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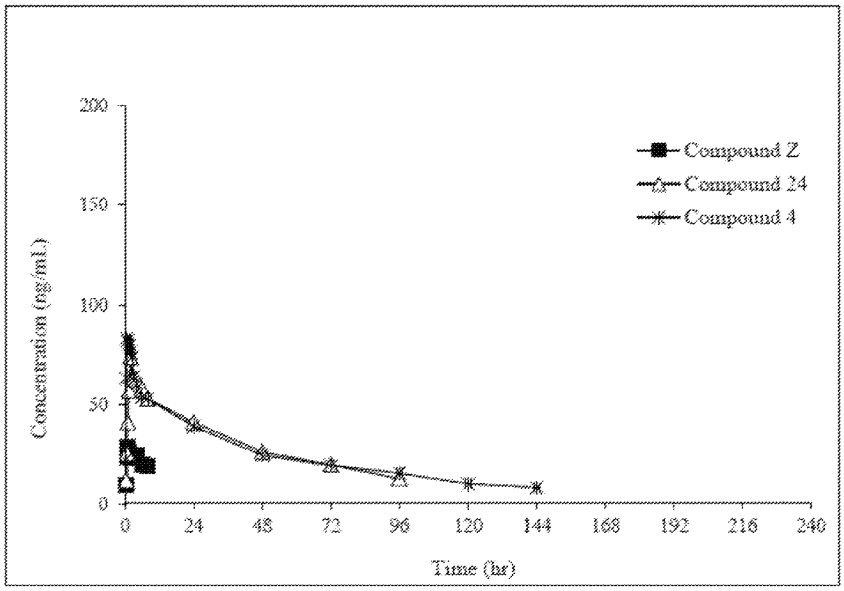

FIG. 1

(57) Abstract: Disclosed herein are oral compