscle and bone growth, among many others (*See* e.g., Robins and Cotran: Pathologic Basis of

Disease, Kumar, V. et al., eds. (2005), p. 1165, which is incorporated herein by reference in its entirety).

[0005] TRs are expressed in most tissues and exist as two isoforms (TRα and TRβ). Tissue distribution studies, mouse knockout studies, and evaluation of patients with resistance to thyroid hormone (RTH) syndrome have established that TRα is the predominant isoform in the heart and regulates most cardiac functions, while the TRβ isoform predominates in the liver and the pituitary and regulates cholesterol metabolism and thyroid stimulating hormone (TSH) production, respectively. In recognition of the potential benefits associated with modulation of TRs, numerous approaches have been pursued to identify a suitable TR agonist to lower plasma cholesterol levels. However, these benefits were offset by deleterious cardiovascular side effects, such as tachycardia, arrhythmia, elevated blood pressure, and heart failure as well as effects on the thyroid hormone axis, muscle metabolism and bone loss.

[0006] TR-mediated pathways are implicated in modulating serum lipid levels, including cholesterol, triglycerides, and associated lipoproteins. *See* Pearce, E.N., Curr. Cardiol. Rep. 6:451-6 (2004) and Duntas, L.H., Thyroid 12:287-93 (2002) both of which are incorporated herein by reference in their entireties. Elevated levels of serum lipids are implicated in the development of atherosclerosis and in the exacerbation of coronary artery disease. *See* Robins and Cotran: Pathologic Basis of Disease, Kumar, V. et al., eds. (2005), p. 523, 572-77, which is incorporated herein by reference in its entirety. Clinical trials have demonstrated that reducing low density lipoprotein/ serum cholesterol levels reduces morbidity and mortality associated with cardiovascular disease. *See* Grundy, S.M., et al., Circulation 110:227-39 (2004), which is incorporated herein by reference in its entirety. While drugs such as statins and PCSK-9 inhibitors, along with dietary and lifestyle interventions, may help to treat hyperlipidemia in some patients, many patients fail to significantly reduce their serum cholesterol levels and many do not tolerate high doses of statins. *See* Pearson, T. et al., Arch Intern Med. 160:459-467 (2000), which is incorporated herein by reference in its entirety. Thus, there is an unmet medical need for additional orally administered lipid-modulating therapies.

[0007] Similarly, nonalcoholic fatty liver disease (NAFLD), a condition linked to the group of metabolic irregularities known as metabolic syndrome, is defined by excessive fat accumulation in the form of triglycerides (steatosis) in the liver. This condition can further include liver cell injury and inflammation, leading to non-alcoholic steatohepatitis (NASH). NASH

generally coincides in patients with type 2 diabetes, hypercholesterolemia, hypertriglyceridemia, and obesity. Patients with NASH risk developing cirrhosis, liver failure, and hepatocellular carcinoma. Treatments for NASH are currently limited to lifestyle interventions. However, the role of thyroid hormone in regulating LDL-C and triglyceride levels makes TR-mediated pathways promising targets for treatments for NASH and NAFLD. For example, in animals, thyroid hormone mimetics have been shown to dramatically reduce liver fat content.

[0008] Selective TRβ agonists were developed as a means of suppressing the cardiac side effects of nonspecific TR agonists while retaining the potential beneficial effects of TRβ activation, such as reduction in cholesterol and serum lipid levels, and reduction in obesity due to increased cellular metabolism. *See* Fujitaki, J. M., et al., Drug Metab. Disp. 36(11) 2393-403 (2008)), which is hereby incorporated by reference in its entirety. However, it has been shown that even targeted TRβ agonists can lead to suppression of the thyroid hormone axis (*see* Erion, M. D., PNAS USA 104(39):15490-5 (2007), which is incorporated herein by reference in its entirety), which may lead to side effects ranging from depression and fatigue to muscle wasting and bone loss.

[0009] Incretin peptides glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are metabolic hormones. GIP and GLP-1 are both secreted within minutes of nutrient ingestion and facilitate the rapid disposal of ingested nutrients. Both peptides share common actions on islet β-cells acting through structurally distinct yet related receptors. Incretin-receptor activation leads to glucose-dependent insulin secretion, induction of β-cell proliferation, and enhanced resistance to apoptosis. GIP also promotes energy storage via direct actions on adipose tissue. In contrast, GLP-1 exerts glucoregulatory actions via slowing of gastric emptying and glucose-dependent inhibition of glucagon secretion. GLP-1 also promotes satiety and sustained GLP-1–receptor activation is associated with weight loss in both preclinical and clinical studies.

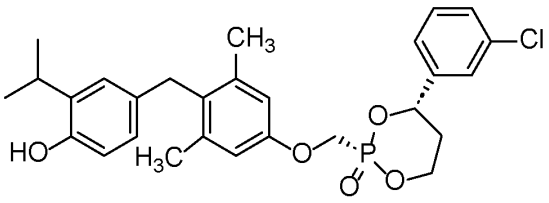
[0010] GIP/GLP-1 dual receptor agonists have been developed for treating NAFLD, non-alcoholic steatohepatitis (NASH), diabetes, obesity, and other diseases. However, the use of GIP/GLP-1 dual receptor agonists is associated with nausea, vomiting, and/or diarrhea. For example, clinical trials of a GIP/GLP1 dual receptor agonist compound found that tolerability at high doses was limited by gastrointestinal adverse events. The dose limitation associated with

gastrointestinal adverse events may prevent dosing to the desired effective dose, may compromise patient compliance with treatment, and may limit the effectiveness of the treatment regimen.

[0011] As liver and metabolic disorders have potential to be treated by both GIP/GLP-1 dual agonists and TRβ agonists, a need exists for combination therapies comprising GIP/GLP-1 dual agonists and TRβ agonists for the treatment of such disorders. Moreover, a need exists for novel pharmaceutical compositions comprising both GIP/GLP-1 dual agonists and TRβ agonists for administering to subjects in a single dosage form.

SUMMARY

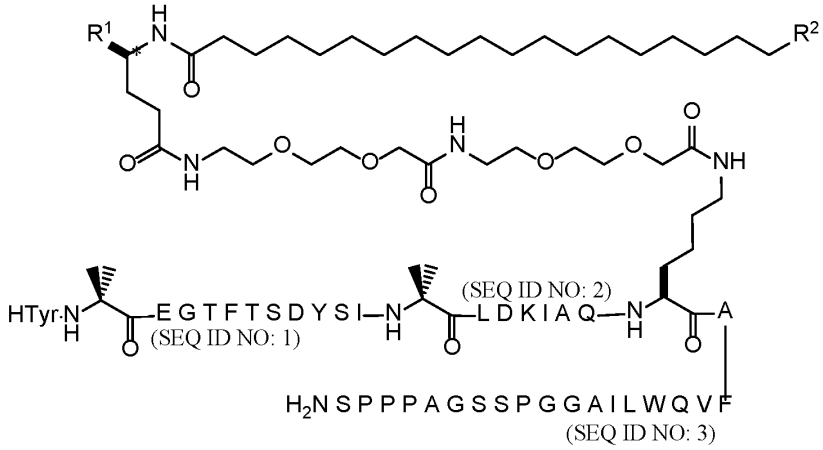
[0012] In one aspect of the present disclosure, provided herein is a pharmaceutical composition, comprising: a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof



(Compound A); and

a therapeutically effective amount of a GIP/GLP-1 dual agonist.

[0013] In some embodiments, the GIP/GLP-1 dual agonist is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from the group consisting of $–C(=O)(OZ^1)$, $–P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

R^2 is selected from the group consisting of $–C(=O)(OZ^2)$, $–P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

each R^7 may be independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

X and Y may each be independently selected from the group consisting of $–OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

each R^4 may be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl, and C_{6-10} aryl alkyl;

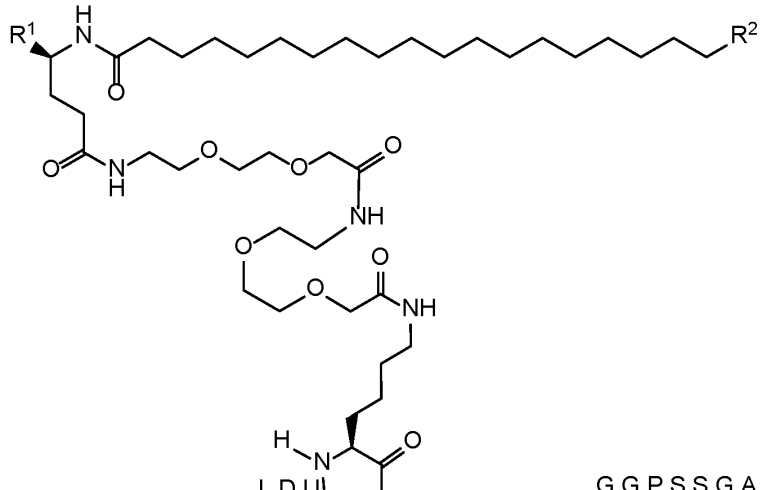
each R^5 may be independently hydrogen or C_{1-6} alkyl;

each R^6 may be independently hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 may each be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0014] In some embodiments wherein the GIP/GLP-1 dual agonist is a compound of Formula (I), at least one of Z^1 and Z^2 is not hydrogen.

[0015] In some embodiments, the GIP/GLP-1 is a compound having the structure of Formula (II),



H-Y Aib E G T F T S D Y S I J^1 L D U^1 U^2 A F V J^2 W L I J^3 G G P S S G A P P P S-NH_2

(SEQ ID NO: 4) (II) (SEQ ID NO: 5)

or a pharmaceutically acceptable salt thereof, wherein:

Aib is 2-aminoisobutyric acid;

each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib, a naturally occurring amino acid, and an unnatural amino acid;

U^1 is $-(J^4)_{n1}-(J^5)_{n2}-(J^6)_{n3}-(J^7)_{n4}-$;

U^2 is $-(J^8)_{n5}-(J^9)_{n6}-(J^{10})_{n7}-(J^{11})_{n8}-$;

each instance of J^4, J^5, J^6, J^7, J^8, J^9, J^{10}, and J^{11} is independently a naturally occurring amino acid or an unnatural amino acid;

each of n1, n2, n3, n4, n5, n6, n7, and n8 is independently 0 or 1, provided that the sum n1 + n2 + n3 + n4 + n5 + n6 + n7 + n8 is 4;

R^1 is selected from the group consisting of $-C(=O)(OZ^1)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

R^2 is selected from the group consisting of $-C(=O)(OZ^2)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6}

alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

each R^7 is independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

X and Y each are independently selected from the group consisting of $-OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

each R^5 is independently hydrogen or C_{1-6} alkyl;

each R^6 is independently hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 each are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0016] In some embodiments wherein the GIP/GLP-1 dual agonist is a compound of Formula (II), at least one of Z^1 and Z^2 is not hydrogen.

[0017] In some embodiments, the composition is formulated as a tablet. In some embodiments, the tablet is a bilayer tablet comprising:

(i) a GIP/GLP-1 dual agonist layer comprising the GIP/GLP-1 dual agonist; and

(ii) a TR-β agonist layer comprising Compound A.

[0018] In some embodiments, the GIP/GLP-1 dual agonist layer further comprises a permeability enhancer. In some embodiments, the permeability enhancer is salcaprozate sodium (SNAC), sodium caprate (C10), or a combination thereof. In some embodiments, the permeability enhancer is salcaprozate sodium. In other embodiments, the permeability enhancer is sodium caprate. In some embodiments, the permeability enhancer is a combination of salcaprozate sodium and sodium caprate. In some embodiments, the GIP/GLP-1 dual agonist layer is enterically coated.

[0019] In some embodiments, the TR-β agonist layer further comprises one or more polymers selected from the group consisting of: polyvinyl pyrrolidone (PVP), polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA), polyvinyl alcohol (PVA), polyacrylic acid (PAA), poly(ethylene oxide) (PEO), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), copovidone, poloxamer 407, hypromellose acetate succinate (HPMCAS),

polyacrylates and combinations thereof. In some embodiments, the polymer is polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA).

[0020] In some embodiments, Compound A and the one or more polymers are combined to form a spray dried dispersion. In other embodiments, Compound A and the one or more polymers are combined to form a hot melt extrusion.

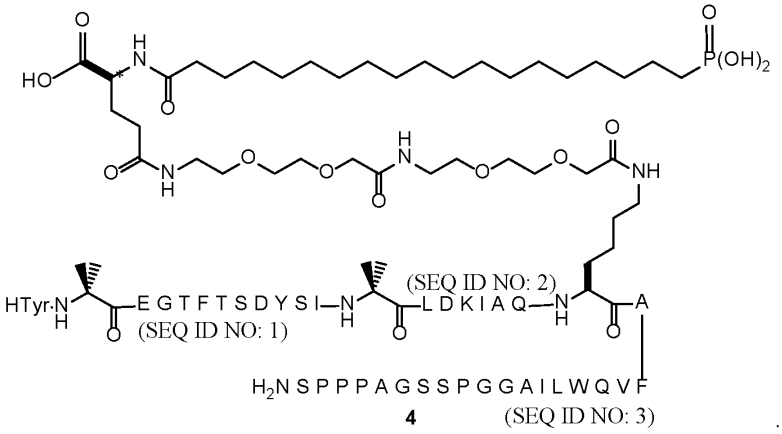
[0021] In some embodiments, the TR-β agonist layer is enterically coated.

[0022] In some embodiments, provided herein is a pharmaceutical composition, comprising:

(i) a GIP/GLP-1 dual agonist layer comprising:

(a) salcaprozate sodium; and

(b) a therapeutically effective amount of the compound having the structure:



4 ; and

(ii) a TR-β agonist layer comprising:

(a) polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA)

(b) a therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof;

wherein Compound A and the one or more polymers are combined to form a spray dried dispersion.

[0023] In another aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a GIP/GLP-1 dual agonist. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are

administered sequentially. In other embodiments, Compound A and the GIP/GLP-1 dual agonist are administered simultaneously. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition described herein. In some embodiments, the metabolic disorder or metabolic syndrome is atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, hypothalamic obesity, or prader-willi syndrome.

[0024] In another aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating ameliorating one or more fatty liver diseases in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof; anda therapeutically effective amount of a GIP/GLP-1 dual agonist. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are administered sequentially. In other embodiments, Compound A and the GIP/GLP-1 dual agonist are administered simultaneously. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition described herein. In some embodiments, the fatty liver disease is selected from the group consisting of steatosis, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease.

[0025] In another aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating one or more one or more diseases or disorders in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof; and a therapeutically effective amount of a GIP/GLP-1 dual agonist; wherein said disease or disorder is liver fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis, primary biliary cirrhosis, or idiopathic fibrosis. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are administered sequentially. In other embodiments, Compound A and the GIP/GLP-1 dual agonist are administered simultaneously. In some embodiments, Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition described herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0026] In some embodiments, pharmaceutical compositions are provided for administration to a subject in need thereof. In some embodiments, the pharmaceutical compositions include a combination of two or more active compounds. In some such embodiments, the pharmaceutical composition includes a TR-β agonist compound (e.g., Compound A described herein) and a GIP/GLP-1 dual agonist compound (e.g., compounds of Formula (I) or Formula (II) described herein). Various embodiments of these pharmaceutical compositions include a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, a pharmaceutically acceptable diluent, and any combination of the foregoing. Some embodiments of the pharmaceutical compositions include a therapeutically effective dosage of a compound, or a pharmaceutically acceptable salt thereof, as described elsewhere herein. Some embodiments of the pharmaceutical compositions are administered for the prevention, treatment, or amelioration of one or more fatty liver diseases in the subject.

Definitions

[0027] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents, applications, published applications, and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0028] "Solvate" refers to the compound formed by the interaction of a solvent and a compound described herein or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0029] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of a compound, which are not biologically or otherwise undesirable for use in a pharmaceutical. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid,

tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

[0030] As used herein, "C_a to C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" or "C_{1-4} alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-.

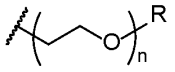
[0031] The term "halogen" or "halo," as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, *e.g.*, fluorine, chlorine, bromine, or iodine, with fluorine and chlorine being preferred.

[0032] As used herein, "alkyl" refers to a straight or branched hydrocarbon chain that is fully saturated (i.e., contains no double or triple bonds). 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 9 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as "C_{1-4} alkyl" or similar designations. By way of example only, "C_{1-4} alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of 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, hexyl, and the like.

[0033] As used herein, "haloalkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain, substituting one or more hydrogens with halogens. Examples of haloalkyl groups include, but are not limited to, $-CF_3$, $-CHF_2$, $-CH_2F$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CF_2CF_3$ and other groups that in light of the ordinary skill in the art and the teachings provided herein, would be considered equivalent to any one of the foregoing examples.

[0034] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl as is defined above, such as "C_{1-9} alkoxy", including but not limited to methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy, and the like.

[0035] As used herein, "polyethylene glycol" refers to the formula 

wherein n is an integer greater than one and R is a hydrogen or alkyl. The number of repeat units "n" may be indicated by referring to a number of members. Thus, for example, "2- to 5-membered polyethylene glycol" refers to n being an integer selected from two to five. In some embodiments, R is selected from methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, and tert-butoxy.

[0036] As used herein, "heteroalkyl" refers to a straight or branched hydrocarbon chain containing one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the chain backbone. The heteroalkyl group may have 1 to 20 carbon atoms although the present definition also covers the occurrence of the term "heteroalkyl" where no numerical range is designated. The heteroalkyl group may also be a medium size heteroalkyl having 1 to 9 carbon atoms. The heteroalkyl group could also be a lower heteroalkyl having 1 to 4 carbon atoms. In various embodiments, the heteroalkyl may have from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, 1 or 2 heteroatoms, or 1 heteroatom. The heteroalkyl group of the compounds may be designated as "C_{1-4} heteroalkyl" or similar designations. The heteroalkyl group may contain one or more heteroatoms. By way of example only, "C_{1-4} heteroalkyl" indicates that there are one to four carbon atoms in the heteroalkyl chain and additionally one or more heteroatoms in the backbone of the chain.

[0037] The term "aromatic" refers to a ring or ring system having a conjugated pi electron system and includes both carbocyclic aromatic (e.g., phenyl) and heterocyclic aromatic groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of atoms) groups provided that the entire ring system is aromatic.

[0038] As used herein, "aryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent carbon atoms) containing only carbon in the ring backbone. When the aryl is a ring system, every ring in the system is aromatic. The aryl group may have 6 to 18 carbon atoms, although the present definition also covers the occurrence of the term "aryl" where no numerical range is designated. In some embodiments, the aryl group has 6 to 10 carbon atoms. The aryl group may be designated as "C_{6-10} aryl," "C_6 or C_{10} aryl," or similar designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

[0039] As used herein, "aryloxy" and "arylthio" refers to RO- and RS-, in which R is an aryl as is defined above, such as "C_{6-10} aryloxy" or "C_{6-10} arylthio" and the like, including but not limited to phenyloxy.

[0040] An "aralkyl" or "arylalkyl" is an aryl group connected, as a substituent, via an alkylene group, such "C_{7-14} aralkyl" and the like, including but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0041] As used herein, "heteroaryl" refers to an aromatic ring or ring system (i.e., two or more fused rings that share two adjacent atoms) that contain(s) one or more heteroatoms, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur, in the ring backbone. When the heteroaryl is a ring system, every ring in the system is aromatic. The heteroaryl group may have 5-18 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heteroaryl" where no numerical range is designated. In some embodiments, the heteroaryl group has 5 to 10 ring members or 5 to 7 ring members. The heteroaryl group may be designated as "5-7 membered heteroaryl," "5-10 membered heteroaryl," or similar designations. In various embodiments, a heteroaryl contains from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, from 1 to 2 heteroatoms, or 1 heteroatom. For example, in various embodiments, a heteroaryl contains 1 to 4 nitrogen atoms, 1 to 3 nitrogen atoms, 1 to 2 nitrogen

atoms, 2 nitrogen atoms and 1 sulfur or oxygen atom, 1 nitrogen atom and 1 sulfur or oxygen atom, or 1 sulfur or oxygen atom. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, phthalazinyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinlinyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, isoindolyl, and benzothienyl.

[0042] A "heteroaralkyl" or "heteroarylalkyl" is heteroaryl group connected, as a substituent, via an alkylene group. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazollylalkyl, and imidazolylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C_{1-4} alkylene group).

[0043] As used herein, "carbocyclyl" means a non-aromatic cyclic ring or ring system containing only carbon atoms in the ring system backbone. When the carbocyclyl is a ring system, two or more rings may be joined together in a fused, bridged or spiro-connected fashion. Carbocyclyls may have any degree of saturation provided that at least one ring in a ring system is not aromatic. Thus, carbocyclyls include cycloalkyls, cycloalkenyls, and cycloalkynyls. The carbocyclyl group may have 3 to 20 carbon atoms, although the present definition also covers the occurrence of the term "carbocyclyl" where no numerical range is designated. The carbocyclyl group may also be a medium size carbocyclyl having 3 to 10 carbon atoms. The carbocyclyl group could also be a carbocyclyl having 3 to 6 carbon atoms. The carbocyclyl group may be designated as "C_{3-6} carbocyclyl" or similar designations. Examples of carbocyclyl rings include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,3-dihydro-indene, bicycle[2.2.2]octanyl, adamantyl, and spiro[4.4]nonanyl.

[0044] A "(carbocyclyl)alkyl" is a carbocyclyl group connected, as a substituent, via an alkylene group, such as "C_{4-10} (carbocyclyl)alkyl" and the like, including but not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

[0045] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0046] As used herein, "cycloalkenyl" means a carbocyclyl ring or ring system having at least one double bond, wherein no ring in the ring system is aromatic. An example is cyclohexenyl.

[0047] As used herein, "heterocyclyl" means a non-aromatic cyclic ring or ring system containing at least one heteroatom in the ring backbone. Heterocyclyls may be joined together in a fused, bridged or spiro-connected fashion. Heterocyclyls may have any degree of saturation provided that at least one ring in the ring system is not aromatic. The heteroatom(s) may be present in either a non-aromatic or aromatic ring in the ring system. The heterocyclyl group may have 3 to 20 ring members (i.e., the number of atoms making up the ring backbone, including carbon atoms and heteroatoms), although the present definition also covers the occurrence of the term "heterocyclyl" where no numerical range is designated. The heterocyclyl group may also be a medium size heterocyclyl having 3 to 10 ring members. The heterocyclyl group could also be a heterocyclyl having 3 to 6 ring members. The heterocyclyl group may be designated as "3-6 membered heterocyclyl" or similar designations.

[0048] In various embodiments, a heterocyclyl contains from 1 to 4 heteroatoms, from 1 to 3 heteroatoms, from 1 to 2 heteroatoms, or 1 heteroatom. For example, in various embodiments, a heterocyclyl contains 1 to 4 nitrogen atoms, 1 to 3 nitrogen atoms, 1 to 2 nitrogen atoms, 2 nitrogen atoms and 1 sulfur or oxygen atom, 1 nitrogen atom and 1 sulfur or oxygen atom, or 1 sulfur or oxygen atom. In preferred six membered monocyclic heterocyclyls, the heteroatom(s) are selected from one up to three of O, N or S, and in preferred five membered monocyclic heterocyclyls, the heteroatom(s) are selected from one or two heteroatoms selected from O, N, or S. Examples of heterocyclyl rings include, but are not limited to, azepinyl, acridinyl, carbazolyl, cinnolinyl, dioxolanyl, imidazolinyl, imidazolidinyl, morpholinyl, oxiranyl, oxepanyl, thiepanyl, piperidinyl, piperazinyl, dioxopiperazinyl, pyrrolidinyl, pyrrolidonyl, pyrrolidionyl, 4-piperidonyl, pyrazolinyl, pyrazolidinyl, 1,3-dioxinyl, 1,3-dioxanyl, 1,4-dioxinyl, 1,4-dioxanyl, 1,3-oxathianyl, 1,4-oxathiinyl, 1,4-oxathianyl, 2*H*-1,2-oxazinyl, trioxanyl, hexahydro-1,3,5-triazinyl, 1,3-dioxolyl, 1,3-dioxolanyl, 1,3-dithiolyl, 1,3-dithiolanyl, isoxazolinyl, isoxazolidinyl, oxazolinyl, oxazolidinyl, oxazolidinonyl, thiazolinyl, thiazolidinyl, 1,3-oxathiolanyl, indolinyl, isoindolinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydro-1,4-thiazinyl, thiamorpholinyl, dihydrobenzofuranyl, benzimidazolidinyl, and tetrahydroquinoline.

[0049] A "(heterocyclyl)alkyl" is a heterocyclyl group connected, as a substituent, via an alkylene group. Examples include, but are not limited to, imidazolinylmethyl and indolinylethyl.

[0050] As used herein, "acyl" refers to –C(=O)R, wherein R is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. Non-limiting examples include formyl, acetyl, propanoyl, benzoyl, and acryl.

[0051] An "O-carboxy" group refers to a "-OC(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0052] A "C-carboxy" group refers to a "-C(=O)OR" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein. A non-limiting example includes carboxyl (i.e., -C(=O)OH).

[0053] A "cyano" group refers to a "-CN" group.

[0054] A "cyanato" group refers to an "-OCN" group.

[0055] An "isocyanato" group refers to a "-NCO" group.

[0056] A "thiocyanato" group refers to a "-SCN" group.

[0057] An "isothiocyanato" group refers to an " -NCS" group.

[0058] A "sulfinyl" group refers to an "-S(=O)R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0059] A "sulfonyl" group refers to an "-SO_2R" group in which R is selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0060] An "S-sulfonamido" group refers to a "-$SO_2NR_AR_B$" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0061] An "N-sulfonamido" group refers to a "-$N(R_A)SO_2R_B$" group in which R_A and R_b are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7}

carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0062] An "O-carbamyl" group refers to a "-OC(=O)NR_AR_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0063] An "N-carbamyl" group refers to an "-$N(R_A)$OC(=O)R_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0064] An "O-thiocarbamyl" group refers to a "-OC(=S)NR_AR_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0065] An "N-thiocarbamyl" group refers to an "-$N(R_A)$OC(=S)R_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0066] A "C-amido" group refers to a "-C(=O)NR_AR_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0067] An "N-amido" group refers to a "-$N(R_A)$C(=O)R_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0068] An "amino" group refers to a "-NR_AR_B" group in which R_A and R_B are each independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} carbocyclyl, C_{6-10} aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0069] An "aminoalkyl" group refers to an amino group connected via an alkylene group.

[0070] An "alkoxyalkyl" group refers to an alkoxy group connected via an alkylene group, such as a "C_{2-8} alkoxyalkyl" and the like.

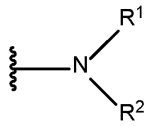
[0071] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be "substituted," it is meant that the group is substituted with one or more subsitutents independently selected from C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 heteroalkyl, C_3-C_7 carbocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), C_3-C_7-carbocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heterocyclyl-C_1-C_6-alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), aryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), 5-10 membered heteroaryl(C_1-C_6)alkyl (optionally substituted with halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkoxy), halo, cyano, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkoxy(C_1-C_6)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C_1-C_6)alkyl (e.g., $-CF_3$), halo(C_1-C_6)alkoxy (e.g., $-OCF_3$), C_1-C_6 alkylthio, arylthio, amino, amino(C_1-C_6)alkyl, nitro, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, acyl, cyanato, isocyanato, thiocyanato, isothiocyanato, sulfinyl, sulfonyl, and oxo (=O). Wherever a group is described as "optionally substituted" that group can be substituted with the above substituents.

[0072] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C_1-C_4 alkyl, amino, hydroxy, and halogen.

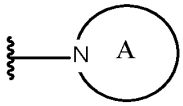
[0073] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For example, a substituent identified as alkyl that requires two points of attachment

includes di-radicals such as –CH_2–, –CH_2CH_2–, –$CH_2CH(CH_3)CH_2$–, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as "alkylene" or "alkenylene."

[0074] When two R groups are said to form a ring (e.g., a carbocyclyl, heterocyclyl, aryl, or heteroaryl ring) "together with the atom to which they are attached," it is meant that the collective unit of the atom and the two R groups are the recited ring. The ring is not otherwise limited by the definition of each R group when taken individually. For example, when the following substructure is present:

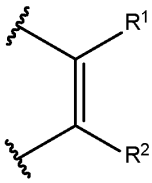


[0075] and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

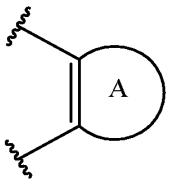


[0076] where ring A is a heterocyclyl ring containing the depicted nitrogen.

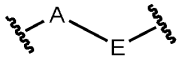
[0077] Similarly, when two "adjacent" R groups are said to form a ring "together with the atoms to which they are attached," it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



[0078] and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the atoms to which they are attached form an aryl or carbocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:



[0079] where A is an aryl ring or a carbocyclyl containing the depicted double bond.

[0080] Wherever a substituent is depicted as a di-radical (*i.e.*, has two points of attachment to the rest of the molecule), it is to be understood that the substituent can be attached in any directional configuration unless otherwise indicated. Thus, for example, a substituent depicted as –AE– or 

includes the substituent being oriented such that the **A** is attached at the leftmost attachment point of the molecule as well as the case in which **A** is attached at the rightmost attachment point of the molecule.

[0081] The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys) and humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rats and mice but also includes many other species.

[0082] "Subject" as used herein, means a human or a non-human mammal, e.g., a dog, a cat, a mouse, a rat, a cow, a sheep, a pig, a goat, a non-human primate or a bird, e.g., a chicken, as well as any other vertebrate or invertebrate.

[0083] An "effective amount" or a "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent that is effective to relieve, to some extent, or to reduce the likelihood of onset of, one or more of the symptoms of a disease or condition, and includes curing a disease or condition. "Curing" means that the symptoms of a disease or condition are eliminated; however, certain long-term or permanent effects may exist even after a cure is obtained (such as extensive tissue damage).

[0084] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a subject who does not yet exhibit symptoms of a disease or condition, but who is susceptible to, or otherwise at risk of, a particular disease or condition, whereby the treatment reduces the likelihood that the patient will develop the disease or condition. The term

"therapeutic treatment" refers to administering treatment to a subject already suffering from a disease or condition.

[0085] The term "pharmaceutically acceptable excipient," as used herein, includes but is not limited to solvents, dispersants, coatings, antimicrobial bacterial agents, adjuvants, isotonic and absorption delaying agents and the like. In some embodiments, the pharmaceutically-acceptable excipients include sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as microcrystalline cellulose, sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; binders such as polyvinylpyrrolidinone (PVP) polyvinyl alcohols, polyethylene glycol, cellulose and derivatives of cellulose (such as methyl cellulose, ethyl cellulose, hydroxy propyl cellulose), polyvinyl alcohol; solid lubricants, such as stearic acid, silicon dioxide and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, and corn oil; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers and surfactants, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives such as benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, and phenylmercuric nitrate; tonicity adjustors such as sodium chloride, potassium chloride, mannitol and glycerin; vehicles such as polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, and hydroxyethyl cellulose; and pyrogen-free water. In some embodiments, the pharmaceutically-acceptable excipient(s) are selected based on the route of administration and can include solid or liquid fillers, binders, diluents, hydrotropies, surface-active agents, and encapsulating substances. For example, in the case of intravenous administration, excipients may include gelatin; carbohydrates such as dextrose, mannitol, and dextran; and antioxidants such as sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. In some embodiments, the pharmaceutically-acceptable excipient(s) include antimicrobial agents such as phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol. Additional examples of suitable pharmaceutically-acceptable excipient(s) are described in Powell, et al., Compendium of Excipients for Parenteral Compositions, *PDA J Pharm Sci and Tech* **1998**, *52* 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current

Usage and Future Directions, *PDA J Pharm Sci and Tech* **2011**, *65* 287-332, each of which are incorporated herein by reference in their entirety.

Compounds

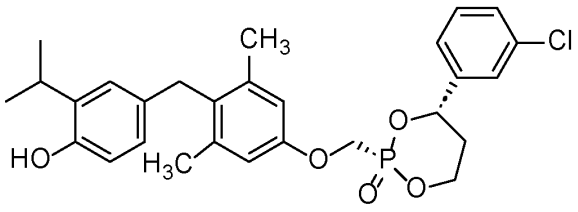
[0086] In some embodiments, the pharmaceutical compositions include compounds that are non-macrocyclic functionalized peptides that act as GIP/GLP-1 dual receptor agonists. In other embodiments, the pharmaceutical compositions include compounds that are non-macrocyclic functionalized peptides that act as GLP-1 receptor monoagonists.

[0087] Where the compounds disclosed herein have at least one chiral center, they may exist as individual enantiomers and diastereomers or as mixtures of such isomers, including racemates. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art. Unless otherwise indicated, all such isomers and mixtures thereof are included in the scope of the compounds disclosed herein. Furthermore, compounds disclosed herein may exist in one or more crystalline or amorphous forms. Unless otherwise indicated, all such forms are included in the scope of the compounds disclosed herein including any polymorphic forms. In addition, some of the compounds disclosed herein may form solvates with water (i.e., hydrates) or common organic solvents. Unless otherwise indicated, such solvates are included in the scope of the compounds disclosed herein.

[0088] The skilled artisan will recognize that some structures described herein may be resonance forms or tautomers of compounds that may be fairly represented by other chemical structures, even when kinetically; the artisan recognizes that such structures may only represent a very small portion of a sample of such compound(s). Such compounds are considered within the scope of the structures depicted, though such resonance forms or tautomers are not represented herein.

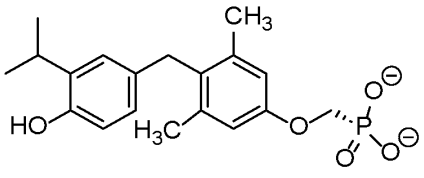
TR-β Agonist Compound A

[0089] Compound A is a low solubility, lipophilic prodrug compound in development for the treatment of chronic liver diseases including non-alcoholic fatty liver disease (NAFLD). Compound A may be prepared according to known methods, including those described in U.S. Patent No. 7,829,552, which is incorporated herein by reference in its entirety.



(Compound A).

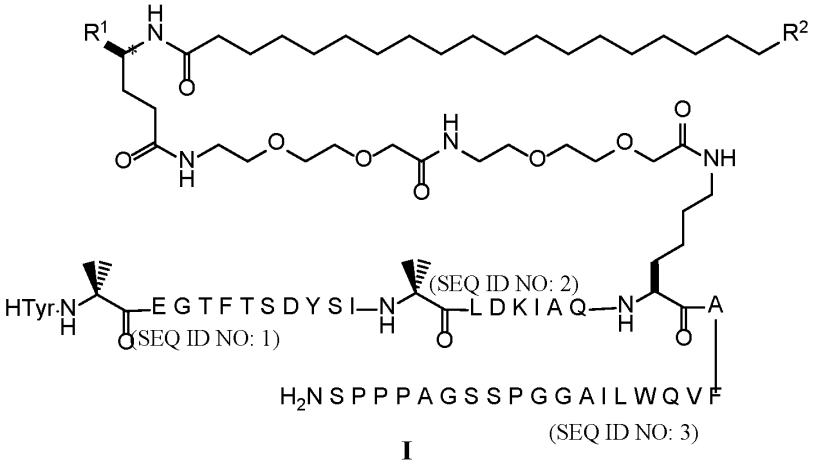
[0090] Compound A' is the active metabolite of Compound A. The structure of Compound A' is shown below.



(Compound A').

Compounds of Formula (I)

[0091] Various embodiments of GIP/GLP-1 dual agonist compounds include compounds having the structure of Formula (I) as described above or pharmaceutically acceptable salts thereof. The structure of Formula (I) encompasses all stereoisomers and racemic mixtures, including the following structure and mixtures thereof:



I

[0092] In some embodiments of compounds of Formula (I):

[0093] R^1 is selected from the group consisting of $-C(=O)(OZ^1)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6}

alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

[0094] R^2 is selected from the group consisting of $–C(=O)(OZ^2)$, $–P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

[0095] each R^7 may be independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

[0096] X and Y may each be independently selected from the group consisting of $–OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

[0097] each R^4 may be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{6-10} arylalkyl;

[0098] each R^5 may be independently hydrogen or C_{1-6} alkyl;

[0099] each R^6 may be independently hydrogen or C_{1-6} alkyl; and

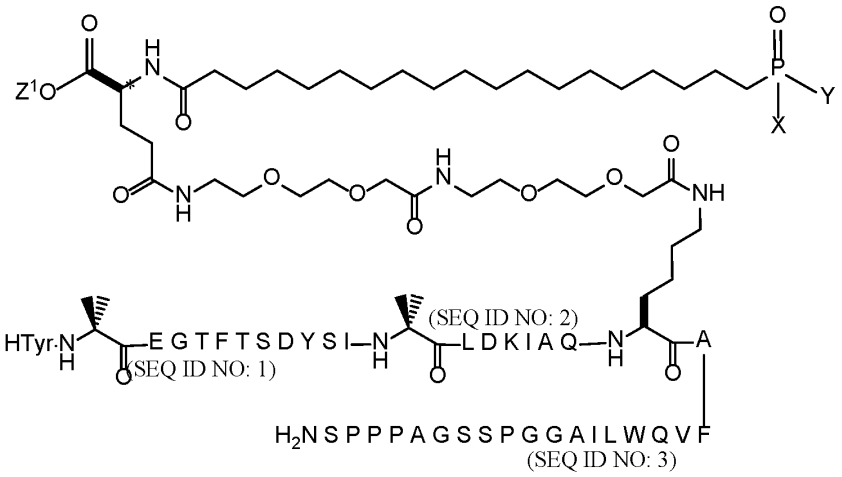
[0100] Z^1 and Z^2 may each be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0101] In some embodiments, at least one of Z^1 and Z^2 is not hydrogen.

[0102] In some embodiments, each R^4 may be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, and haloC_{1-6} alkyl;

[0103] In some embodiments, Z^1 and Z^2 may each be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0104] Some embodiments of compounds of Formula I include compounds having the structure of Formula (I-a):



I-a

or pharmaceutically acceptable salts thereof.

[0105] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is selected from hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl, and C_{6-10} aryl; and X and Y each are $-OR^4$.**[0106]** In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is selected from hydrogen, haloC_{1-6} alkyl and C_{1-6} alkyl; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

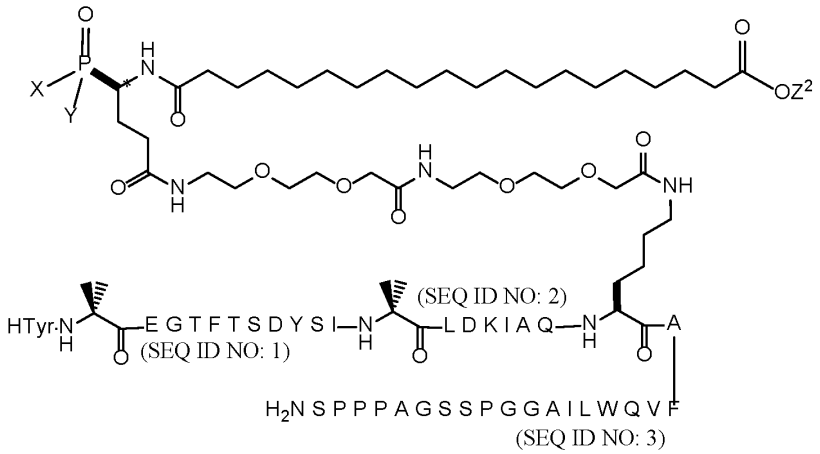
[0106] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is hydrogen; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

[0107] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is hydrogen and each R^4 may be independently hydrogen or C_{6-10} arylalkyl.

[0108] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; each R^4 is hydrogen.

[0109] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is hydrogen and each R^4 is hydrogen.

[0110] Some embodiments of compounds of Formula (I) include compounds having the structure of Formula (I-b):



I-b

or pharmaceutically acceptable salts thereof.

[0111] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is selected from hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

[0112] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is selected from hydrogen, haloC_{1-6} alkyl, and C_{1-6} alkyl; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

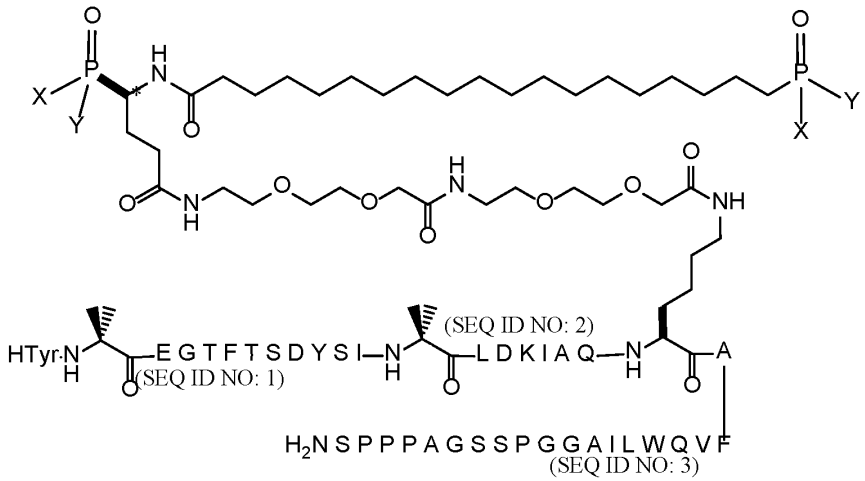
[0113] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is hydrogen; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

[0114] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is hydrogen and each R^4 may be independently hydrogen or C_{6-10} arylalkyl.

[0115] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; each R^4 is hydrogen.

[0116] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is hydrogen and each R^4 is hydrogen.

[0117] Some embodiments of compounds of Formula (I) include compounds having the structure of Formula (I-c):



I-c

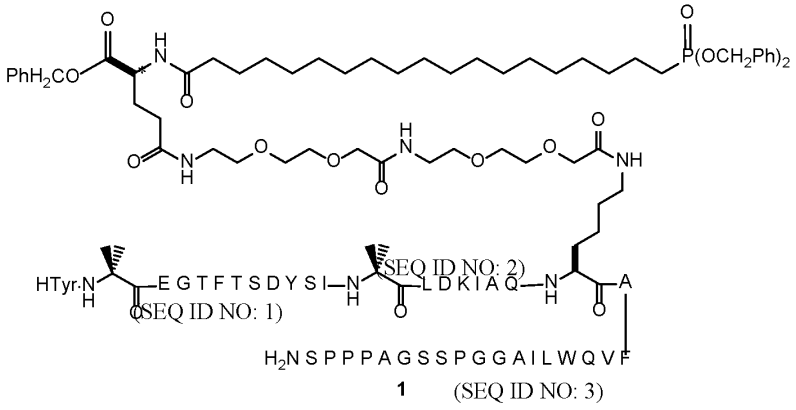
or pharmaceutically acceptable salts thereof.

[0118] In some embodiments of compounds of Formula (I-c) or their pharmaceutically acceptable salts; X and Y each are $-OR^4$.

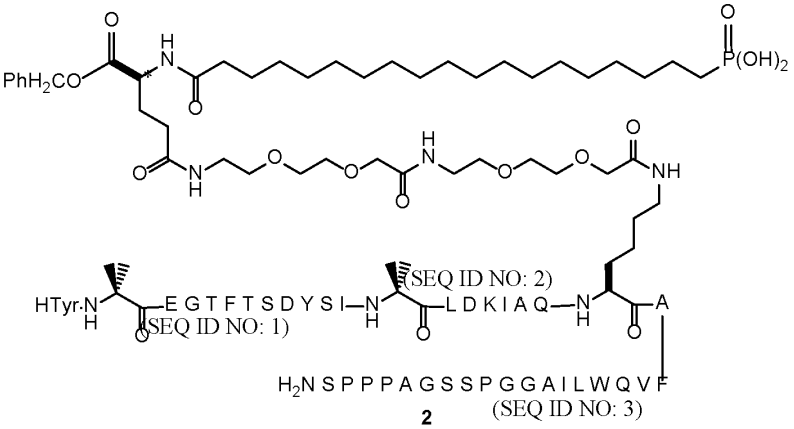
[0119] In some embodiments of compounds of Formula (I-c) or their pharmaceutically acceptable salts; each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

[0120] In some embodiments of compounds of Formula (I-c) or their pharmaceutically acceptable salts; each R^4 is hydrogen.

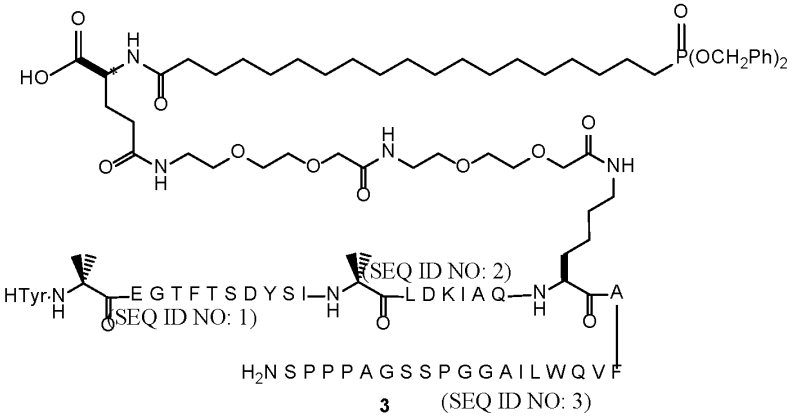
[0121] Some embodiments include a compound having the structure selected from the group consisting of:



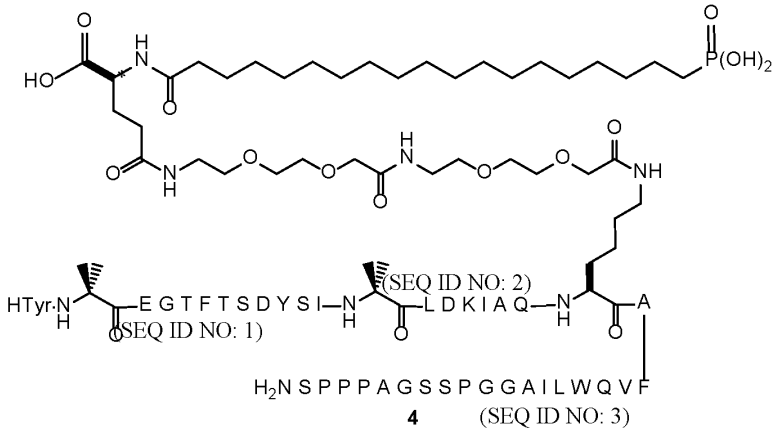
1


PhH2CO
P(OH)2
HTyr
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

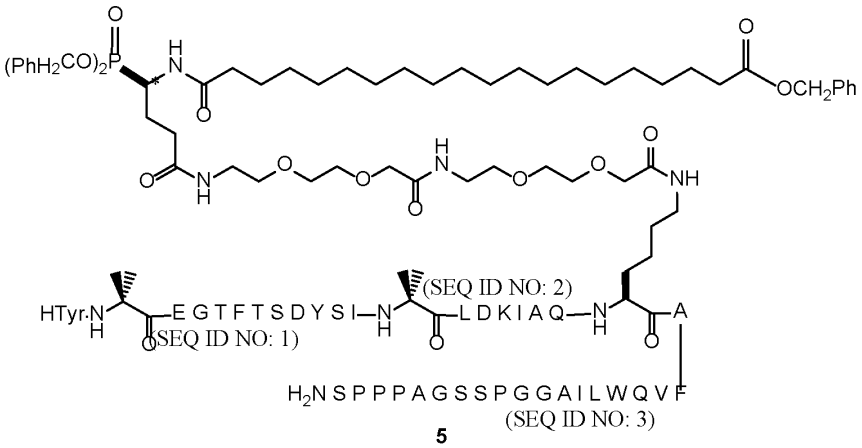
2


HO
P(OCH2Ph)2
HTyr
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

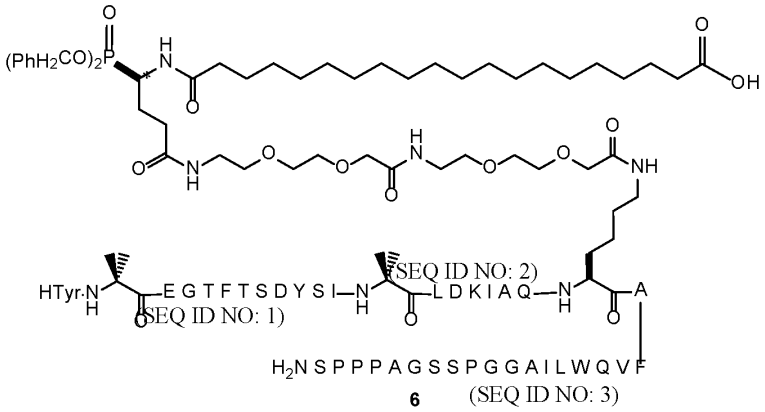
3


HO
P(OH)2
HTyr
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

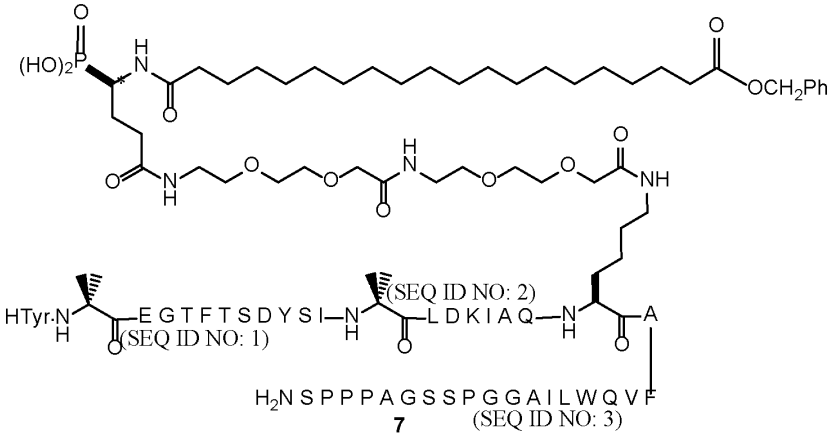
4


(PhH2CO)2P
OCH2Ph
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

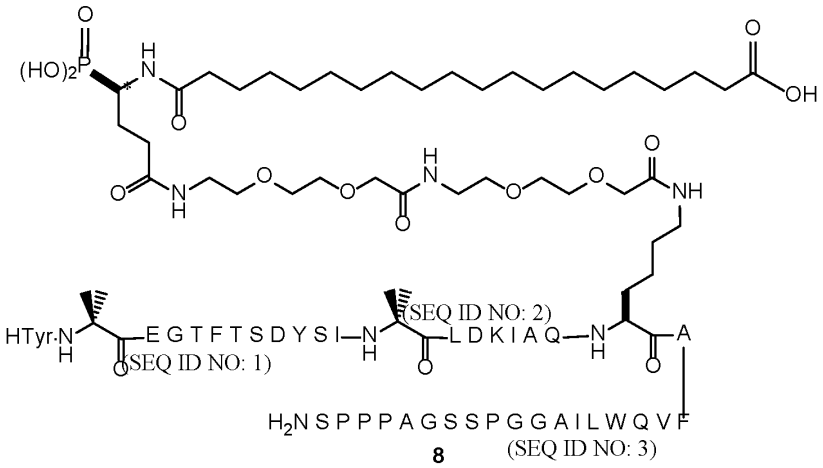
5


(PhH2CO)2P
OH
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

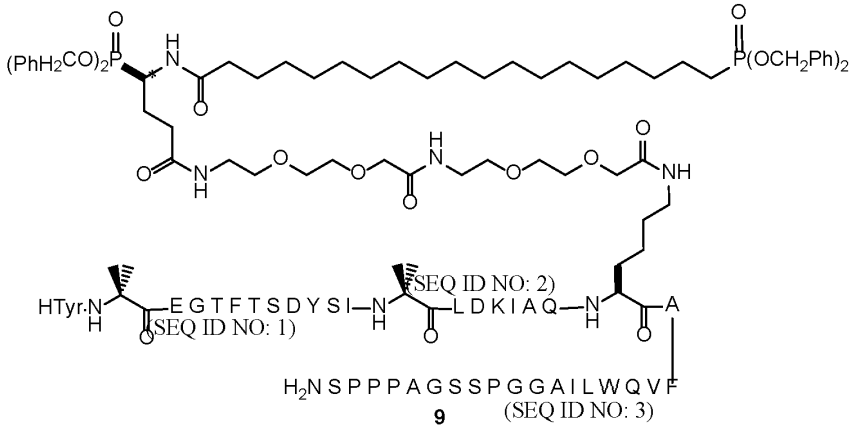
6


(HO)2P
OCH2Ph
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

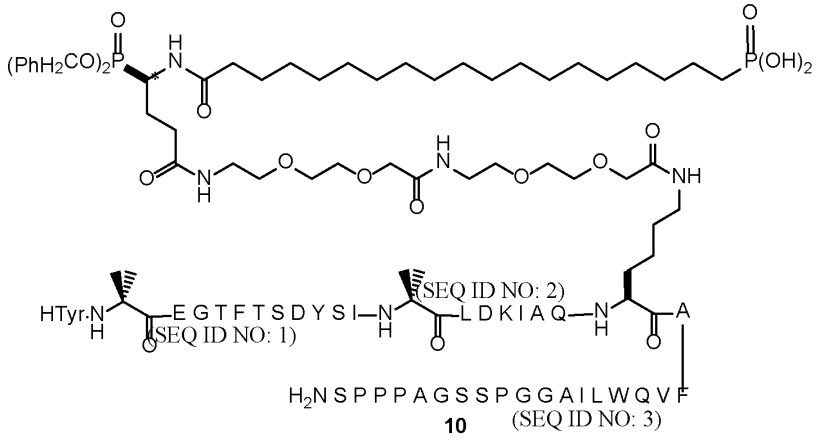
7


(HO)2P
OH
HTyr-
E G T F T S D Y S I
(SEQ ID NO: 2)
L D K I A Q
A
(SEQ ID NO: 1)
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

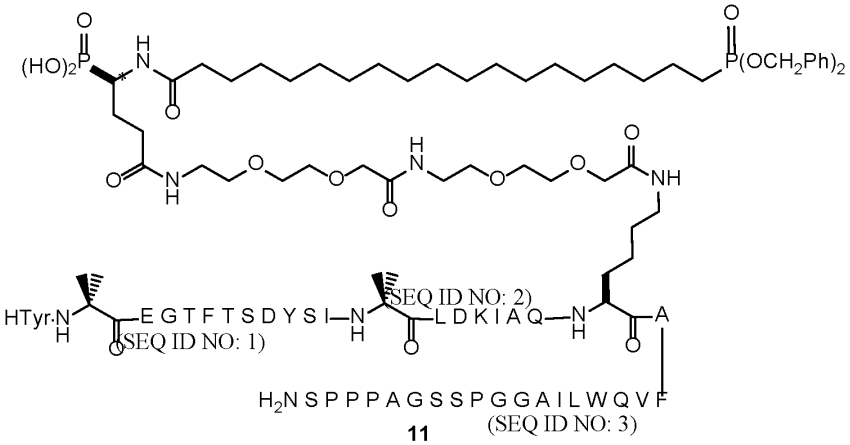
8


(PhH2CO)2P
P(OCH2Ph)2
HTyr-
E G T F T S D Y S I
(SEQ ID NO: 2)
L D K I A Q
A
(SEQ ID NO: 1)
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

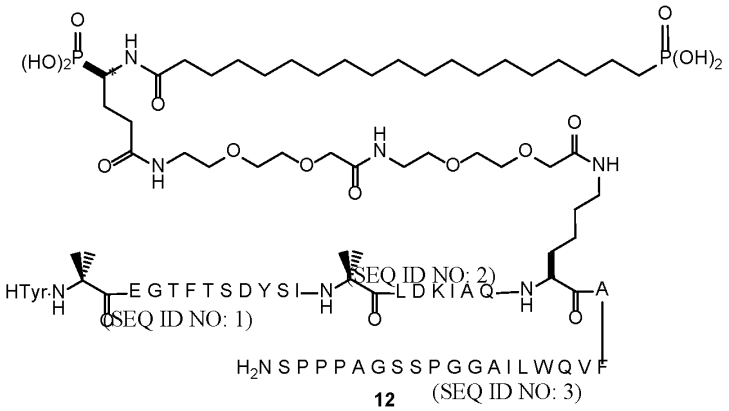
9


(PhH2CO)2P
P(OH)2
HTyr-
E G T F T S D Y S I
(SEQ ID NO: 2)
L D K I A Q
A
(SEQ ID NO: 1)
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

10



11



12

and pharmaceutically acceptable salts thereof.

[0122] Some embodiments include a compound wherein "*" indicates a chiral carbon with "S" configuration.

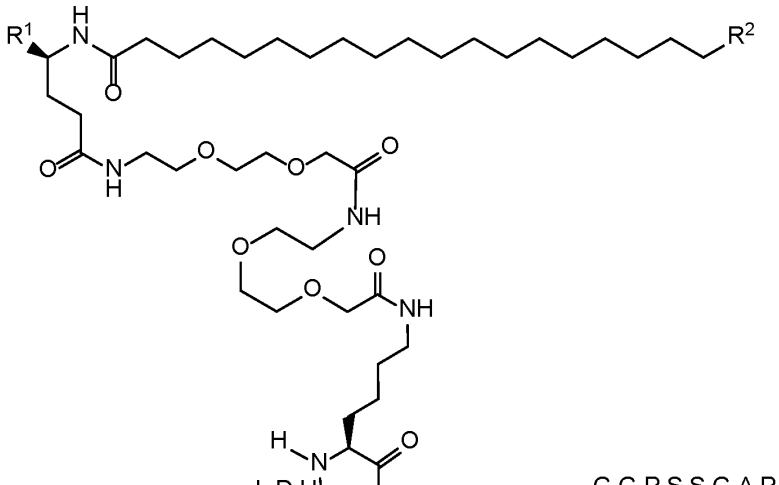
[0123] Some embodiments include a compound wherein "*" indicates a chiral carbon with "R" configuration.

[0124] The compounds of Formula (I) described herein, e.g., Compounds 1-12, may be prepared according to methods described in International Patent Publication No. WO 2022/159395, the disclosure of which is incorporated herein in its entirety.

Compounds Formula (II)

[0125] Various embodiments of GIP/GLP-1 dual agonist compounds include compounds having the structure of Formula (II) as described herein or pharmaceutically acceptable

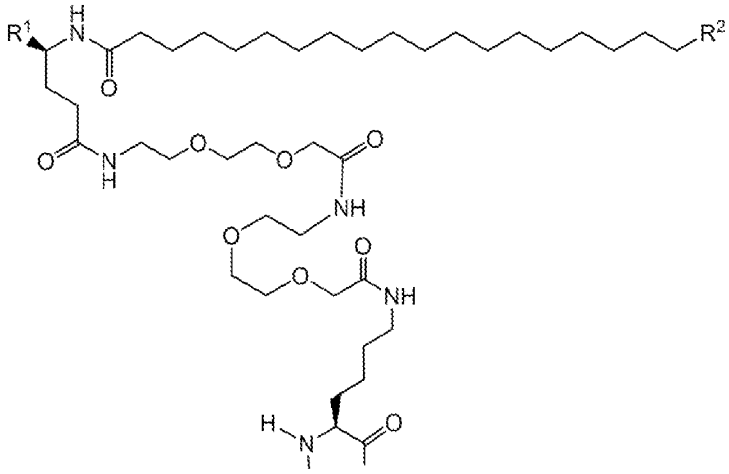
salts thereof. The structure of Formula (II) encompasses all stereoisomers and racemic mixtures, including the following structure and mixtures thereof:



H-Y Aib E G T F T S D Y S I J^1 L D U$_1$ U^2 A F V J^2 W L I J^3 G G P S S G A P P P S -NH$_2$

(II)

or a pharmaceutically acceptable salt thereof. Formula (II) can also be written as:



SEQ ID NO: 4 SEQ ID NO: 5

In Formula (II) and the compounds described herein, "H-" represents hydrogen on the N-terminal amine and "-NH_2" represents an amino forming a C-terminal amide.

[0126] In some embodiments of compounds of Formula (II):

Aib is 2-aminoisobutyric acid;

each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib, a naturally occurring amino acid, and an unnatural amino acid.

[0127] In some embodiments of compounds of Formula (II):

U^1 is $-(J^4)_{n1}-(J^5)_{n2}-(J^6)_{n3}-(J^7)_{n4}-$;

U^2 is $-(J^8)_{n5}-(J^9)_{n6}-(J^{10})_{n7}-(J^{11})_{n8}-$;

each instance of J^4, J^5, J^6, J^7, J^8, J^9, J^{10}, and J^{11} is independently a naturally occurring amino acid or an unnatural amino acid;

each of n1, n2, n3, n4, n5, n6, n7, and n8 is independently 0 or 1, provided that the sum n1 + n2 + n3 + n4 + n5 + n6 + n7 + n8 is 4;

R^1 is selected from the group consisting of $-C(=O)(OZ^1)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

R^2 is selected from the group consisting of $-C(=O)(OZ^2)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

each R^7 is independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

X and Y each are independently selected from the group consisting of $-OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

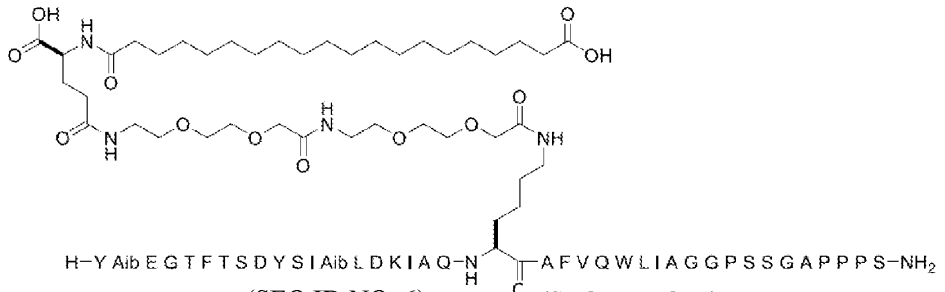
each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

each R^5 is independently hydrogen or C_{1-6} alkyl;

each R^6 is independently hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 each are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0128] In some embodiments, the compound is not:



(SEQ ID NO: 6) (SEQ ID NO: 7) .

[0129] In some embodiments of compounds of Formula (II), each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib and a naturally occurring amino acid.

[0130] In some embodiments of compounds of Formula (II), each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib, A, F, N, R, and Q. In some embodiments, J^1 is Aib or F. In some embodiments, J^1 F. In some embodiments, J^2 is N or Q. In some embodiments, J^2 is N. In some embodiments, J^3 is A or R. In some embodiments, J^3 is R.

[0131] In some embodiments of compounds of Formula (II), each instance of J^4, J^5, J^6, and J^7 is independently an amino acid selected from A, I, K, R, Q, S, T, and V. In some embodiments, J^4 is K or R. In some embodiments, J^4 is R. In some embodiments, J^5 is I, T, or V. In some embodiments, J^5 is T or V. In some embodiments, J^6 is A or S. In some embodiments, J^6 is S. In some embodiments, J^7 is Q. In some embodiments, J^7 is K.

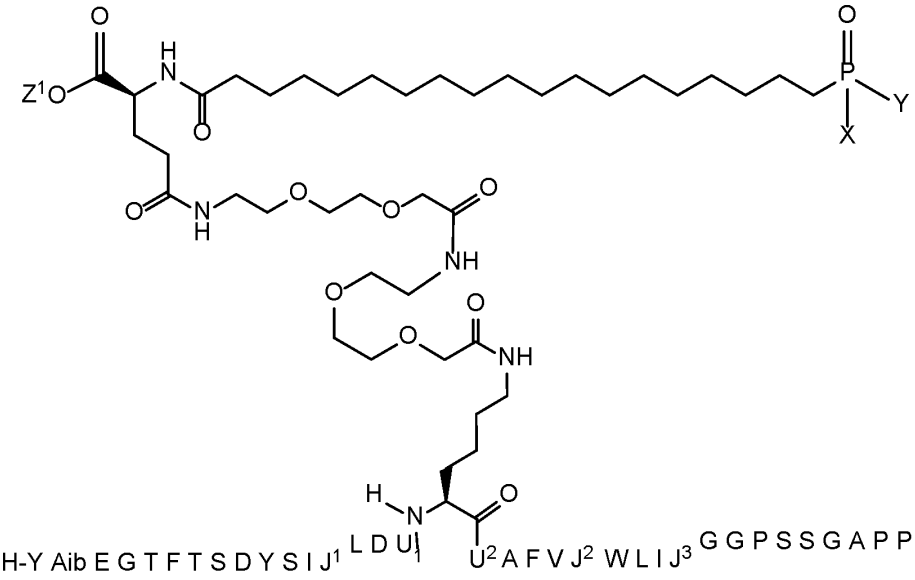
[0132] In some embodiments of compounds of Formula (II), each instance of J^8, J^9, J^{10}, and J^{11} is independently an amino acid selected from A, I, and Q. In some embodiments, J^8 is I or Q. In some embodiments, J^9 is A or Q. In some embodiments, J^{10} is Q. In some embodiments, J^{11} is Q.

[0133] In some embodiments of compounds of Formula (II), J^1 is selected from Aib or F; J^2 is selected from Q or N; J^3 is selected from A or R; U^1 is selected from -K-V-A-, -K-I-A-Q- (SEQ ID NO: 8), -K-T-A-Q- (SEQ ID NO: 9), -K-T-S-Q- (SEQ ID NO: 10), -K-V-A-Q- (SEQ ID NO: 11), -R-I-A-Q- (SEQ ID NO: 12), -K-I-A-K- (SEQ ID NO: 13), -K-I-S-Q- (SEQ ID NO: 14), or is absent; and U^2 is selected from -Q-, -I-A-Q-Q- (SEQ ID NO: 15), -I-A-Q-K- (SEQ ID NO: 16), -V-A-Q-K- (SEQ ID NO: 17) or is absent.

[0134] In some embodiments of compounds of Formula (II), each instance of n1, n2, n3, and n4 is zero. In some embodiments, each instance of n4, n6, n7, and n8 is zero. In some embodiments, each instance of n5, n6, n7, and n8 is zero.

[0135] In some embodiments of compounds of Formula (II), at least one of Z^1 and Z^2 is not hydrogen.

[0136] Some embodiments of compounds of Formula (II) include compounds having the structure of Formula (II-a):



II-a

or a pharmaceutically acceptable salt thereof.

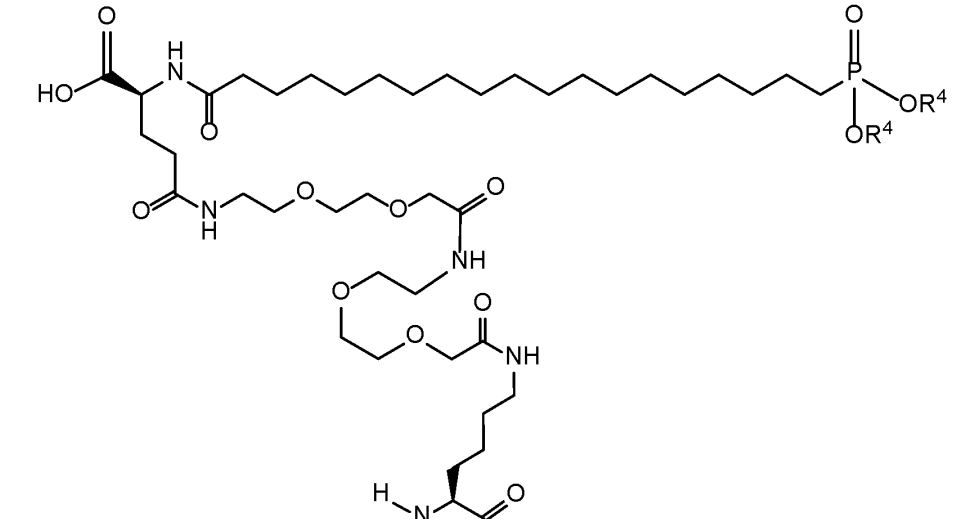
[0137] In some embodiments of compounds of Formula (II-a) or their pharmaceutically acceptable salts, Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

[0138] In some embodiments of compounds of Formula (II-a) or their pharmaceutically acceptable salts, Z^1 is hydrogen and each R^4 independently is hydrogen or C_{7-11} arylalkyl.

[0139] In some embodiments of compounds of Formula (II-a) or their pharmaceutically acceptable salts, each R^4 is hydrogen.

[0140] In some embodiments of compounds of Formula (II-a) or their pharmaceutically acceptable salts, Z^1 is hydrogen and each R^4 is hydrogen.

[0141] Some embodiments of compounds of Formula (II) include compounds having the structure of Formula (II-b):



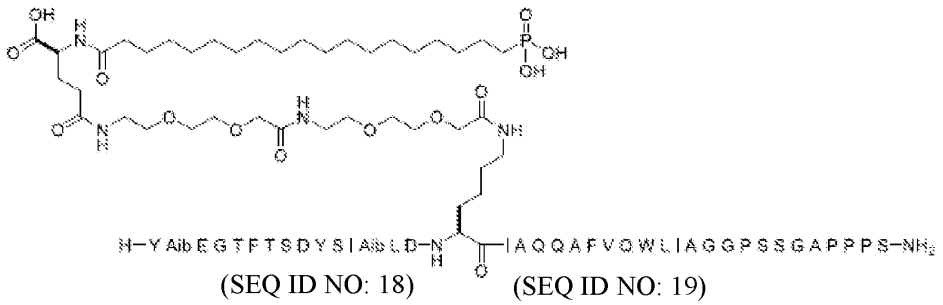
II-b

or a pharmaceutically acceptable salt thereof.

[0142] In some embodiments of compounds of Formula (II-b) or their pharmaceutically acceptable salts, each R^4 is independently selected from the group consisting of hydrogen, C_{6-10} aryl and C_{7-11} arylalkyl.

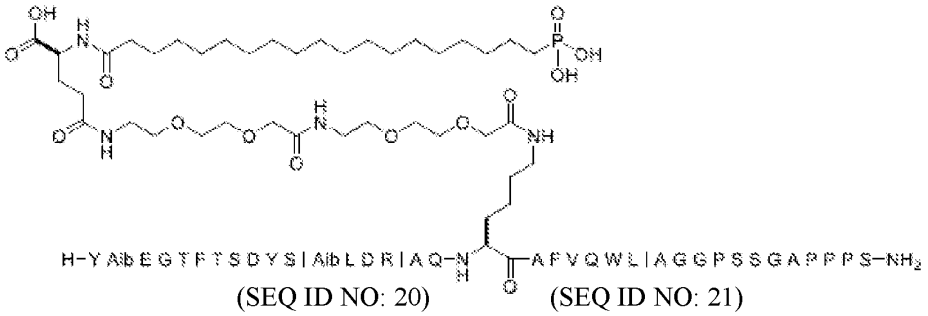
[0143] In some embodiments of compounds of Formula (II-b) or their pharmaceutically acceptable salts, each R^4 is hydrogen.

[0144] Some embodiments include a compound having the structure selected from the group consisting of:



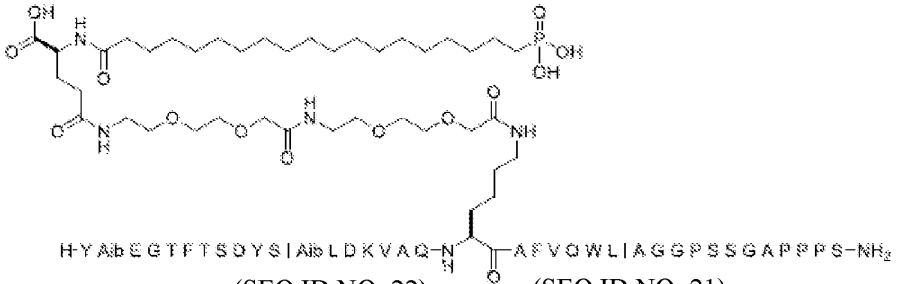
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13



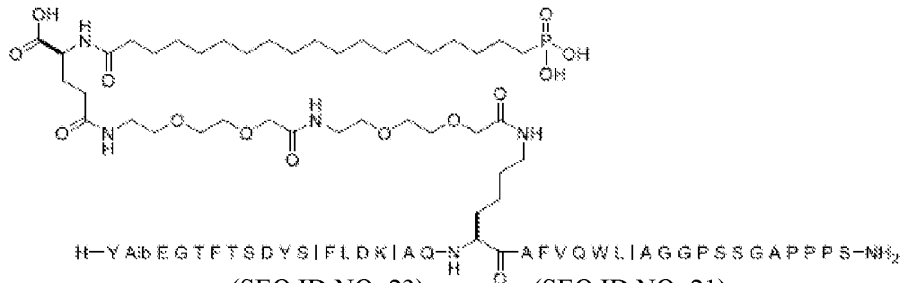
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14



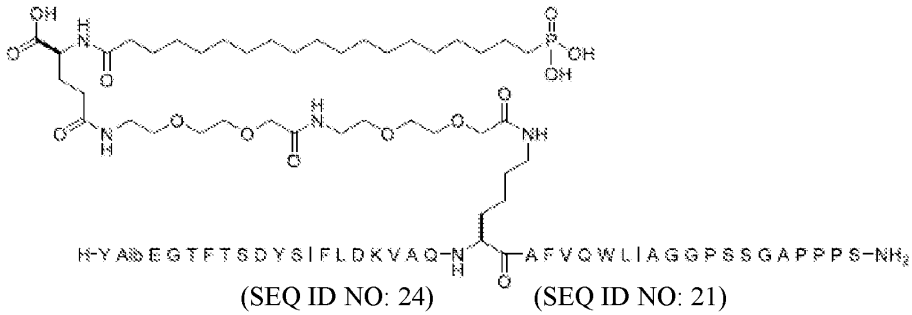
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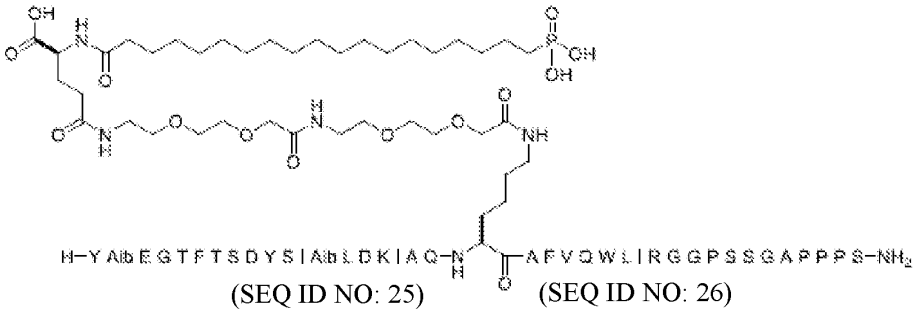
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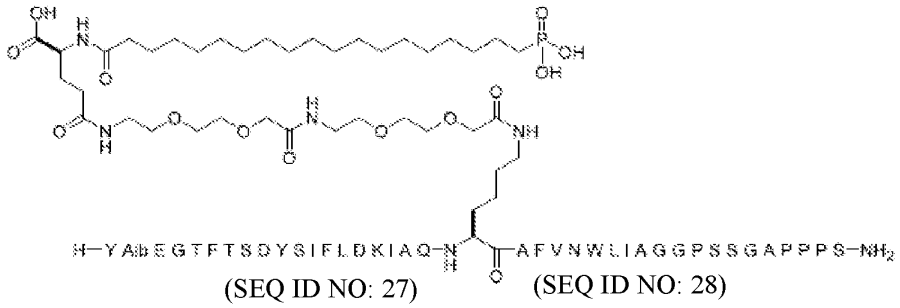
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17



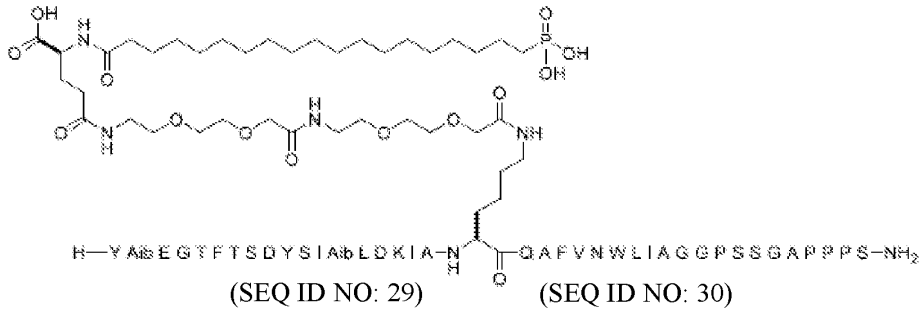
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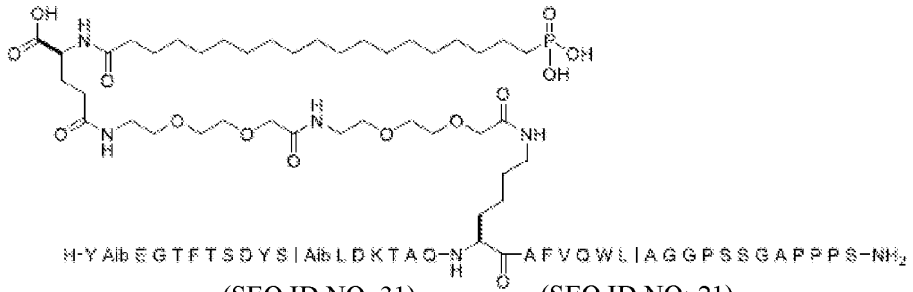
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19



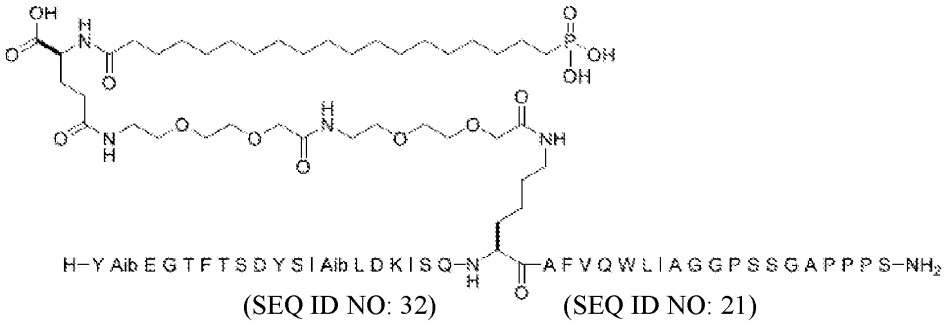
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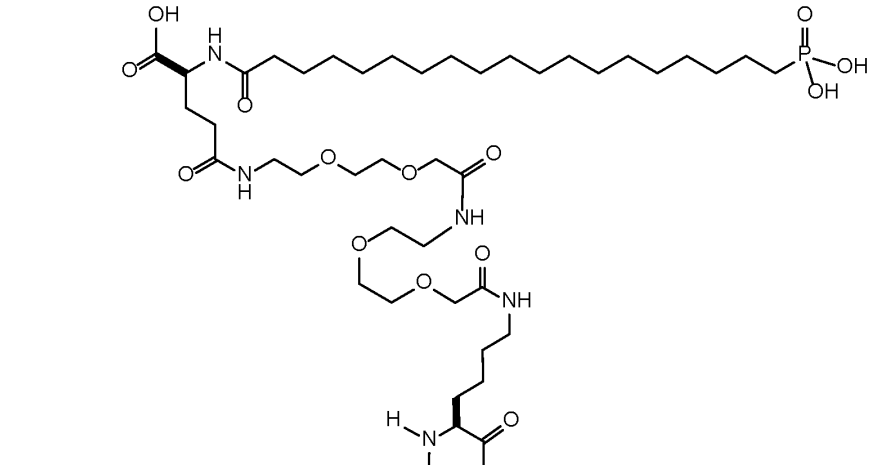
(SEQ ID NO: 31) (SEQ ID NO: 21)

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(SEQ ID NO: 32) (SEQ ID NO: 21)

22



(SEQ ID NO: 22) (SEQ ID NO: 26)

23

or pharmaceutically acceptable salts thereof.

[0145] The compounds of Formula (II) described herein, e.g., Compounds 13-23, may be prepared according to methods described in International Patent Publication No. 2023/044290, the disclosure of which is incorporated herein in its entirety.

Pharmaceutical Compositions

[0146] Some embodiments include pharmaceutical compositions comprising Compound A, or a pharmaceutically acceptable salt thereof; and a compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a) or (II-b), or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutical composition comprises one or more permeability enhancer. In some embodiments, the pharmaceutical composition further comprises one or more

pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is suitable for use as an oral dosage form, e.g., a tablet or capsule.

[0147] In some embodiments, the oral dosage form may be a tablet. In some such embodiments, the tablet may comprise Compound A, or a pharmaceutically acceptable salt thereof; and a compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a) or (II-b), or a pharmaceutically acceptable salt thereof. In some embodiments, Compound A and the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a) or (II-b) may be formulated together in a single monolayer tablet. In other embodiments, Compound A and the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a) or (II-b) may be formulated as separate layers and then combined in a bilayer tablet.

[0148] Compounds that normally cannot be administered orally due to poor oral bioavailability may be formulated with a permeability enhancer. Permeability enhancers may increase absorption of an active pharmaceutical ingredient by enhancing membrane permeation. In some embodiments, the permeability enhancer is present in the pharmaceutical composition at a weight percentage of about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 85%, or more, or within a range defined by any two of the aforementioned weight percentages. For example, in some embodiments, the permeability enhancer is present in the pharmaceutical composition a weight percentage of from about 30% to about 80%, from about 40% to about 80%, from about 40% to about 60%, from about 50% to about 80%, from about 50% to about 75%, from about 60% to about 75%, or from about 70% to about 75% percent.

[0149] In some embodiments, the amount of permeability enhancer in the pharmaceutical compositions described herein is about 1 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 480 mg, 490 mg, 500 mg, 510 mg, 520 mg, 530 mg, 540 mg, 550 mg, 560 mg, 570 mg, 580 mg, 590 mg, 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 680 mg, 690 mg, 700 mg, 710 mg, 720 mg, 730 mg, 740 mg, 750 mg, 760 mg, 770 mg, 780 mg, 790 mg, 800 mg, 810 mg, 820 mg, 830 mg, 840 mg, 850 mg, 860 mg, 870 mg, 880 mg, 890 mg, 900 mg. 910 mg, 920 mg, 930 mg, 940 mg, 950 mg, 960 mg, 970 mg, 980 mg, 990 mg, 1000 mg, or more, or within a range defined

by any two of the aforementioned values. For example, in some embodiments, the amount of permeability enhancer in the pharmaceutical compositions described herein is from about 1 mg to about 1000 mg, from about 350 mg to about 900 mg, from about 350 mg to about 800 mg, from about 400 mg to about 800 mg, from about 400 mg to about 600 mg, or from about 500 mg to about 750 mg. In some embodiments, the amount of permeability enhancer in the pharmaceutical compositions described herein is greater than 300 mg, greater than 350 mg, greater than 400 mg, greater than 450 mg, greater than 500 mg, greater than 550 mg, greater than 600 mg, greater than 650 mg, greater than 700 mg, greater than 750 mg, greater than 800 mg greater than 850 mg, greater than 900 mg, greater than 950 mg, or greater than 1000 mg.

[0150] In some embodiments, the permeability enhancer is salcaprozate sodium (i.e., sodium 8-(2-hydroxybenzamido)octanoate or "SNAC"), sodium caproate (C10), or a combination thereof. In some embodiments, the permeability enhancer is SNAC. In other embodiments, the permeability enhancer is C10. In yet other embodiments, the permeability enhancer is a combination of SNAC and C10.

[0151] In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition has a weight percentage of about 0.5%, 0.6%, 0.7%, 0.8%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, 10.0%, or higher, or within a range defined by any two of the aforementioned values. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is in the range of from about 1.0% to about 5.0%, from about 2.0% to about 4.0%, from about 2.0% to about 3.0%, from about 2.0% to about 2.5%, from about 3.0% to about 4.0%, or from about 3.5% to about 4.0% by weight. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is about 2.3% by weight.

[0152] In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is about 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg,

15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg, 48.5 mg, 49 mg, 49.5 mg, 50 mg, or more, or within a range defined by any two of the aforementioned values. For example, in some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is from about 1 mg to about 30 mg, from about 5 mg to about 25 mg, from about 10 mg to about 20 mg, from about 10 mg to about 30 mg, or from about 20 mg to about 30 mg. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is about 25 mg. In some embodiments, the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is Compound 4.

[0153] In some embodiments, the mass ratio of the permeability enhancer to the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is about 1:1, 2:1, 3:1, 5:1, 10:1, 15:1, 16:1, 17:1, 18:1, 19:1, 20:1, 21:1, 22:1, 23:1, 24:1, 25:1, 26:1, 27:1, 28:1, 29:1, 30:1, 35:1, 40:1, 45:1, 50:1, or more, or within a range defined by any two of the aforementioned ratios. For example, in some embodiments, the mass ratio of the permeability enhancer to the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the pharmaceutical composition is from about 1:1 to about 50:1, from about 10:1 to about 25:1, from about 15:1 to about 25:1, or from about 20:1 to about 25:1.

[0154] In some embodiments, the amount of Compound 4 in the pharmaceutical composition is from about 5 mg to about 30 mg and the amount of SNAC is from about 350 mg to about 1000 mg. In some embodiments, the amount of Compound 4 in the pharmaceutical composition is from about 10 mg to about 30 mg and the amount of SNAC is from about 400 mg to about 800 mg. In some embodiments, the amount of Compound 4 in the pharmaceutical composition is from about 15 mg to about 25 mg and the amount of SNAC is from about 450 mg to about 750 mg. In some embodiments, the amount of Compound 4 in the pharmaceutical composition is about 20 mg to and the amount of SNAC is about 450 mg. In some embodiments,

the amount of Compound 4 in the pharmaceutical composition is about 25 mg to and the amount of SNAC is about 500 mg.

[0155] In some embodiments, Compound A may be included in the pharmaceutical composition. In some embodiments, Compound A may first be combined with one or more polymers and then further formulated into a desired dosage form. In some embodiments, Compound A is in the form of a spray dried dispersion (SDD). In other embodiments, Compound A is in the form of a hot melt extrusion. In some embodiments, the dosage form is an oral dosage form. In some specific embodiments, the oral dosage form is a tablet. In other embodiments, the oral dosage from is a capsule.

[0156] In some embodiments, the polymer for preparation of the spray dried dispersion comprising Compound A may be selected from one or more of polyvinyl pyrrolidone (PVP) polyvinyl pyrrolidone-vinyl acetate copolymer (PVP-VA), polyvinyl alcohol (PVA), polyacrylic acid (PAA), poly(ethylene oxide) (PEO), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), copovidone, poloxamer 407, hypromellose acetate succinate (HPMCAS), Eudragit®, and polyacrylates. In some embodiments, the polymer may be PVP. In some embodiments, the polymer may be PVP-VA. In other embodiments the polymer may be HPMCAS. In yet other embodiments, the polymer may be HPMC. In some embodiments, the polymer may be Eudragit®. In some embodiments, the polymer for the preparation of the spray dried dispersion of Compound A may be a combination of PVP-VA and poloxamer 407.

[0157] Spray dried dispersions of Compound A with one or more polymers may be prepared by combining Compound A and polymer in a suitable solvent and then spraying the feed into a hot drying medium to remove the solvent. Preparing a spray dried dispersion (SDD) of Compound A and one or more polymers may increase the aqueous solubility (and consequently the bioavailability) of Compound A and may increase the stability of Compound A such that storage under normal conditions is possible.

[0158] In some embodiments, the mass ratio of Compound A to polymer in the SDD is from about 1:10 to about 10:1. For example, in some embodiments, the mass ratio of Compound A to polymer in the SDD is about 1:1, 1.5:1, 2:1, 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1 or 5:1. In some embodiments, the mass ratio of Compound A to polymer in the SDD can be in the range of about 1:1 to 5:1, 1.5:1 to 5:1, 2:1 to 4:1, 2.5:1 to 3.5:1 or 3:1 to 5:1. In some embodiments, the mass ratio of Compound A to polymer in the SDD can be in the range of about 1:1 to 1:5, 1:1 to 1:4, 1:1

to 1:3, or 1:2 to 1:4. In some embodiments, the mass ratio of Compound A to polymer in the SDD can be about 1:3.

[0159] In some embodiments, the amount of Compound A in the pharmaceutical composition is about 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 3.5 mg, 4 mg, 4.5 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 9.5 mg, 10 mg, 10.5 mg, 11 mg, 11.5 mg, 12 mg, 12.5 mg, 13 mg, 13.5 mg, 14 mg, 14.5 mg, 15 mg, 15.5 mg, 16 mg, 16.5 mg, 17 mg, 17.5 mg, 18 mg, 18.5 mg, 19 mg, 19.5 mg, 20 mg, 20.5 mg, 21 mg, 21.5 mg, 22 mg, 22.5 mg, 23 mg, 23.5 mg, 24 mg, 24.5 mg, 25 mg, 25.5 mg, 26 mg, 26.5 mg, 27 mg, 27.5 mg, 28 mg, 28.5 mg, 29 mg, 29.5 mg, 30 mg, 30.5 mg, 31 mg, 31.5 mg, 32 mg, 32.5 mg, 33 mg, 33.5 mg, 34 mg, 34.5 mg, 35 mg, 35.5 mg, 36 mg, 36.5 mg, 37 mg, 37.5 mg, 38 mg, 38.5 mg, 39 mg, 39.5 mg, 40 mg, 40.5 mg, 41 mg, 41.5 mg, 42 mg, 42.5 mg, 43 mg, 43.5 mg, 44 mg, 44.5 mg, 45 mg, 45.5 mg, 46 mg, 46.5 mg, 47 mg, 47.5 mg, 48 mg, 48.5 mg, 49 mg, 49.5 mg, 50 mg, or more, or within a range defined by any two of the aforementioned values. For example, in some embodiments, the amount of Compound A in the pharmaceutical composition is from about 1 mg to about 50 mg, from about 5 mg to about 40 mg, from about 10 mg to about 30 mg, from about 20 mg to about 30 mg, or from about 25 mg to about 35 mg. In some embodiments, the amount of Compound A in the pharmaceutical composition is about 30 mg.

[0160] In some embodiments, the amount of spray dried dispersion (SDD) comprising Compound A and polymer in the pharmaceutical composition is about 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, or more, or within a range defined by any two of the aforementioned values. For example, in some embodiments, the amount of SDD comprising Compound A and polymer in the pharmaceutical composition is from about 10 mg to about 200 mg, from about 50 mg to about 150 mg, from about 100 mg to about 150 mg, from about 120 mg to about 150 mg, or from about 100 mg to about 125 mg. In some embodiments, the amount of spray dried dispersion (SDD) comprising Compound A and polymer in the pharmaceutical composition is about 120 mg.

[0161] In some embodiments, the pharmaceutical composition described herein may be in the form of a tablet. In some such embodiments, the tablet may be a bilayer tablet comprising: a first layer comprising a compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a) or (II-b), or a pharmaceutically acceptable salt thereof; and a second layer comprising Compound A, or a

pharmaceutically acceptable salt thereof. In some such embodiments, the first layer, second layer, or both the first layer and second layer may be enterically coated.

[0162] In some embodiments, wherein the pharmaceutical composition is formulated as a bilayer tablet, the permeability enhancer may initially formulated with the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) to make a first layer. In some such embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the first layer has a weight percentage of about 0.5%, 0.6%, 0.7%, 0.8%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, 10.0%, or higher, or within a range defined by any two of the aforementioned values. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the first layer is in the range of from about 1.0% to about 5.0%, from about 2.0% to about 4.0%, from about 2.0% to about 3.0%, from about 2.0% to about 2.5%, from about 3.0% to about 4.0%, or from about 3.5% to about 4.0% by weight. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the first layer is about 3.6% by weight.

[0163] In some such embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the composition has a weight percentage of about 0.5%, 0.6%, 0.7%, 0.8%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.5%, 6.0%, 6.5%, 7.0%, 7.5%, 8.0%, 8.5%, 9.0%, 9.5%, 10.0%, or higher, or within a range defined by any two of the aforementioned values. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the composition is in the range of from about 1.0% to about 5.0%, from about 2.0% to about 4.0%, from about 2.0% to about 3.0%, from about 2.0% to about 2.5%, from about 3.0% to about 4.0%, or from about 3.5% to about 4.0% by weight. In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) in the composition is about 2.3% by weight.

[0164] In some embodiments of the pharmaceutical compositions described herein, the first layer (i.e., the GIP/GLP-1 dual agonist layer) may comprise the compound of Formula (I), (I-

a), (I-b), (I-c), (II), (II-a), or (II-b) and SNAC. In some such embodiments, the first layer may further comprise microcrystalline cellulose, croscarmellose sodium (AcDiSol), magnesium stearate, or a combination thereof.

[0165] In some embodiments of the pharmaceutical compositions described herein, the first layer may comprise the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b) and C10. In some such embodiments, the first layer may further comprise microcrystalline cellulose, croscarmellose sodium (AcDiSol), magnesium stearate, or a combination thereof.

[0166] In some embodiments of the pharmaceutical compositions described herein, the first layer may comprise the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b)) and a combination of SNAC and C10. In some such embodiments, the first layer may further comprise microcrystalline cellulose, croscarmellose sodium (AcDiSol), magnesium stearate, or a combination thereof.

[0167] In some embodiments of the pharmaceutical compositions described herein, the first layer may comprise microcrystalline cellulose in an amount of about 5%, 10%, 15%,16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, or more by weight, or within a range defined by any two of the aforementioned percentages. For example, the first layer may comprise about from 10% to 50%, 10% to 40%, 10% to 30%, 15% to 30%, 15% to 25%, or 15% to 20% by weight microcrystalline cellulose. In some embodiments, the first layer comprises about 17.3% microcrystalline cellulose by weight.

[0168] In some embodiments, the first layer may comprise magnesium stearate in an amount of about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2.%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.5%, or 5.0% by weight, or within a range defined by any two of the aforementioned percentages. For example, the first layer may comprise from about 1.0% to about 5.0%, from about 1.0% to about 4.0%, from about 1.0% to about 3.0%, from about 1.5% to about 3.0%, from about 1.5% to about 2.5%, or from about 1.5% to about 2.0% by weight magnesium stearate. In some embodiments, the first layer comprises about 2.3% magnesium stearate by weight.

[0169] In some embodiments, first layer may comprise croscarmellose sodium in an amount of about 0.5%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%,

2.1%, 2.2.%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1% 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9% or 5.0% by weight, or within a range defined by any two of the aforementioned percentages. For example, the first layer may comprise from about 1.0% to about 5.0%, from about 2.0% to about 5.0%, from about 2.5% to about 5%, from about 3% to about 5%, from about 1.5% to about 2.5%, or from about 1.5% to about 2.0% by weight croscarmellose sodium. In some embodiments, the first layer comprises about 4.7% croscarmellose sodium by weight.

[0170] In some embodiments, the first layer may comprise from about 1.0 to about 5.0% by weight of the of compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b); from about 50% to about 80% by weight salcaprozate sodium; from about 10% to about 30% by weight microcrystalline cellulose; from about 1.0% to about 5.0% by weight croscarmellose sodium; and from about 1.0% to about 3.0% by weight magnesium stearate. In some such embodiments, first layer comprises: about 3.6% by weight of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), or (II-b); about 72% by weight salcaprozate sodium; about 17.3% by weight microcrystalline cellulose; about 2.3% by weight magnesium stearate; and about 4.7% croscarmellose sodium.

[0171] In some embodiments, wherein the pharmaceutical composition is formulated as a bilayer tablet, the second layer (TR-β agonist layer) comprises Compound A, or a pharmaceutically acceptable salt thereof. In some embodiments, the second layer may comprise Compound A in an amount from about 0.5%, 0.6%, 0.7%, 0.8%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.1%, 5.2%, 5.3%, 5.4%, 5.5%, 5.6%, 5.7%, 5.8%, 5.8%, 5.9%, 6.0%, 6.1%, 6.2%, 6.3%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, 10.0%, or higher, or within a range defined by any two of the aforementioned values. In some embodiments, the amount of Compound A or a pharmaceutically acceptable salt thereof in the second layer of the composition is in the range of from about 1.0% to about 10.0%, from about 2.0% to about 8.0%, from about 4.0% to about 7.0%, from about 5.0% to about 8.0%, from about 7.5% to about 8.0%, or from about 3.5% to about 9.0% by weight. In some embodiments, the amount of

Compound A or a pharmaceutically acceptable salt thereof in the second layer of composition is about 7.5% by weight.

[0172] In some embodiments, the composition may comprise Compound A in an amount from about 0.5%, 0.6%, 0.7%, 0.8%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.1%, 2.2%, 2.3%, 2.4%, 2.5%, 2.6%, 2.7%, 2.8%, 2.9%, 3.0%, 3.1%, 3.2%, 3.3%, 3.4%, 3.5%, 3.6%, 3.7%, 3.8%, 3.9%, 4.0%, 4.1%, 4.2%, 4.3%, 4.4%, 4.5%, 4.6%, 4.7%, 4.8%, 4.9%, 5.0%, 5.1%, 5.2%, 5.3%, 5.4%, 5.5%, 5.6%, 5.7%, 5.8%, 5.8%, 5.9%, 6.0%, 6.1%, 6.2%, 6.3%, 6.4%, 6.5%, 6.6%, 6.7%, 6.8%, 6.9%, 7.0%, 7.1%, 7.2%, 7.3%, 7.4%, 7.5%, 7.6%, 7.7%, 7.8%, 7.9%, 8.0%, 8.1%, 8.2%, 8.3%, 8.4%, 8.5%, 8.6%, 8.7%, 8.8%, 8.9%, 9.0%, 9.1%, 9.2%, 9.3%, 9.4%, 9.5%, 9.6%, 9.7%, 9.8%, 9.9%, 10.0%, or higher, or within a range defined by any two of the aforementioned values. In some embodiments, the amount of Compound A or a pharmaceutically acceptable salt thereof in the composition is in the range of from about 1.0% to about 10.0%, from about 2.0% to about 8.0%, from about 1.0% to about 5.0%, from about 5.0% to about 8.0%, from about 1.5% to about 3.0%, or from about 2.0% to about 4.0% by weight. In some embodiments, the amount of Compound A or a pharmaceutically acceptable salt thereof in the composition is about 2.7% by weight.

[0173] The tablet formulations comprising Compound A described herein may further comprise one or more additional pharmaceutically-acceptable excipient(s). In some embodiments, the pharmaceutically acceptable excipients may comprise microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, SiO_2, magnesium stearate, or a combination thereof. In some embodiments, the second layer of bilayer formulations described herein may comprise microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, SiO_2, magnesium stearate, or a combination thereof.

[0174] The pharmaceutical compositions can be administered with a route of administration including, but not limited to, enteral, intravenous, oral, intraarticular, intramuscular, subcutaneous, intraperitoneal, epidural, intranasal, topical, intrapulmonary, vaginal, rectal, transdermal, and transmucosal. In some embodiments, the route of administration selected from the group consisting of enteral, intravenous, oral, intraarticular, intramuscular, subcutaneous, intraperitoneal, epidural, transdermal, and transmucosal. In some embodiments, the pharmaceutical compositions are administered subcutaneously. In some embodiments, the

pharmaceutical compositions are administered intravenously. In some embodiments, the pharmaceutical compositions are administered orally.

[0175] In some embodiments, the pharmaceutical compositions are administered to a subject that is a mammal. In some such embodiments, the pharmaceutical compositions are administered to a subject that is a human.

Methods of Treatment

[0176] The pharmaceutical compositions disclosed herein include compounds or their tautomers and/or pharmaceutically acceptable salts thereof that can effectively act as GIP/GLP1 dual receptor agonists and can include compounds that can act as a TR-β agonist. The pharmaceutical compositions further comprise one or more pharmaceutically acceptable carriers and one or more pharmaceutically acceptable diluents.

[0177] Some embodiments provide a method of preventing, treating, or ameliorating one or more fatty liver diseases in a subject. In some embodiments, the method includes administering one or more of the pharmaceutical compositions disclosed herein to a subject in need thereof.

[0178] Some embodiments provide a method preventing, treating, or ameliorating steatosis, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease. In some embodiments, the method includes administering one or more of the pharmaceutical compositions disclosed herein to a subject in need thereof.

[0179] In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the prevention, treatment, or amelioration, of a fibrosis, fibrotic condition, or fibrotic symptoms.

[0180] In some embodiments, the pharmaceutical compositions described herein can be used to treat a host of conditions arising from fibrosis or inflammation, and specifically including those associated with myofibroblast differentiation. Example conditions include progressive liver fibrosis (alcoholic, viral, autoimmune, metabolic and hereditary chronic disease), renal fibrosis (e.g., resulting from chronic inflammation, infections or type II diabetes), lung fibrosis (idiopathic or resulting from environmental insults including toxic particles, sarcoidosis, asbestosis, hypersensitivity pneumonitis, bacterial infections including tuberculosis, medicines, etc.), interstitial fibrosis, systemic scleroderma (autoimmune disease in which many organs become fibrotic), macular degeneration (fibrotic disease of the eye), pancreatic fibrosis (resulting

from, for example, alcohol abuse and chronic inflammatory disease of the pancreas), fibrosis of the spleen (from sickle cell anemia, other blood disorders), cardiac fibrosis (resulting from infection, inflammation and hypertrophy), mediastinal fibrosis, myelofibrosis, endomyocardial fibrosis, retroperitoneal fibrosis, progressive massive fibrosis, nephrogenic systemic fibrosis, diabetic nephropathy, non-alcoholic steatohepatitis, primary sclerosing cholangitis, corneal fibrosis, liver cirrhosis, fibrotic complications of surgery, chronic allograft vasculopathy and/or chronic rejection in transplanted organs, ischemic reperfusion injury associated fibrosis, injection fibrosis, cirrhosis, diffuse parenchymal lung disease, post-vasectomy pain syndrome, and rheumatoid arthritis diseases or disorders.

[0181] In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the reduction in the amount of extracellular matrix proteins present in one or more tissues of said subject.

[0182] In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the reduction in the amount of collagen present in one or more tissues of said subject.

[0183] In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the reduction in the amount of Type I, Type Ia, or Type III collagen present in one or more tissues of said subject.

[0184] Some embodiments provide a method of preventing, treating, or ameliorating one or more of liver fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis, primary biliary cirrhosis, or idiopathic fibrosis in a subject. In some embodiments, the method includes administering one or more of the pharmaceutical compositions disclosed herein to a subject in need thereof.

[0185] Some embodiments provide a method of preventing, treating, or ameliorating one or more of nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis, or primary biliary cirrhosis in a subject. In some embodiments, the method includes administering one or more of the pharmaceutical compositions disclosed herein to a subject in need thereof.

[0186] Some embodiments provide a method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes. In some embodiments, said disease or

disorder is atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, hypothalamic obesity, or prader-willi syndrome. In some embodiments, the method includes administering one or more of the pharmaceutical compositions disclosed herein to a subject in need thereof.

[0187] Some embodiments include co-administering a pharmaceutical composition and/or a compound, or pharmaceutically acceptable salt thereof, described herein, with an additional medicament. By "co-administration," it is meant that the two or more agents may be found in the patient's bloodstream at the same time, regardless of when or how they are actually administered. In one embodiment, the agents are administered simultaneously. In one such embodiment, administration in combination is accomplished by combining the agents in a single dosage form. In another embodiment, the agents are administered sequentially. In one embodiment the agents are administered through the same route, such as orally. In another embodiment, the agents are administered through different routes, such as one being administered subcutaneously, another being administered orally and another being administered i.v.

[0188] Some embodiments disclosed herein include co-administration of a composition comprising TR-β agonist (e.g., Compound A) and a dual GIP/GLP-1 agonist (e.g., Compound 4), to a patient in need thereof. Other embodiments include administration of separate compositions of a TR-β agonist and a dual GIP/GLP-1 agonist. In some such embodiments, these separate compositions may be administered sequentially. For example, in some embodiments, the TR-β agonist may be administered to the patient prior to administering the dual GIP/GLP-1 agonist to the patient. In some such embodiments, the TR-β agonist may be administered to the patient 1, 2, 3, 4, 5, 10, 15, 20, 30, 40, 50, 60, 90 or 120 minutes or more prior to administering the dual GIP/GLP-1 agonist to the patient. In other embodiments, the dual GIP/GLP-1 agonist may be administered to the patient prior to administering the TR-β agonist to the patient. In some such embodiments, the dual GIP/GLP-1 agonist may be administered 1, 2, 3, 4, 5, 10, 15, 20, 30, 40, 50, 60, 90 or 120 minutes or more prior to the patient prior to administering the TR-β.

[0189] To further illustrate this disclosure, the following examples are included. The examples should not, of course, be construed as specifically limiting the disclosure. Variations of these examples within the scope of the claims are within the purview of one skilled in the art and are considered to fall within the scope of the disclosure as described, and claimed herein. The

reader will recognize that the skilled artisan, armed with the present disclosure, and skill in the art is able to prepare and use the disclosure without exhaustive examples. The following examples will further describe the present disclosure, and are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

General procedures

[0190] Trademarks used herein are examples only and reflect illustrative materials used at the time of the disclosure. The skilled artisan will recognize that variations in lot, manufacturing processes, and the like, are expected. Hence the examples, and the trademarks used in them are non-limiting, and they are not intended to be limiting, but are merely an illustration of how a skilled artisan may choose to perform one or more of the embodiments of the disclosure.

[0191] The following abbreviations have the indicated meanings:

λz = lambda z (the apparent elimination rate constant)

AUC = area under the plasma concentration versus time curve

AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration

AUC_{inf} = AUC from time 0 extrapolated to infinity

Aib = aminoisobutyric acid

BLQ = below limit of quantification

C_{max} = maximum observed concentration, occurring at T_{max}

CL/F = total body clearance following extravascular administration

CV% = percent coefficient of variation

DMF = dimethylformamide

HPLC = high-performance liquid chromatography

LC-MS/MS = liquid chromatography tandem mass spectrometry

LLOQ = lower limit of quantification

N = number of samples with numerical values

NMR = nuclear magnetic resonance

PCC = pyridinium chlorochromate

PEG = polyethylene glycol

PK = pharmacokinetics

PO = oral administration

PVP = polyvinylpyrrolidinone

R^2 = correlation coefficient of regression

T_{max} = time at which C_{max} occurred

$t_{1/2}$ = half-life

V_z/F = volume of distribution following extravascular administration

[0192] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compositions provided herein. Furthermore, other methods for preparing compositions described herein will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above.

EXAMPLE 1

Bilayer Tablet Formulation 1

[0193] A batch of tablets (Tablet 1) with TR-β agonist Compound A and dual GIP/GLP-1 agonist Compound 4 as the active compounds were prepared by a dry granulation process. The amounts of each component are found in Tables 1 and 2 below, shown as mg/tablet and total mg in the 18.6 gram batch.

Table 1 - Compounding Table for Tablet Formulation 1 (per tablet)

Component	1st Fraction (mg)		2nd Fraction (mg)		Extragranular (mg)	
	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2
Compound 4	-	N/A	25.00*	-	-	-
25% Compound A:PVP-VA SDD	-		-	120.00	-	-
SNAC	500.00		-	-	-	-
Microcrystalline Cellulose	-		120.00	162.20	-	-
Lactose Monohydrate	-		-	75.00	-	-
AcDiSol (Primellose)	-		33.30	24.00	-	16.00
SiO2	-		-	0.80	-	-
Mg Stearate	12.83		-	1.00	3.33	1.00
Layer Total	512.83		178.30	383.00	3.33	17.00
Tablet Total	512.83		561.30		20.33	

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg and a final Compound A tablet strength of 30 mg.

Table 2- Compounding Table for Tablet Formulation 1 (per 18.6 g)

Component	1st Fraction		2nd Fraction		Extragranular	
	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2
Compound 4	-	N/A	0.425 g*	-	-	-
25% Compound A:PVP-VA SDD	-		-	2.040 g	-	-
SNAC	8.500 g		-	-	-	-
Microcrystalline Cellulose	-		2.040 g	2.757 g	-	-
Lactose Monohydrate	-		-	1.275 g	-	-
AcDiSol (Primellose)	-		0.566 g	0.408 g	-	0.272 g
SiO_2	-		-	0.014 g	-	-
Mg Stearate	0.218 g		-	0.017 g	0.057 g	0.017 g
Layer Total	8.718 g		3.031 g	6.511 g	0.057 g	0.289 g
Tablet Total	8.718 g		9.542 g		0.346 g	

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg and a final Compound A tablet strength of 30 mg.

[0194] Preparation of Layer 1 - First Fraction Granulation: Magnesium stearate was passed through a 355 µm sieve and geometrically diluted 2x with SNAC in a stainless steel bowl. The remaining SNAC was added to a V-blender and mixed for 2 minutes at 25 rpm. The SNAC and magnesium stearate mixture was then added to the V-blender and mixed for 20 minutes at 25 rpm. The mixture was pressed into tablets with a tooling size of 0.6875 inch round and a setting of 3 & 8/16. The slugs were then crushed into granules by mortar and pestle and sieved through a 212 µm mesh.

[0195] Preparation of Layer 1 - Second Fraction Granulation: Microcrystalline Cellulose, Compound 4, and primellose were combined into a stainless-steel bowl in the order listed and mixed manually for at least 3 minutes until visually homogenous. This mixture was then transferred to a V-blender and tumbled for 1 minute. This mixture was then pressed into tablets (Tooling Size: 0.6875 inch Round; Setting: 4 & 4/16), crushed into granules by mortar and pestle, and sieved through a 212µm mesh.

[0196] Preparation of Layer 1 - Combining Granules: The first fraction granules and the second fraction granules were added to a V-blender and mixed for 5 minutes at 32 rpm. The extragranular magnesium stearate was then added to the blender, mixed manually, and then mixed in the V-blender for 30 seconds at 32 rpm. The resulting mixture was then pressed into granules.

[0197] Preparation of Layer 2 - First Fraction Granulation: Magnesium stearate was passed through a 355 µm sieve and geometrically diluted 2x with SNAC in a stainless steel bowl. The remaining SNAC was added to a V-blender and mixed for 2 minutes at 25 rpm. The SNAC

and magnesium stearate mixture was then added to the V-blender and mixed for 20 minutes at 25 rpm. The mixture was pressed into tablets with a tooling size of 0.6875 inch round and a setting of 3 & 8/16. The slugs were then crushed into granules by mortar and pestle and sieved through a 212 μm mesh.

[0198] Preparation of Layer 2 - Second Fraction Granulation: Compound A/PVP-VA SDD, microcrystalline cellulose, lactose monohydrate, primellose, SiO_2, and magnesium stearate were weighed into a stainless steel bowl in the order listed and mixed for at least 3 minutes until visually homogeneous. The contents of the bowl were transferred to a V-blender, tumbled for 1 minute and then pressed into tablets with a tooling size of 0.6875 inch round and a setting of 4.75. The slugs were then crushed into granules by mortar and pestle and sieved through a 212 μm mesh.

[0199] Preparation of Layer 2 - Combining Granules: The first fraction granules and the second fraction granules were added to a V-blender and mixed for 5 minutes at 32 rpm. The extragranular magnesium stearate was then added to the blender, mixed manually, and then mixed in the V-blender for 30 seconds at 32 rpm. The resulting mixture was then pressed into granules.

[0200] Tableting of Bilayer Tablet – About 700 mg of Layer 1 granules were partially pressed into a tablet using a tooling press (0.400 x 0.7500 in oval). 400 mg of Layer 2 granules were then pressed on top of the Layer 1 slug while still in the tooling press.

EXAMPLE 2

Monolayer Tablet Formulation 2

[0201] A batch of tablets (Tablet 2) with TR-β agonist Compound A and dual GIP/GLP-1 agonist Compound 4 as the active compounds were prepared by a dry granulation process. The amounts of each component are found in Tables 3 and 4 below, shown as mg/tablet and total mg in the 32.9 gram batch.

Table 3 - Compounding Table for Tablet Formulation 2 (per tablet)

Component	1st Fraction	2nd Fraction	Extragranular
Compound 4	-	25 mg*	-
25% Compound A:PVP-VA SDD	-	120 mg	-
SNAC	500 mg	-	-
Microcrystalline Cellulose	-	162.2 mg	-
Lactose Monohydrate	-	75 mg	-
Mg Stearate	12.83 mg	2.4 mg	2.4 mg
SiO_2	-	0.8 mg	-
AcDiSol (Primellose)	-	24 mg	16 mg
Total	512.83 mg	409.4 mg*	18.4 mg

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg and a final Compound A tablet strength of 30 mg.

Table 4- Compounding Table for Tablet Formulation 2 (per 32.9 g)

Component	1st Fraction	2nd Fraction	Extragranular
Compound 4	-	0.875 g*	-
25% Compound A:PVP-VA SDD	-	4.2 g	-
SNAC	17.5 g	-	-
Microcrystalline Cellulose	-	5.677 g	-
Lactose Monohydrate	-	2.625 g	-
Mg Stearate	0.449 g	0.084 g	0.084 g
SiO2	-	0.028 g	-
AcDiSol (Primellose)	-	0.840 g	0.560 g
Total	17.949 g	14.329 g*	0.644 g

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg and a final Compound A tablet strength of 30 mg.

[0202] Preparation of First Fraction Granulation: Magnesium stearate was passed through a 355 µm sieve and geometrically diluted 2x with SNAC in a stainless steel bowl. The remaining SNAC was added to a V-blender and mixed for 2 minutes at 25 rpm. The SNAC and magnesium stearate mixture was then added to the V-blender and mixed for 20 minutes at 25 rpm. The mixture was pressed into tablets with a tooling size of 0.6875 inch round and a setting of 3 & 8/16. The slugs were then crushed into granules by mortar and pestle and sieved through a 212 µm mesh.

[0203] Preparation of Second Fraction Granulation: Microcrystalline cellulose, Compound 4, Compound A/PVP-VA SDD, lactose monohydrate, primellose, SiO_2, and magnesium stearate were combined into a stainless-steel bowl in the order listed and mixed

manually for at least 3 minutes until visually homogenous. This mixture was then transferred to a V-blender and tumbled for 1 minute. This mixture was then pressed into tablets (Tooling Size: 0.6875 inch Round; Setting: 4 & 4/16), crushed into granules by mortar and pestle, and sieved through a 212µm mesh.

[0204] Combining Granules: The first fraction granules and the second fraction granules were added to a V-blender and mixed for 5 minutes at 32 rpm. The extragranular magnesium stearate was then added to the blender, mixed manually, and then mixed in the V-blender for 30 seconds at 32 rpm.

[0205] Tableting: About 946 mg of the combined granules were pressed into a tablet (0.400 x 0.7500 in oval).

EXAMPLE 3

TR-β Agonist with disintegrant Tablet Formulation 3

[0206] A batch of tablets (Tablet 3) with GIP/GLP-1 dual agonist Compound 4 as the active compound was prepared. The tablet included the use of a disintegrant. The amounts of each component are found in Tables 5 and 6 below, shown as mg/tablet and total mg in the 34.7 gram batch.

Table 5 - Compounding Table for Tablet Formulation 3 (per tablet)

Component	**1st Fraction**	**2nd Fraction**	**Extragranular**
Compound 4	-	25 mg*	-
SNAC	500 mg	-	-
Microcrystalline Cellulose	-	120 mg	-
PVP K90	-	13.3 mg	-
Mg Stearate	12.85 mg	-	3.34 mg
AcDiSol (Primellose)	-	13.3 mg	-

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg

Table 6- Compounding Table for Tablet Formulation 3 (per 34.7 g)

Component	1st Fraction	2nd Fraction	Extragranular
Compound 4	-	1.26 g*	-
SNAC	25.2 g	-	-
Microcrystalline Cellulose	-	6.05 g	-
PVP K90	-	0.670 g	-
Mg Stearate	0.648 g	-	0.166 g
AcDiSol (Primellose)	-	0.670 g	-

*Adjusted for peptide content and %purity to obtain a final Compound 4 tablet strength of 25 mg

[0207] Preparation of First Fraction Granulation: Magnesium stearate was passed through a 355 µm sieve and geometrically diluted 2x with SNAC in a stainless steel bowl. The remaining SNAC was added to a V-blender and mixed for 2 minutes at 25 rpm. The SNAC and magnesium stearate mixture was then added to the V-blender and mixed for 20 minutes at 25 rpm. The mixture was pressed into tablets with a tooling size of 0.6875 inch round and a setting of 3 & 8/16. The slugs were then crushed into granules by mortar and pestle and sieved through a 212 µm mesh.

[0208] Preparation of Second Fraction Granulation: Microcrystalline cellulose, Compound 4, primellose, and PVP-K90 were combined into a stainless-steel bowl in the order listed and mixed manually for at least 3 minutes until visually homogenous. This mixture was then transferred to a V-blender and tumbled for 1 minute. This mixture was then pressed into tablets (Tooling Size: 0.6875 inch Round; Setting: 4 & 4/16), crushed into granules by mortar and pestle, and sieved through a 212µm mesh.

[0209] Combining Granules: The first fraction granules and the second fraction granules were added to a V-blender and mixed for 5 minutes at 32 rpm. The extragranular magnesium stearate was then added to the blender, mixed manually, and then mixed in the V-blender for 30 seconds at 32 rpm.

[0210] Tableting: About 694 mg of the combined granules were pressed into a tablet (0.3552 x 0.6659 in oval).

EXAMPLE 4

TR-β Agonist with disintegrant Tablet Formulation 4

[0211] A batch of tablets (Tablet 4) with TR-β agonist Compound A as the active compound was prepared. The tablet included the use of a disintegrant. The amounts of each component are found in Table 8 below, shown as mg/tablet and total mg in the 45.0 gram batch.

Table 7 - Compounding Table for Tablet Formulation 4 (per tablet)

Component	1st Fraction	2nd Fraction	Extragranular
25% Compound A:PVP-VA SDD	N/A	120 mg	-
Microcrystalline Cellulose		454.2 mg	-
Lactose Monohydrate		226.8 mg	-
AcDiSol (Primellose)		54 mg	36 mg
SiO2		4.8 mg	-
Mg Stearate		2.4 mg	2.4 mg
Total		862.2 mg	38.4 mg

*Adjusted for a final Compound A tablet strength of 30 mg.

Table 8- Compounding Table for Tablet Formulation 4 (per 45.0 g)

Component	1st Fraction	2nd Fraction	Extragranular
25% Compound A:PVP-VA SDD	N/A	6.0 g	-
Microcrystalline Cellulose		22.71 g	-
Lactose Monohydrate		11.34 g	-
AcDiSol (Primellose)		2.7 g	1.8 g
SiO2		0.24 g	-
Mg Stearate		0.12 g	0.12 g
Total		43.11	1.92 g

*Adjusted for a final Compound A tablet strength of 30 mg.

[0212] Preparation of Granules: Microcrystalline cellulose, Compound A/PVP-VA SDD, lactose monohydrate, primellose, SiO_2, and magnesium stearate were combined into a stainless-steel bowl in the order listed and mixed manually for at least 3 minutes until visually homogenous. This mixture was then transferred to a V-blender and tumbled for 1 minute. This mixture was then pressed into tablets (Tooling Size: 0.6875 inch Round; Setting: 4 & 4/16), crushed into granules by mortar and pestle, and sieved through a 212µm mesh. The granules were added to a V-blender and mixed for 5 minutes at 32 rpm. The extragranular primellose and

extragranular magnesium stearate were then added to the blender, mixed manually, and then mixed in the V-blender for 30 seconds at 32 rpm.

[0213] Tableting: About 901 mg of the combined granules were pressed into a tablet (0.3440 x 0.7480 in oval).

EXAMPLE 5

Formulation Studies

[0214] The pharmacokinetics of different tablet formulations of Compound 4 and/or Compound A were studied in male cynomolgus monkeys. The animals were acclimated to the study room for a minimum of 3 days prior to initiation of dosing. Monkeys were administered doses of in 5 groups: Group 1 (N=4, Formulation 1); Group 2 (N=5, Formulation 2); Group 3 (N=5, Formulation 3); Group 4 (N=5, Formulation 4); Group 5(N=5, Formulation 3 + Formulation 4) and tablets orally (2 tablets for Group 5). Blood samples (0.5 mL) were taken from the monkeys at Day 1 (pre-dose only), Day 2 (pre-dose only), and Day 3 (pre-dose and 1, 2, 4, 8, 24, 48, 72, 96, 120, 168, and 240 hours after administration). Sample analysis was measured with a LC-MS/MS method based on multiple reaction monitoring (MRM) of fragment ions for the monkey pharmacokinetic study. All samples from the study were stored at -80 °C until ready to be analyzed as a single batch. Pharmacokinetic parameters were calculated with Phoenix® WinNonlin® software (version 8.3) using non-compartmental analyses.

[0215] The mean pharmacokinetic parameters for Compound 4, Compound A, and Compound A' (which is the active form of Compound A) are provided in Table 9, 10, and 11 below.

Table 9 – Compound 4 Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Formulation 1	3.5	90.3	4370	266000
2	Formulation 2	2.20	100	505	37700
3	Formulation 3	1.80	102	1290	131000
4	Formulation 4	--	--	--	--
5	Formulation 3 + 4	2.0	108	431	38600

Table 10– Compound A Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Formulation 1	7.25	34.3	17.0	822
2	Formulation 2	7320	11.2	58.8	747
3	Formulation 3	--	--	--	--
4	Formulation 4	2.2	9.10	58.3	540
5	Formulation 3 + 4	11.2	--	18.5	--

Table 11 – Compound A' Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Formulation 1	20.0	17.8	406	23700
2	Formulation 2	8.40	9.10	58.3	20800
3	Formulation 3	--	--	--	--
4	Formulation 4	3.60	23.0	648	7310
5	Formulation 3 + 4	11.1	57.4	281	8190

[0216] The data shows that a single administration of Formulation 1 can achieve adequate concentrations of both Compound 4 and Compound A as compared with monolayer tablet Formulation 2 or separate administration of tablet Formulations 3 and 4.

EXAMPLE 6

GIP/GLP-1 Dual Agonist without disintegrant Tablet Formulation 5

[0217] A batch of tablets (Tablet 5) with GIP/GLP-1 Dual Agonist Compound 4 as the active compound was prepared according to the methods described in Example 3, above. The amount of Compound 4 in the tablet was 25 mg. The tablet was made without the use of a disintegrant. The amounts of each component are found in Table 12 below, shown with each component as a percentage on a dry basis.

Table 12 - GIP/GLP-1 Dual Agonist (without disintegrant) Tablet Formulation 5

Component	Percent (dry basis)
Compound 4	3.71
SNAC	74.13
Microcrystalline Cellulose	17.79
PVP K90	1.97
Mg Stearate	2.40
Total	100

EXAMPLE 7

TR-β Agonist with disintegrant Tablet Formulation 6

[0218] A batch of tablets (Tablet 6) with TR-β Agonist Compound A as the active compound was prepared according to the methods described in Example 4. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The tablet was made without the use of a disintegrant. The amounts of each component are found in Table 12 below, shown with each component as a percentage on a dry basis.

Table 13 - TR-β Agonist (with disintegrant) Tablet Formulation 6

Component	Percent (dry basis)
25% Compound A:PVP-VA SDD	12.55
Microcrystalline Cellulose	47.50
Lactose monohydrate	23.72
AcDiSol (Primellose)	9.41
SiO2	0.50
Mg Stearate	0.50
L-100 (enteric coating)	5.81
Total	100

EXAMPLE 8

Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 7 (no disintegrant)

[0219] A batch of tablets (Tablet 7) with GIP/GLP-1 Dual Agonist Compound 4 and TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The amount of Compound 4 in the composition was 25 mg. The tablet was made without the use of a disintegrant. The amounts of each component are found in Table 14 below, shown with each

component as a percentage on a dry basis. The tablets were prepared in a manner analogous to that described in Example 1.

Table 14 - Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 7

Component	Percent (dry basis)
Compound 4	2.25
25% Compound A:PVP-VA SDD	10.78
SNAC	44.92
Microcrystalline Cellulose	26.25
Lactose monohydrate	6.74
L-100 (enteric coating)	7.37
SiO2	0.07
Mg Stearate	1.63
Total	100

EXAMPLE 9

Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 8 (with disintegrant)

[0220] A batch of tablets (Tablet 8) with GIP/GLP-1 Dual Agonist Compound 4 and TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The amount of Compound 4 in the composition was 25 mg. The tablet was made with the use of a disintegrant. The amounts of each component are found in Table 15 below, shown with each component as a percentage on a dry basis and Table 16 showing the compounding per tablet.

Table 15 - Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 8

Component	Percent (dry basis)
Compound 4	2.59
25% Compound A:PVP-VA SDD	12.41
SNAC	51.70
Microcrystalline Cellulose	16.77
Lactose monohydrate	7.76
Mg Stearate	1.82
SiO2	0.08
AcDiSol (Primellose)	4.14
L-100 (enteric coating)	2.73
Total	100

Table 16 – Compounding Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 8

Component	1st Fraction	2nd Fraction	3rd Fraction	Extragranular
Compound 4		25		-
25% Compound A:PVP-VA SDD			120 mg	-
SNAC	500 mg			-
Microcrystalline Cellulose		120 mg	42.4 mg	36 mg
Lactose monohydrate			75 mg	-
Mg Stearate	12.83 mg		2.4 mg	2.4 mg
SiO2			0.8 mg	
AcDiSol (Primellose)			24 mg	16
L-100 (enteric coating)			26.4 mg	
Total	512.83 mg	145 mg	298.9 mg	18.4 mg

*Adjusted for a final Compound A tablet strength of 30 mg and a final Compound 4 strength of 25 mg.

[0221] The tablets were prepared by preparing a first fraction by passing the magnesium stearate through a 355 µm sieve. The magnesium stearate was then weighed into a stainless steel bowl. Next, the SNAC was weighed and then added to the magnesium stearate to geometrically dilute it three times. The remaining SNAC and the contents of the bowl were then transferred to a HDPE bottle and tumbled for one hour. This mixture was pressed into tablets and then crushed and passed through a 600µm mesh

[0222] A second fraction by weighing out the appropriate amount of microcrystalline cellulose and Compound 4, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh.

[0223] A third fraction was prepared by weighing out the appropriate amount of the 25% Compound A:PVP-VA SDD, microcrystalline cellulose, Lactose Monohydrate, Primellose, SiO2, and magnesium stearate, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. The granules formed in the third fraction were then coated using a 10% solution of L-100 to obtain a 5% coating by weight. The coating was performed using an overhead mixer with an impeller and appropriately sized beaker. The granules were added to the beaker and the L-100 solution was added dropwise. After addition of the coating, the mixer was run for 5-10 minutes. The granules were then transferred into a shallow, wide dish and allowed to dry overnight in a lyophilizer at room temperature.

[0224] To prepare the tablets, the granules from each of the three fractions were combined along with extragranular magnesium stearate in an HDPE bottle and mixed for 30 minutes to form the final blend. About 983 mg of the final blend was pressed into a tablet.

EXAMPLE 10

Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 9 (with disintegrant)

[0225] A batch of tablets (Tablet 9) with GIP/GLP-1 Dual Agonist Compound 4 and TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The amount of Compound 4 in the composition was 25 mg. The tablet was made with the use of a disintegrant. The amounts of each component are found in Table 17 below, shown with each component as a percentage on a dry basis and Table 18 showing the compounding per tablet.

Table 17 - Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 9

Component	Percent (dry basis)
Compound 4	2.21
25% Compound A:PVP-VA SDD	10.59
SNAC	44.14
Microcrystalline Cellulose	24.91
Lactose monohydrate	6.62
Mg Stearate	1.60
SiO2	0.07
AcDiSol	6.47
L-100 (enteric coating)	3.38
Total	100

Table 18 – Compounding for Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 9

Component	1st Fraction		2nd Fraction		Extragranular	
	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2
Compound 4			25 mg			-
25% Compound A:PVP-VA SDD				120 mg		-
SNAC	500 mg					-
Microcrystalline Cellulose			120 mg	162.2 mg		
Lactose monohydrate				75 mg		-
AcDiSol (Primellose)			33.3 mg	24.0 mg		16 mg
L-100 (enteric coating)						38.3
SiO2				0.8 mg		
Mg Stearate	12.83 mg			1 mg	3.33 mg	1 mg
Layer Total	512.83 mg		178.3 mg	383 mg	3.33 mg	55.3 mg
Total	512.83 mg		561.3 mg		56.63 mg	

*Adjusted for a final Compound A tablet strength of 30 mg and a final Compound 4 strength of 25 mg.

[0226] The tablets were prepared by preparing a Fraction 1 of Layer 1 by passing the magnesium stearate through a 355 µm sieve. The magnesium stearate was then weighed into a stainless steel bowl. Next, the SNAC was weighed and then added to the magnesium stearate to geometrically dilute it three times. The remaining SNAC and the contents of the bowl were then transferred to a HDPE bottle and tumbled for one hour. This mixture was pressed into tablets and then crushed and passed through a 600 µm mesh. Layer 1 of Fraction 2 was prepared by weighing out the appropriate amount of microcrystalline cellulose, primellose and Compound 4, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. Fraction 1 and Fraction 2 of layer 1 were added to a HDPE bottle and extragranular magnesium stearate was added and then mixed by rotating the bottle for 30 minutes to form Layer 1 final blend.

[0227] Layer 2, Fraction 2 was prepared by weighing out the appropriate amount of the 25% Compound A:PVP-VA SDD, microcrystalline cellulose, Lactose Monohydrate, Primellose, SiO2, and magnesium stearate, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. The granules formed were then coated using a 10% solution of L-100 to obtain a 5% coating

by weight. The coating was performed using an overhead mixer with an impeller and appropriately sized beaker. The granules were added to the beaker and the L-100 solution was added dropwise. After addition of the coating, the mixer was run for 5-10 minutes. The granules were then transferred into a shallow, wide dish and allowed to dry overnight in a lyophilizer at room temperature. The Layer 2 final blend was prepared by dried granules to a HDPE bottle with extragranular magnesium stearate and mixing by rotating the bottle for 30 minutes to form Layer 2 final blend.

[0228] To prepare the tablets, 694.4 mg of the layer 1 granulation was pressed part-way into a tablet. Next, about 438.3 mg of the layer 2 granulation was added and pressed completely to make the bilayer tablet.

EXAMPLE 11

Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 10 (no disintegrant)

[0229] A batch of tablets (Tablet 10) with GIP/GLP-1 Dual Agonist Compound 4 and TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The amount of Compound 4 in the composition was 25 mg. The tablet was made without the use of a disintegrant. The amounts of each component are found in Table 19 below, shown with each component as a percentage on a dry basis and Table 20 showing the compounding per tablet.

Table 19 - Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 10

Component	Percent (dry basis)
Compound 4	2.70
25% Compound A:PVP-VA SDD	12.98
SNAC	54.08
Microcrystalline Cellulose	17.54
Lactose monohydrate	8.11
Mg Stearate	1.91
SiO2	0.09
L-100 (enteric coating)	2.60
Total	100

Table 20 – Compounding Monolayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 10

Component	1st Fraction	2nd Fraction	3rd Fraction	Extragranular
Compound 4		25		-
25% Compound A:PVP-VA SDD			120 mg	-
SNAC	500 mg			-
Microcrystalline Cellulose		120 mg	42.2 mg	
Lactose monohydrate			75 mg	-
Mg Stearate	12.83 mg		2.4 mg	2.4 mg
SiO2			0.8 mg	
L-100 (enteric coating)			26.4 mg	
Total	512.83 mg	145 mg	264.4 mg	2.4 mg

*Adjusted for a final Compound A tablet strength of 30 mg and a final Compound 4 strength of 25 mg.

[0230] The tablets were prepared by preparing a first fraction by passing the magnesium stearate through a 355 µm sieve. The magnesium stearate was then weighed into a stainless steel bowl. Next, the SNAC was weighed and then added to the magnesium stearate to geometrically dilute it three times. The remaining SNAC and the contents of the bowl were then transferred to a HDPE bottle and tumbled for one hour. This mixture was pressed into tablets and then crushed and passed through a 600µm mesh.

[0231] A second fraction by weighing out the appropriate amount of microcrystalline cellulose and Compound 4, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh.

[0232] A third fraction was prepared by weighing out the appropriate amount of the 25% Compound A:PVP-VA SDD, microcrystalline cellulose, Lactose Monohydrate, SiO2, and magnesium stearate, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. The granules formed in the third fraction were then coated using a 10% solution of L-100 to obtain a 5% coating by weight. The coating was performed using an overhead mixer with an impeller and appropriately sized beaker. The granules were added to the beaker and the L-100 solution was added dropwise. After addition of the coating, the mixer was run for 5-10 minutes. The granules were then transferred into a shallow, wide dish and allowed to dry overnight in a lyophilizer at room temperature.

[0233] To prepare the tablets, the granules from each of the three fractions were combined along with extragranular magnesium stearate in an HDPE bottle and mixed for 30 minutes to form the final blend. About 928 mg of the final blend was pressed into a tablet.

EXAMPLE 12

Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 11 (no disintegrant)

[0234] A batch of tablets (Tablet 11) with GIP/GLP-1 Dual Agonist Compound 4 and TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 30 mg. The amount of Compound 4 in the composition was 25 mg. The tablet was made without the use of a disintegrant. The amounts of each component are found in Table 21 below, shown with each component as a percentage on a dry basis and Table 22 showing the compounding per tablet.

Table 21 – Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 11

Component	Percent (dry basis)
Compound 4	2.37
25% Compound A:PVP-VA SDD	11.35
SNAC	47.30
Microcrystalline Cellulose	26.70
Lactose monohydrate	7.10
SiO2	0.08
Mg Stearate	1.72
L-100 (enteric coating)	3.40
Total	100

Table 22 – Compounding for Bilayer TR-β Agonist and GIP/GLP-1 Dual Agonist Tablet Formulation 11

Component	1st Fraction		2nd Fraction		Extragranular	
	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2
Compound 4			25 mg			-
25% Compound A:PVP-VA SDD				120 mg		-
SNAC	500 mg					-
Microcrystalline Cellulose			120 mg	162.2 mg		
Lactose monohydrate				75 mg		-
L-100 (enteric coating)						35.9
SiO2				0.8 mg		
Mg Stearate	12.83 mg			1 mg	3.33 mg	1 mg
Layer Total	512.83 mg		145 mg	383 mg	3.33 mg	36.9 mg
Total	512.83 mg		504 mg		40.23 mg	

*Adjusted for a final Compound A tablet strength of 30 mg and a final Compound 4 strength of 25 mg.

[0235] The tablets were prepared by preparing a Fraction 1 of Layer 1 by passing the magnesium stearate through a 355 µm sieve. The magnesium stearate was then weighed into a stainless steel bowl. Next, the SNAC was weighed and then added to the magnesium stearate to geometrically dilute it three times. The remaining SNAC and the contents of the bowl were then transferred to a HDPE bottle and tumbled for one hour. This mixture was pressed into tablets and then crushed and passed through a 600 µm mesh. Layer 1 of Fraction 2 was prepared by weighing out the appropriate amount of microcrystalline cellulose, and Compound 4, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. Fraction 1 and Fraction 2 of layer 1 were added to a HDPE bottle and extragranular magnesium stearate was added and then mixed by rotating the bottle for 30 minutes to form Layer 1 final blend.

[0236] Layer 2, Fraction 2 was prepared by weighing out the appropriate amount of the 25% Compound A:PVP-VA SDD, microcrystalline cellulose, Lactose Monohydrate, SiO2, and magnesium stearate, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600µm mesh. The granules formed were then coated using a 10% solution of L-100 to obtain a 5% coating by weight. The coating was performed using an overhead mixer with an impeller and appropriately sized beaker.

The granules were added to the beaker and the L-100 solution was added dropwise. After addition of the coating, the mixer was run for 5-10 minutes. The granules were then transferred into a shallow, wide dish and allowed to dry overnight in a lyophilizer at room temperature. The Layer 2 final blend was prepared by dried granules to a HDPE bottle with extragranular magnesium stearate and mixing by rotating the bottle for 30 minutes to form Layer 2 final blend.

[0237] To prepare the tablets, 664.5 mg of the layer 1 granulation was pressed part-way into a tablet. Next, about 395.9 mg of the layer 2 granulation was added and pressed completely to make the bilayer tablet.

EXAMPLE 13

Monolayer TR-β Agonist Tablet Formulation 12

[0238] A batch of tablets (Tablet 12) with TR-β Agonist Compound A as the active compounds was prepared. Compound A was included in the formulation as Compound A/PVP-VA SDD, with a total amount of Compound A of 5 mg. The amounts of each component are found in Table 23 below, shown with each component as a percentage on a dry basis. Compounding information is provided in Table 24.

Table 23 - Monolayer TR-β Agonist Tablet Formulation 12

Component	Percent (dry basis)
25% Compound A:PVP-VA SDD	13.33
Microcrystalline Cellulose	50.45
Lactose monohydrate	25.22
Mg Stearate	0.50
SiO2	0.50
AcDiSol (Primellose)	10.00
Total	100.00

Table 24 – Compounding for Monolayer TR-β Agonist Tablet Formulation 12 (For Total Batch Weight of 3331.1 g)

Component	Pregranulation	Extragranular
25% Compound A:PVP-VA SDD	445.2 g	-
Microcrystalline Cellulose	1684.9 g	--
Lactose monohydrate	842.3 g	-
Mg Stearate	8.3 g	7.777 g
SiO2	16.7 g	
AcDiSol (Primellose)	200.4 g	125.57 g
Total	3197.8	133.347

*Adjusted for a final Compound A tablet strength of 5 mg.

[0239] The tablets were prepared by weighing out the appropriate amount of the 25% Compound A:PVP-VA SDD, primellose, microcrystalline cellulose, Lactose Monohydrate, SiO2, and magnesium stearate, tumbling the powder and subsequently pressing the mixture into tablets. The tablets were then crushed into granules and sieved through a 600μm mesh. The resulting granules were combined with extragranular magnesium stearate and primelllose in an HDPE bottle and mixed for 30 minutes to form the final blend. The blend was subsequently pressed into tablets having a Compound A strength of 5 mg.

EXAMPLE 14

Formulation Studies

[0240] The pharmacokinetics of different tablet formulations of Compound 4 and/or Compound A were studied in male cynomolgus monkeys. The animals were acclimated to the study room for a minimum of 3 days prior to initiation of dosing. Monkeys were administered doses of in 8 groups: Group 5 (N=4, Tablet 5); Group 2 (N=5, Tablet 6); Group 3 (N=5, Tablet 7); Group 4 (N=5, Tablet 8); Group 5 (N=5, Tablet 9); Group 6 (N=4, Tablet 10); Group 7 (N=5, Tablet 11); Group 8 (N=5, Tablet 12); and administered 1 tablet per day on Day 1, Day 2, and Day 3 of the study, with the exception of Group 8, which was administered 6 tablets per day.. Blood samples (0.5 mL) were taken from the monkeys at Day 1 (pre-dose only), Day 2 (pre-dose only), and Day 3 (pre-dose and 1, 2, 4, 8, 24, 48, 72, 96, 120, 168, and 240 hours after administration). Sample analysis was measured with a LC-MS/MS method based on multiple reaction monitoring (MRM) of fragment ions for the monkey pharmacokinetic study. All samples from the study were stored at -80 °C until ready to be analyzed as a single batch. Pharmacokinetic parameters were calculated with Phoenix® WinNonlin® software (version 8.3) using non-compartmental analyses.

[0241] The mean pharmacokinetic parameters for Compound 4, Compound A, and Compound A' (which is the active form of Compound A) are provided in Table 24, 25, and 22 below.

Table 24 – Compound 4 Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Tablet 5	2.00	124	1360	102000
2	Tablet 6	--	--	--	--
3	Tablet 7	2.40	105	3130	284000
4	Tablet 8	2.20	106	645	74000
5	Tablet 9	2.60	94.9	2660	230000
6	Tablet 10	2.40	88.1	1340	86500
7	Tablet 11	2.60	98.1	2360	145000
8	Tablet 12	--	--	--	--

Table 25– Compound A Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Tablet 5			--	--
2	Tablet 6	20.7	12.2	12.1	495
3	Tablet 7	52.8	4.80	31.0	413
4	Tablet 8	10.5	17.2	28.9	1300
5	Tablet 9	139	4.00	58.0	1110
6	Tablet 10	45.8	12.0	35.6	650
7	Tablet 11	56.1	3.60	25.5	355
8	Tablet 12	5.21	12.2	12.1	495

Table 26 – Compound A' Pharmacokinetics

Group	Tablet	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} (ng/mL)	AUC_{INF} (hr•ng/mL)
1	Tablet 5	--	--	--	--
2	Tablet 6	23.9	21.6	320	13400
3	Tablet 7	13.9	5.20	393	7710
4	Tablet 8	19.3	27.2	663	25000
5	Tablet 9	31.6	4.80	780	12300
6	Tablet 10	20.5	12.8	585	19000
7	Tablet 11	18.9	4.40	480	5500
8	Tablet 12	27.1	21.6	320	13400

[0242] The data shows that a single administration of Tablet 8 can achieve adequate concentrations of both Compound 4 and Compound A as compared with administration of Tablets 1-4 or 6-8.

[0243] While some embodiments have been illustrated and described, a person with ordinary skill in the art, after reading the foregoing specification, can effect changes, substitutions of equivalents and other types of alterations to the compounds of the present technology or salts, pharmaceutical compositions, derivatives, prodrugs, metabolites, tautomers or racemic mixtures thereof as set forth herein. Each aspect and embodiment described above can also have included or incorporated therewith such variations or aspects as disclosed in regard to any or all of the other aspects and embodiments.

[0244] The present technology is also not to be limited in terms of the particular aspects described herein, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. It is to be understood that this present technology is not limited to particular methods, reagents, compounds, compositions, labeled compounds or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting. Thus, it is intended that the specification be considered as exemplary only with the breadth, scope and spirit of the present technology indicated only by the appended claims, definitions therein and any equivalents thereof.

[0245] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms "comprising," "including," "containing," etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed

technology. Additionally, the phrase "consisting essentially of" will be understood to include those elements specifically recited and those additional elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase "consisting of" excludes any element not specified.

[0246] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the present technology. This includes the generic description of the present technology with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0247] All publications, patent applications, issued patents, and other documents (for example, journals, articles and/or textbooks) referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[0248] Other embodiments are set forth in the following claims, along with the full scope of equivalents to which such claims are entitled.

[0249] While the disclosure has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the disclosure.

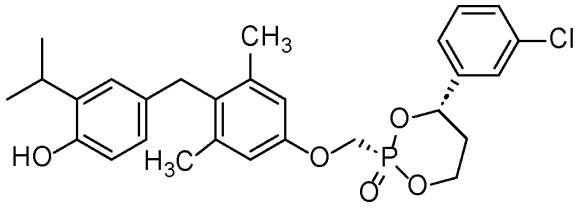
[0250] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes.

[0251] Although the disclosure has been described with reference to embodiments and examples, it should be understood that numerous and various modifications can be made without departing from the spirit of the disclosure. Accordingly, the disclosure is limited only by the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising:

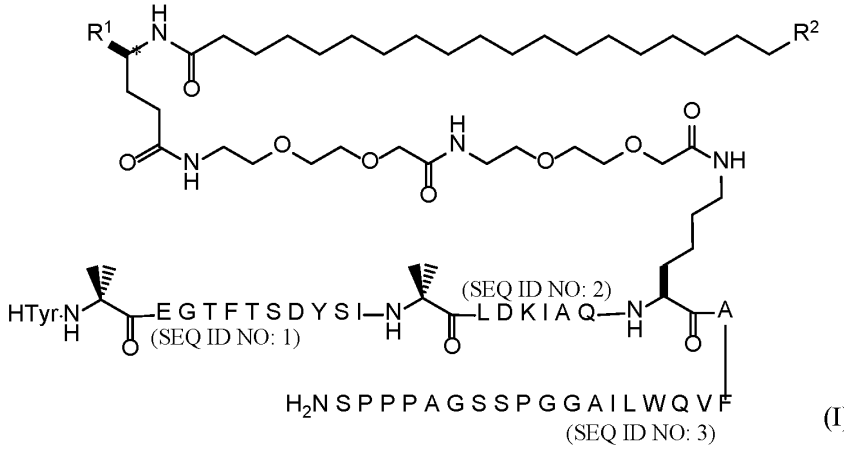
a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof



(Compound A); and

a therapeutically effective amount of a GIP/GLP-1 dual agonist.

2. The pharmaceutical composition of claim 1, wherein the GIP/GLP-1 dual agonist is a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from the group consisting of $–C(=O)(OZ^1)$, $–P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

R^2 is selected from the group consisting of $–C(=O)(OZ^2)$, $–P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $–OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

each R^7 may be independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

X and Y may each be independently selected from the group consisting of $-OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

each R^4 may be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{6-10} aryl alkyl;

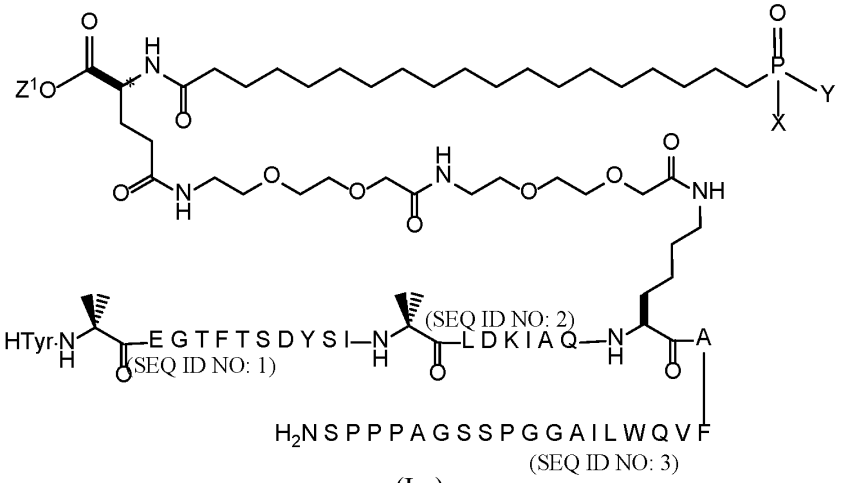
each R^5 may be independently hydrogen or C_{1-6} alkyl;

each R^6 may be independently hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 may each be independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl.

3. The pharmaceutical composition of claim 2, wherein at least one of Z^1 and Z^2 is not hydrogen.

4. The pharmaceutical composition of claim 2 or 3, wherein the GIP/GLP-1 dual agonist is a compound having the structure of Formula (I-a):



(I-a)

or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of claim 4, wherein Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

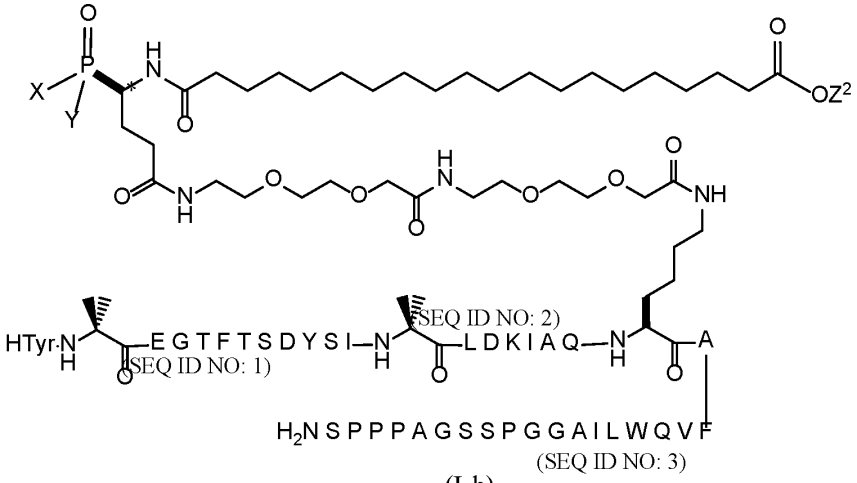
6. The pharmaceutical composition of claim 4 or 5, wherein Z^1 is selected from the group consisting of hydrogen, haloC_{1-6} alkyl and C_{1-6} alkyl; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryl and C_{6-10} aryl alkyl.

7. The pharmaceutical composition of any one of claims 4 to 6, wherein Z^1 is hydrogen and each R^4 independently is hydrogen or C_{6-10} aryl alkyl.

8. The pharmaceutical composition of any one of claims 4 to 7, wherein each R^4 is hydrogen.

9. The pharmaceutical composition of any one of claims 4 to 8, wherein Z^1 is hydrogen and each R^4 is hydrogen.

10. The pharmaceutical composition of claim 2, wherein the GIP/GLP-1 dual agonist is a compound having the structure of Formula (I-b):



(I-b)

or a pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of claim 10, wherein Z^2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

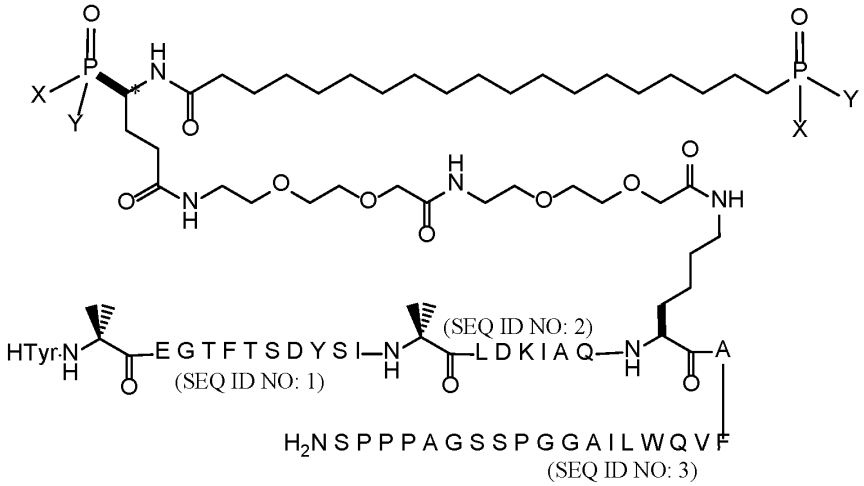
12. The pharmaceutical composition of claim 10 or 11, wherein Z^2 is selected from the group consisting of hydrogen, haloC_{1-6} alkyl and C_{1-6} alkyl; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryl and C_{6-10} aryl alkyl.

13. The pharmaceutical composition of claim 10 or 11, wherein Z^2 is hydrogen and each R^4 is hydrogen or C_{6-10} aryl alkyl.

14. The pharmaceutical composition of any one of claims 10 to 13, wherein each R^4 is hydrogen.

15. The pharmaceutical composition of any of claims 10 to 14, wherein Z^2 is hydrogen and each R^4 is hydrogen.

16. The pharmaceutical composition of claim 2, wherein the GIP/GLP-1 dual agonist is a compound having the structure of Formula (I-c):



(I-c)

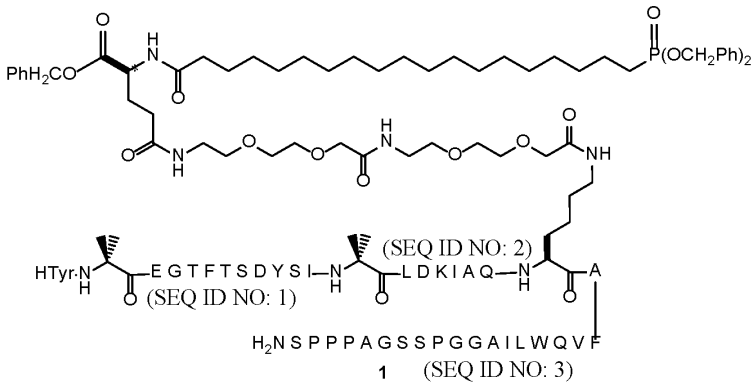
or a pharmaceutically acceptable salt thereof.

17. The pharmaceutical composition of claim 16, wherein X and Y each are $–OR^4$.

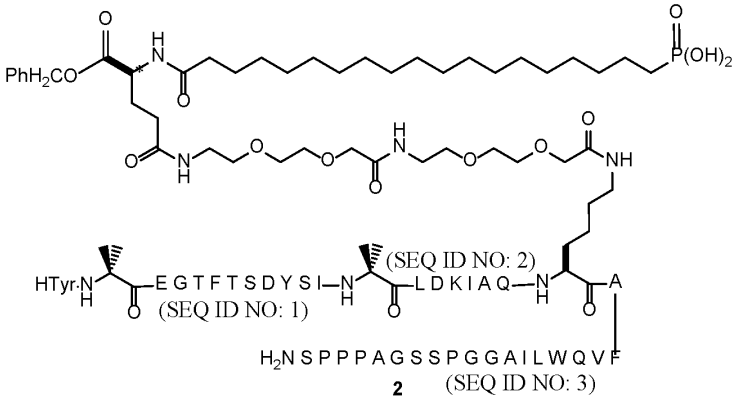
18. The pharmaceutical composition of claim 16 or 17, wherein each R^4 is independently selected from the group consisting of hydrogen, C_{6-10} aryl and C_{6-10} aryl alkyl.

19. The pharmaceutical composition of any one of claims 16 to 18, wherein each R^4 is hydrogen.

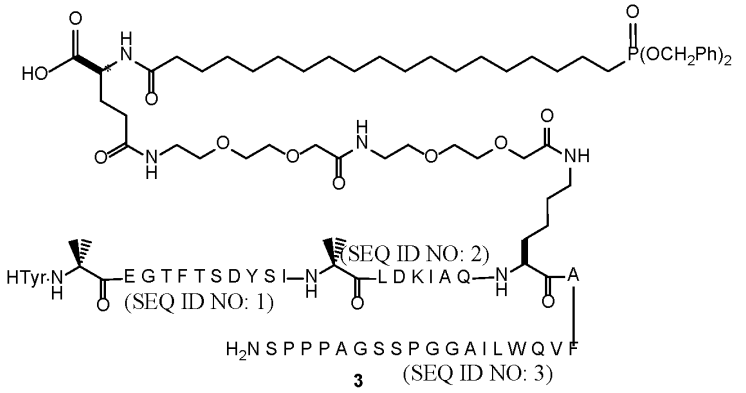
20. The pharmaceutical composition of claim 2 or 3, wherein the compound is a compound having the structure selected from the group consisting of:


PhH2CO
P(OCH2Ph)2
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

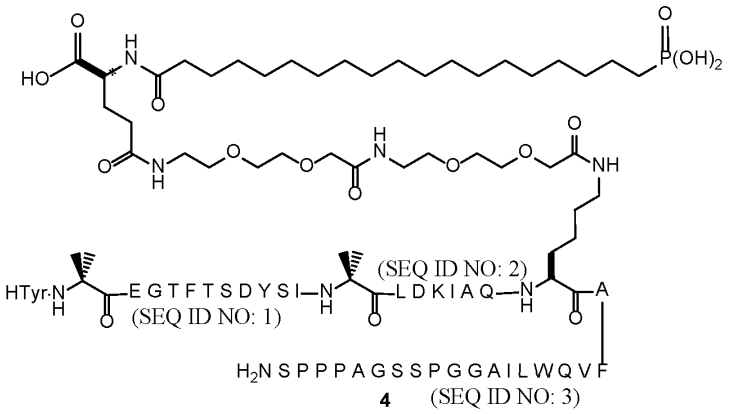
1


PhH2CO
P(OH)2
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

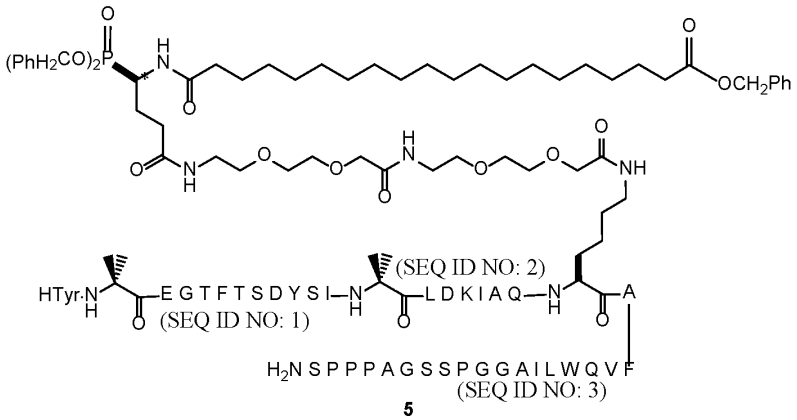
2


HO
P(OCH2Ph)2
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

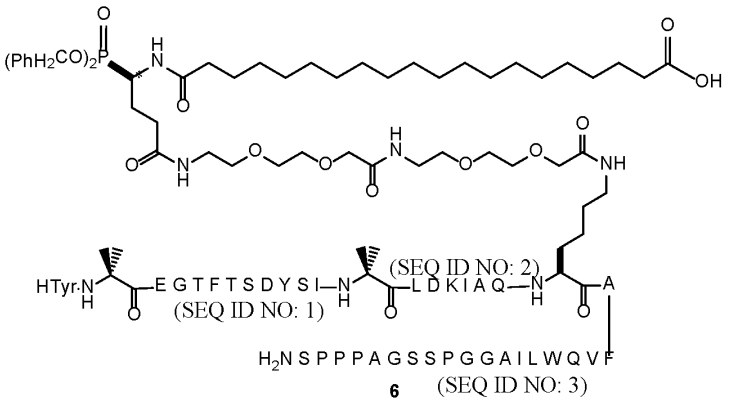
3


HO
P(OH)2
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

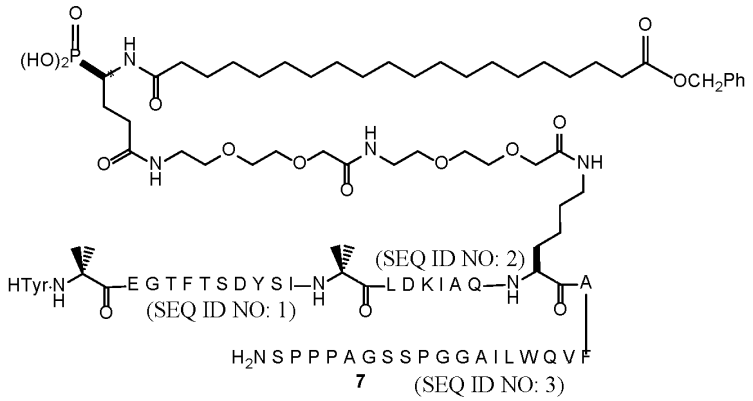
4


(PhH2CO)2P
OCH2Ph
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

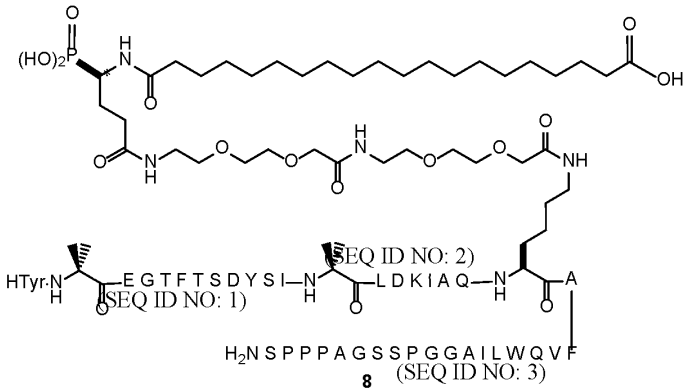
5


(PhH2CO)2P
OH
HTyr-N
E G T F T S D Y S I
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

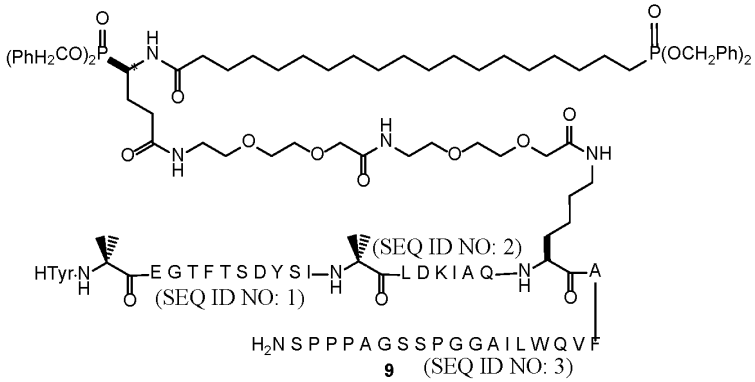
6


(HO)2P
OCH2Ph
HTyr-N
E G T F T S D Y S I—N
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q—N
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

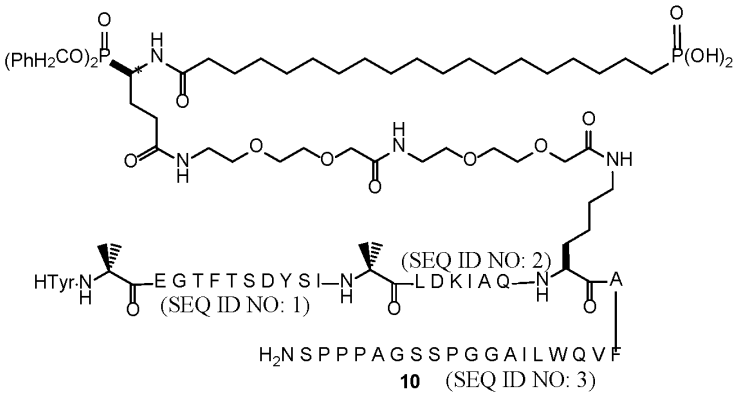
7


(HO)2P
OH
HTyr-N
E G T F T S D Y S I—N
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q—N
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

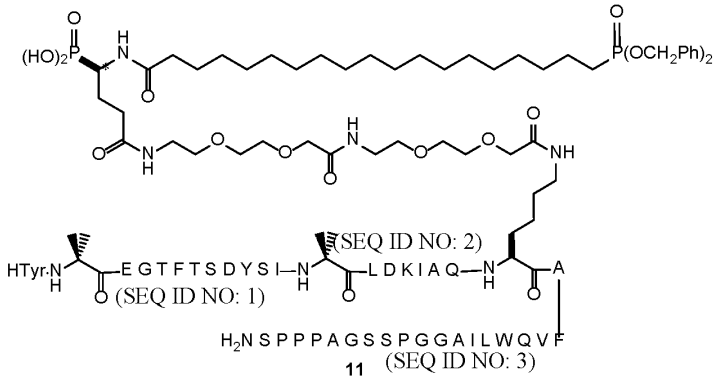
8


(PhH2CO)2P
P(OCH2Ph)2
HTyr-N
E G T F T S D Y S I—N
(SEQ ID NO: 1)
(SEQ ID NO: 2)
L D K I A Q—N
A
H2N S P P P A G S S P G G A I L W Q V F
(SEQ ID NO: 3)

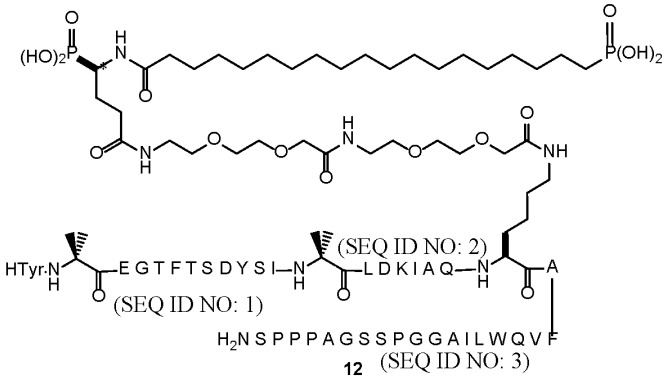
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10



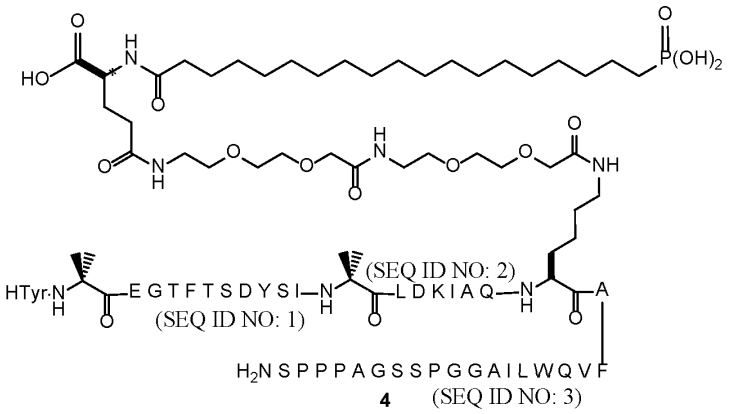
11



12

and pharmaceutically acceptable salts thereof.

21. The pharmaceutical composition of claim 20, wherein the GIP/GLP-1 is a compound having the structure:

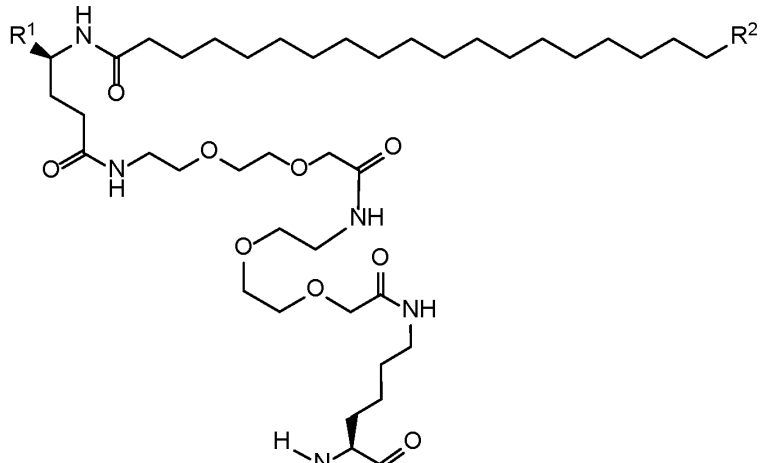


or a pharmaceutically acceptable salt thereof.

22. The pharmaceutical composition of any one of claims 2 to 21, wherein "*" indicates a chiral carbon with "S" configuration.

23. The pharmaceutical composition of any one of claims 2 to 21, wherein "*" indicates a chiral carbon with "R" configuration.

24. The pharmaceutical composition of claim 1, wherein the GIP/GLP-1 is a compound having the structure of Formula (II),



H-Y Aib E G T F T S D Y S I J^1 L D U^1 U^2 A F V J^2 W L I J^3 G G P S S G A P P P S-NH$_2$

(SEQ ID NO: 4) (II) (SEQ ID NO: 5)

or a pharmaceutically acceptable salt thereof, wherein:

Aib is 2-aminoisobutyric acid;

each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib, a naturally occurring amino acid, and an unnatural amino acid;

U^1 is $-(J^4)_{n1}-(J^5)_{n2}-(J^6)_{n3}-(J^7)_{n4}-$;

U^2 is $-(J^8)_{n5}-(J^9)_{n6}-(J^{10})_{n7}-(J^{11})_{n8}-$;

each instance of J^4, J^5, J^6, J^7, J^8, J^9, J^{10}, and J^{11} is independently a naturally occurring amino acid or an unnatural amino acid;

each of n1, n2, n3, n4, n5, n6, n7, and n8 is independently 0 or 1, provided that the sum n1 + n2 + n3 + n4 + n5 + n6 + n7 + n8 is 4;

R^1 is selected from the group consisting of $-C(=O)(OZ^1)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

R^2 is selected from the group consisting of $-C(=O)(OZ^2)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-2 heteroatoms selected from N, O and S, the heteroaryl optionally substituted with 1-2 R^7 independently selected from halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, $-OR^5$, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

each R^7 is independently selected from the group consisting of halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl, C_{6-10} aryl, 5-10 membered heteroaryl and 5-10 membered heterocyclyl;

X and Y each are independently selected from the group consisting of $-OR^4$, NR^5R^6, C_{1-6} alkyl and haloC_{1-6} alkyl;

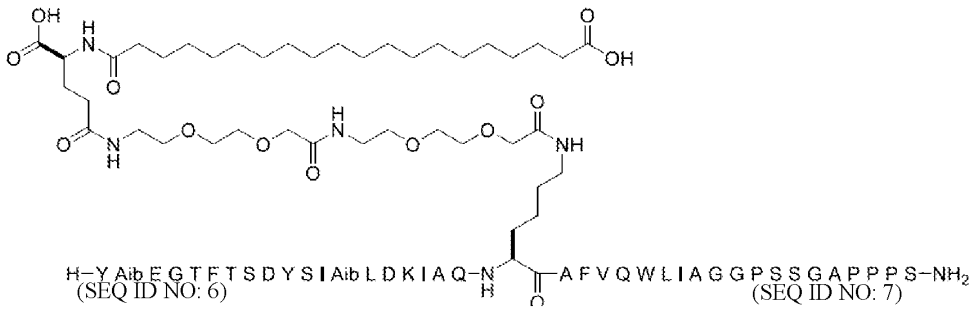
each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

each R^5 is independently hydrogen or C_{1-6} alkyl;

each R^6 is independently hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 each are independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl.

25. The pharmaceutical composition of claim 24, wherein the compound is not:



26. The pharmaceutical composition of claim 24 or 25, wherein each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib and a naturally occurring amino acid.

27. The pharmaceutical composition of any one of claims 24 to 26, wherein each instance of J^1, J^2, and J^3 is independently an amino acid selected from Aib, A, F, N, R, and Q.

28. The pharmaceutical composition of any one of claims 24 to 27, wherein J^1 is Aib or F.

29. The pharmaceutical composition of any one of claims 24 to 28, wherein J^1 is F.

30. The pharmaceutical composition of any one of claims 24 to 29, wherein J^2 is N or Q.

31. The pharmaceutical composition of any one of claims 24 to 30, wherein J^2 is N.

32. The pharmaceutical composition of any one of claims 24 to 31, wherein J^3 is A or R.

33. The pharmaceutical composition of any one of claims 24 to 32, wherein J^3 is R.

34. The pharmaceutical composition of any one of claims 24 to 33, wherein each instance of J^4, J^5, J^6, and J^7 is independently an amino acid selected from A, I, K, R, Q, S, T, and V.

35. The pharmaceutical composition of any one of claims 24 to 34, wherein J^4 is K or R.

36. The pharmaceutical composition of any one of claims 24 to 35, wherein J^4 is R.

37. The pharmaceutical composition of any one of claims 24 to 36, wherein J^5 is I, T, or V.

38. The pharmaceutical composition of any one of claims 24 to 37, wherein J^5 is T or V.

39. The pharmaceutical composition of any one of claims 24 to 38, wherein J^6 is A or S.

40. The pharmaceutical composition of any one of claims 24 to 39, wherein J^6 is S.

41. The pharmaceutical composition of any one of claims 24 to 40, wherein J^7 is Q or K.

42. The pharmaceutical composition of any one of claims 24 to 41, wherein each instance of J^8, J^9, J^{10}, and J^{11} is independently an amino acid selected from A, I, and Q.

43. The pharmaceutical composition of any one of claims 24 to 42, wherein J^8 is I or Q.

44. The pharmaceutical composition of any one of claims 24 to 43, wherein J^9 is A or Q.

45. The pharmaceutical composition of any one of claims 24 to 44, wherein J^{10} is Q.

46. The pharmaceutical composition of any one of claims 24 to 45, wherein J^{11} is Q.

47. The pharmaceutical composition of any one of claims 24 to 27, wherein

J^1 is selected from Aib or F;

J^2 is selected from Q or N;

J^3 is selected from A or R;

U^1 is selected from -K-V-A-, -K-I-A-Q- (SEQ ID NO: 8), -K-T-A-Q- (SEQ ID NO: 9), -K-T-S-Q- (SEQ ID NO: 10), -K-V-A-Q- (SEQ ID NO: 11), -R-I-A-Q- (SEQ ID NO: 12), K-I-A-K- (SEQ ID NO: 13), -K-I-S-Q- (SEQ ID NO: 14), or is absent; and

U^2 is selected from -Q-, -I-A-Q-Q- (SEQ ID NO: 15), -I-A-Q-K- (SEQ ID NO: 16), -V-A-Q-K (SEQ ID NO: 17), or is absent.

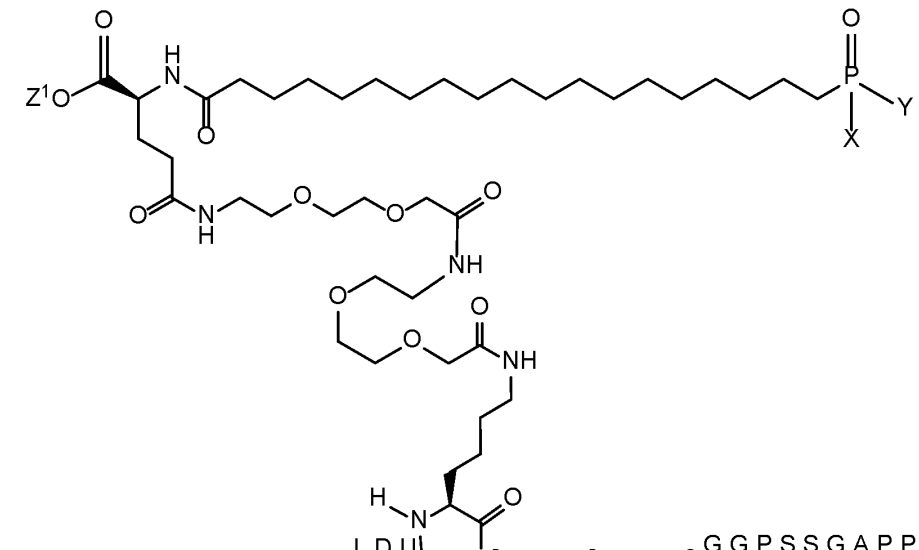
48. The pharmaceutical composition of any one of claims 24 to 47, wherein each instance of n1, n2, n3, and n4 is zero.

49. The pharmaceutical composition of any one of claims 24 to 47, wherein each instance of n4, n6, n7, and n8 is zero.

50. The pharmaceutical composition of any one of claims 24 to 47, wherein each instance of n5, n6, n7, and n8 is zero.

51. The pharmaceutical composition of any one of claims 24 to 50, wherein at least one of Z^1 and Z^2 is not hydrogen.

52. The pharmaceutical composition of any one of claims 24 to 51, wherein the compound is a compound having the structure of Formula (II-a):



(II-a)

or a pharmaceutically acceptable salt thereof.

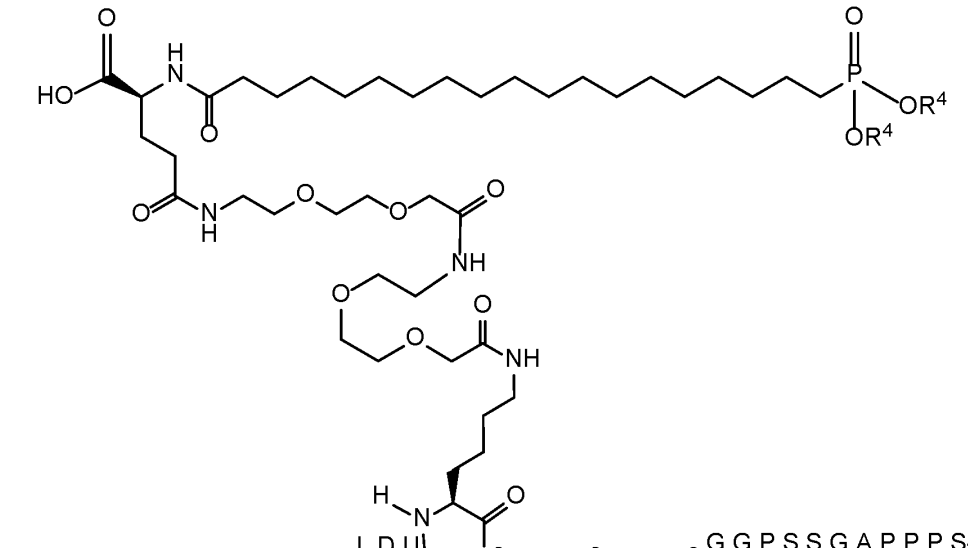
53. The pharmaceutical composition of claim 52, wherein Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

54. The pharmaceutical composition of claim 51, wherein Z^1 is hydrogen and each R^4 independently is hydrogen or C_{7-11} arylalkyl.

55. The pharmaceutical composition of claim 53 or 54, wherein each R^4 is hydrogen.

56. The pharmaceutical composition of claim 51, wherein Z^1 is hydrogen and each R^4 is hydrogen.

57. The pharmaceutical composition of any one of claims 23 to 51, wherein the GIP/GLP-1 is a compound having the structure of Formula (II-b):



H-Y Aib E G T F T S D Y S I J^1 L D U$_1$ U^2 A F V J^2 W L I J^3 G G P S S G A P P P S-NH$_2$
(SEQ ID NO: 4) (SEQ ID NO: 5)

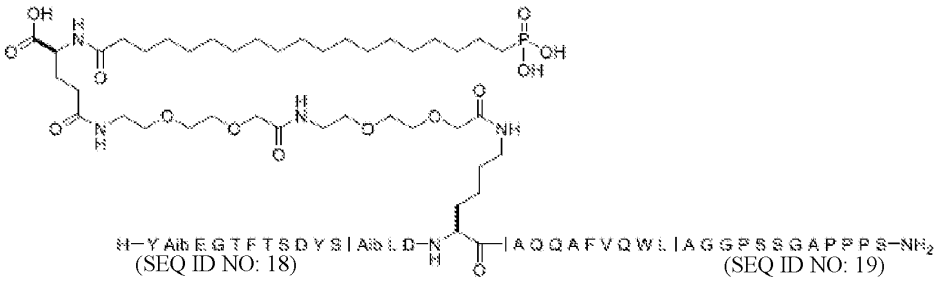
(II-b)

or a pharmaceutically acceptable salt thereof.

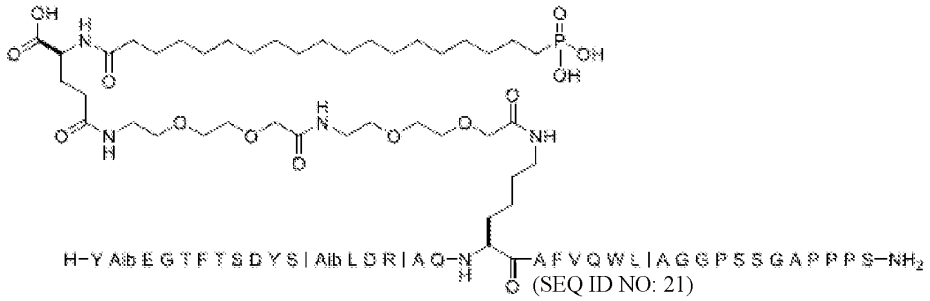
58. The pharmaceutical composition of claim 57, wherein each R^4 is independently selected from the group consisting of hydrogen, C_{6-10} aryl and C_{7-11} arylalkyl.

59. The pharmaceutical composition of claim 58, wherein each R^4 is hydrogen.

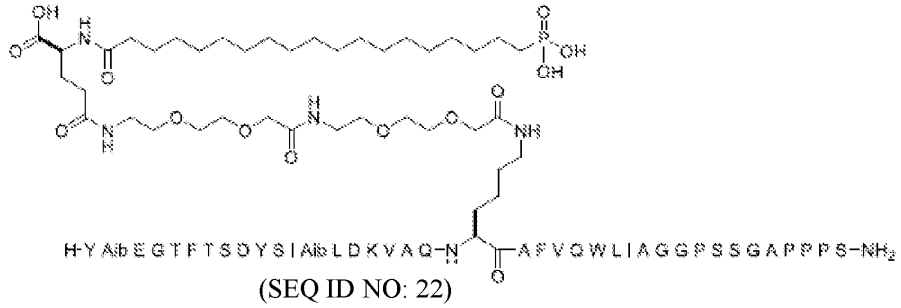
60. The pharmaceutical composition of claim 24 or 25, wherein the compound is a compound having the structure selected from the group consisting of:



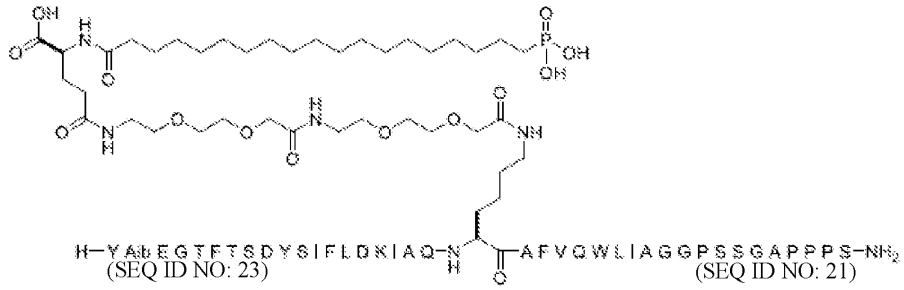
(SEQ ID NO: 18) (SEQ ID NO: 19)



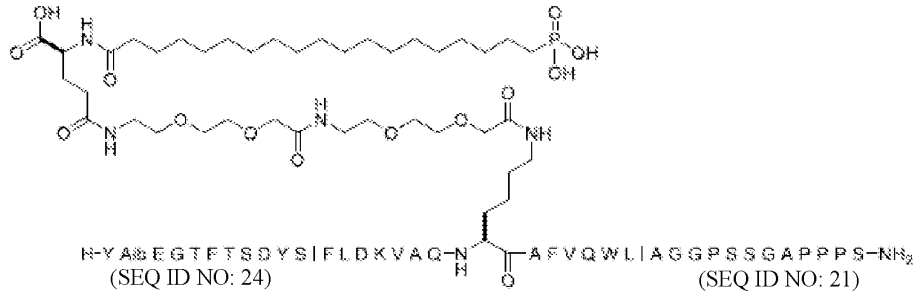
(SEQ ID NO: 21)



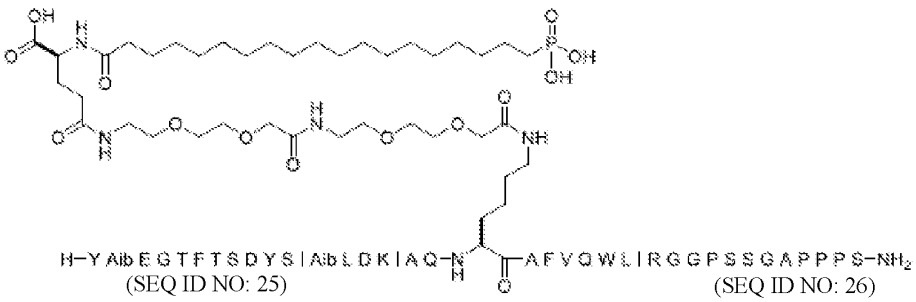
(SEQ ID NO: 22)



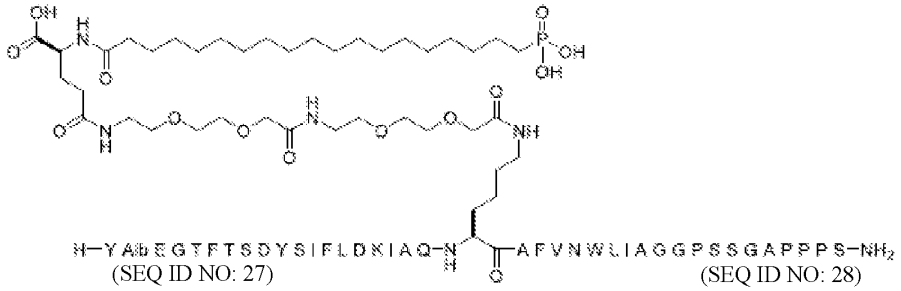
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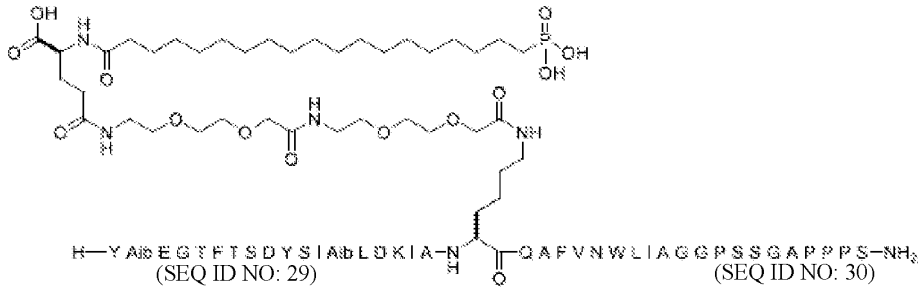
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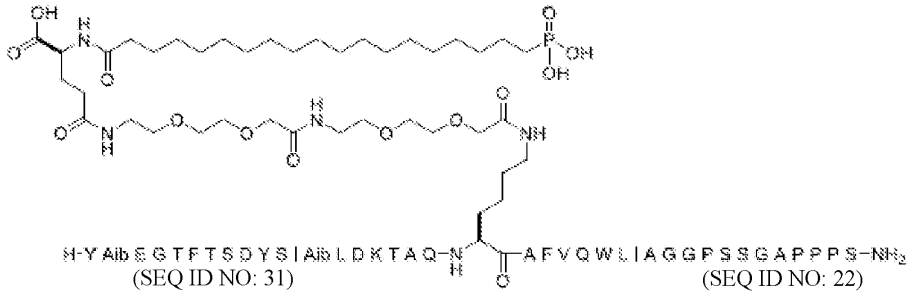
(SEQ ID NO: 25) (SEQ ID NO: 26)



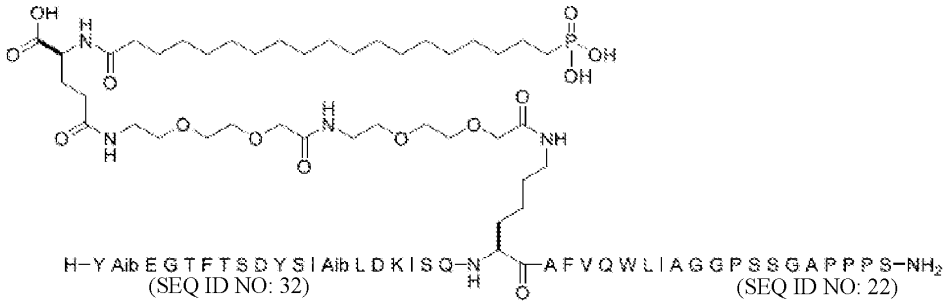
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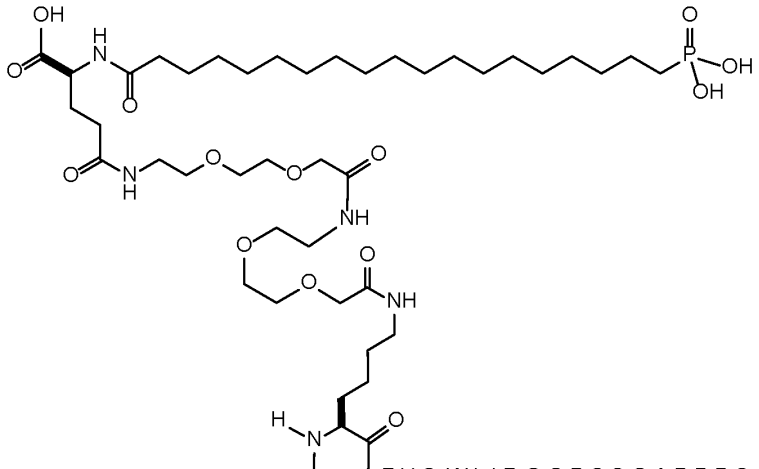
(SEQ ID NO: 29) (SEQ ID NO: 30)



(SEQ ID NO: 31) (SEQ ID NO: 22)



(SEQ ID NO: 32) (SEQ ID NO: 22)



(SEQ ID NO: 22) (SEQ ID NO: 26)

and pharmaceutically acceptable salts thereof.

61. The pharmaceutical composition of any one of claims 24 to 60, wherein "*" indicates a chiral carbon with "S" configuration.

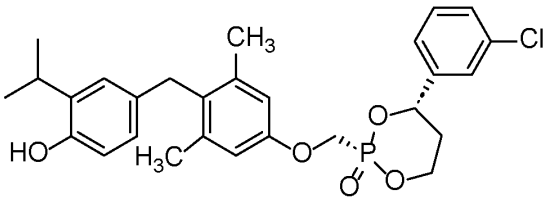
62. The pharmaceutical composition of any one of claims 24 to 60, wherein "*" indicates a chiral carbon with "R" configuration.

63. The pharmaceutical composition of any one of Claims 1 to 62, wherein the composition is formulated as a tablet.

64. The pharmaceutical composition of Claim 63, wherein the tablet is a bilayer tablet comprising:

(iii) a GIP/GLP-1 dual agonist layer comprising the GIP/GLP-1 dual agonist; and

(iv) a TR-β agonist layer comprising



(Compound A).

65. The method of Claim 64, wherein the GIP/GLP-1 dual agonist layer further comprises a permeability enhancer.

66. The pharmaceutical composition of Claim 65, wherein the mass of the permeability enhancer is from about 350 mg to about 1000 mg.

67. The pharmaceutical composition of Claim 64 or 65, wherein the mass of the permeability enhancer is from about 400 mg to about 800 mg.

68. The pharmaceutical composition of Claim 64 or 65, wherein the mass of the permeability enhancer is from about 500 mg to about 750 mg.

69. The pharmaceutical composition of Claim 64 or 65, wherein the mass of the permeability enhancer is about 500 mg or about 600 mg.

70. The pharmaceutical composition of any one of Claims 64 to 69, wherein the permeability enhancer comprises from about 20% to about 70% by weight of the composition.

71. The pharmaceutical composition of any one of Claims 64 to 69, wherein the permeability enhancer comprises from about 30% to about 60% by weight of the composition.

72. The pharmaceutical composition of any one of Claims 64 to 69, wherein the one or more permeability enhancer comprises from about 40% to about 50% by weight of the composition.

73. The pharmaceutical composition of any one of Claims 64 to 69, wherein the permeability enhancer comprises about 44% of the composition.

74. The pharmaceutical composition of any one of Claims 64 to 73, wherein the permeability enhancer comprises from about 40% to about 90% by weight of the dual agonist layer.

75. The pharmaceutical composition of any one of Claims 64 to 73, wherein the permeability enhancer comprises from about 50% to about 80% by weight of the dual agonist layer.

76. The pharmaceutical composition of any one of Claims 64 to 73, wherein the one or more permeability enhancer comprises from about 70% to about 80% by weight of the dual agonist layer.

77. The pharmaceutical composition of any one of Claims 64 to 73, wherein the permeability enhancer comprises about 72% of the dual agonist layer.

78. The pharmaceutical composition of any one of Claims 64 to 77, wherein the permeability enhancer is salcaprozate sodium (SNAC), sodium caprate (C10), or a combination thereof.

79. The pharmaceutical composition of any one of Claims 64 to 77, wherein the permeability enhancer is salcaprozate sodium.

80. The pharmaceutical composition of any one of Claims 64 to 77, wherein the permeability enhancer is sodium caprate.

81. The pharmaceutical composition of any one of Claims 64 to 77, wherein the one or more permeability enhancer is a combination of salcaprozate sodium and sodium caprate.

82. The pharmaceutical composition of any one of Claims 1 to 81, comprising from about 5 mg to about 40 mg of the GIP/GLP-1 dual agonist.

83. The pharmaceutical composition of any one of Claims 1 to 81, comprising from about 10 mg to about 30 mg of the GIP/GLP-1 dual agonist.

84. The pharmaceutical composition of any one of Claims 1 to 81, comprising from about 20 mg to about 30 mg of the GIP/GLP-1 dual agonist.

85. The pharmaceutical composition of any one of Claims 1 to 81, comprising about 25 mg of the GIP/GLP-1 dual agonist.

86. The pharmaceutical composition of any one of Claims 64 to 77, wherein the GIP/GLP-1 dual agonist layer is enterically coated.

87. The pharmaceutical composition of any one of Claims 64 to 77, wherein the TR-β agonist layer further comprises one or more polymers selected from the group consisting of: polyvinyl pyrrolidone (PVP), polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA), polyvinyl alcohol (PVA), polyacrylic acid (PAA), poly(ethylene oxide) (PEO), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), copovidone, poloxamer 407, hypromellose acetate succinate (HPMCAS), polyacrylates and combinations thereof.

88. The pharmaceutical composition of Claim 87, wherein the polymer is polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA).

89. The pharmaceutical composition of Claim 87 or Claim 84, wherein Compound A and the one or more polymers are combined to form a spray dried dispersion.

90. The pharmaceutical composition of Claim 87 or Claim 84, wherein Compound A and the one or more polymers are combined to form a hot melt extrusion.

91. The pharmaceutical composition of any one of Claim 87 to 90, wherein the mass ratio of Compound A and the one or more polymers in the composition is from about 1:10 to about 10:1.

92. The pharmaceutical composition of Claim 91, wherein the mass ratio of Compound A and the one or more polymers in the composition is from about 1:1 to about 1:4.

93. The oral pharmaceutical composition of Claim 91 or 92, wherein the mass ratio of Compound A and the one or more polymers in the composition is about 1:3.

94. The pharmaceutical composition of any one of Claims 64 to 93, wherein the TR-β agonist layer is enterically coated.

95. The pharmaceutical composition of any one of Claims 1 to 94, comprising from about 1 mg to about 30 mg of Compound A.

96. The pharmaceutical composition of any one of Claims 1 to 94, comprising from about 2.5 mg to about 20 mg of Compound A.

97. The pharmaceutical composition of any one of Claims 1 to 94, comprising from about 5 mg to about 15 mg of Compound A.

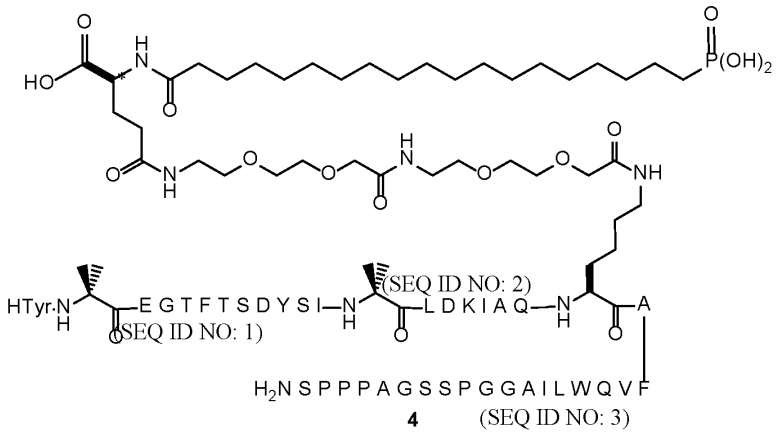
98. The pharmaceutical composition of any one of Claims 1 to 94, comprising about 10 mg of Compound A.

99. A pharmaceutical composition, comprising:

(i) a GIP/GLP-1 dual agonist layer comprising:

(a) salcaprozate sodium; and

(b) a therapeutically effective amount of the compound having the structure:

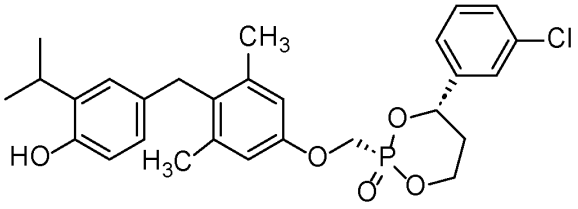


; and

(ii) a TR-β agonist layer comprising:

(a) polyvinyl pyrrolidinone-vinyl acetate copolymer (PVP-VA)

(b) a therapeutically effective amount of Compound A



(Compound A);

wherein Compound A and the PVP-VA are combined to form a spray dried dispersion.

100. The pharmaceutical composition of any one of Claims 64 to 99, wherein the GIP/GLP-1 dual agonist layer of the pharmaceutical composition comprises:

from about 1.0 to about 5.0% by weight of the GIP/GLP-1 dual agonist;

from about 50% to about 80% by weight salcaprozate sodium;

from about 10% to about 30% by weight microcrystalline cellulose;

from about 1.0% to about 5.0% by weight croscarmellose sodium; and

from about 1.0% to about 3.0% by weight magnesium stearate.

101. The pharmaceutical composition of any one of Claims 64 to 100, wherein the GIP/GLP-1 dual agonist layer of the pharmaceutical composition comprises:

about 3.6% by weight of the GIP/GLP-1 dual agonist;

about 72.0% by weight salcaprozate sodium;

about 17.3% by weight microcrystalline cellulose;

about 2.3% by weight magnesium stearate; and

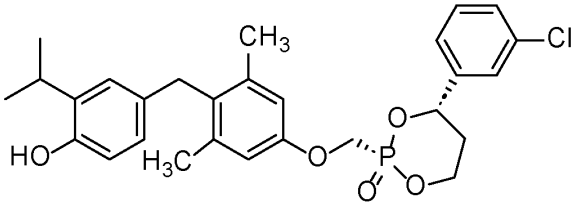
about 4.8% by weight croscarmellose sodium.

102. The pharmaceutical composition of any one of Claims 64 to 101, wherein the TR-β layer of the pharmaceutical composition comprises about 5% to about 25% by weight by weight of the spray-dried dispersion comprising Compound A.

103. The pharmaceutical composition of any one of Claims 64 to 102, wherein the TR-β layer of the pharmaceutical composition comprises about 10% to about 15% by weight by weight of the spray-dried dispersion comprising Compound A.

104. The pharmaceutical composition of any one of Claims 1 to 103, wherein the composition is formulated for oral administration.

105. A method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof



(Compound A); and

a therapeutically effective amount of a GIP/GLP-1 dual agonist.

106. The method of Claim 105, wherein Compound A and the GIP/GLP-1 dual agonist are administered sequentially.

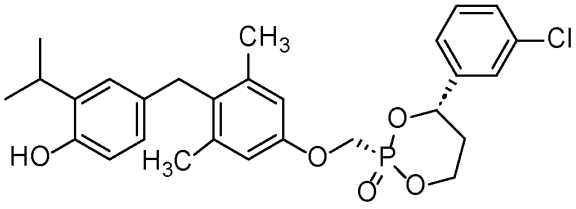
107. The method of Claim 105, wherein Compound A and the GIP/GLP-1 dual agonist are administered simultaneously.

108. The method of Claim 107, wherein Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition of any one of Claims 1 to 100.

109. The method of any one of Claims 105 to 108, wherein the metabolic disorder or metabolic syndrome is atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, hypothalamic obesity, or prader-willi syndrome.

110. The method of any one of Claims 105 to 109, wherein the metabolic disorder or metabolic syndrome is obesity or hypothalamic obesity.

111. A method of preventing, treating, or ameliorating one or more fatty liver diseases in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof



(Compound A); and

a therapeutically effective amount of a GIP/GLP-1 dual agonist.

112. The method of Claim 111, wherein Compound A and the GIP/GLP-1 dual agonist are administered sequentially.

113. The method of Claim 111, wherein Compound A and the GIP/GLP-1 dual agonist are administered simultaneously.

114. The method of Claim 113, wherein Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition of any one of Claims 1 to 100.

115. The method of any one of Claims 111 to 114, wherein said wherein said fatty liver disease is selected from the group consisting of steatosis, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease.

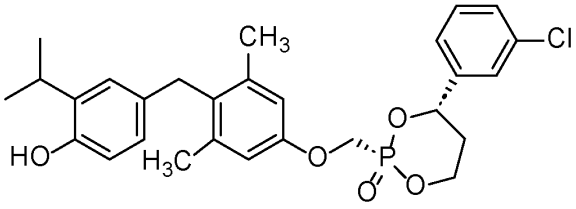
116. The method of Claim 114 or 115, wherein said administration of said pharmaceutical composition results in the prevention, treatment, or amelioration, of a fibrosis, fibrotic condition, or fibrotic symptoms.

117. The method of any one of Claims 114 to 116, wherein said administration of said pharmaceutical composition results in the reduction in the amount of extracellular matrix proteins present in one or more tissues of said subject.

118. The method of any of Claims 114 to 117, wherein said administration of said pharmaceutical composition results in the reduction in the amount of collagen present in one or more tissues of said subject.

119. The method of Claim 118, wherein said administration of said pharmaceutical composition results in the reduction in the amount of Type I, Type Ia, or Type III collagen present in one or more tissues of said subject.

120. A method of preventing, treating, or ameliorating one or more one or more diseases or disorders in a subject, comprising administering a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt thereof



(Compound A); and

a therapeutically effective amount of a GIP/GLP-1 dual agonist; wherein said disease or disorder is liver fibrosis, renal fibrosis, biliary fibrosis, pancreatic fibrosis, nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis, primary biliary cirrhosis, or idiopathic fibrosis.

121. The method of Claim 120, wherein Compound A and the GIP/GLP-1 dual agonist are administered sequentially.

122. The method of Claim 120, wherein Compound A and the GIP/GLP-1 dual agonist are administered simultaneously.

123. The method of Claim 122, wherein Compound A and the GIP/GLP-1 dual agonist are administered as a pharmaceutical composition of any one of Claims 1 to 100.

124. The method of any one Claims 120 to 123, wherein said disease or disorder is nonalcoholic steatohepatitis, non-alcoholic fatty liver disease, chronic kidney disease, diabetic kidney disease, primary sclerosing cholangitis, or primary biliary cirrhosis.

125. The method of any one of Claims 105 to 124, wherein the route of administration is oral.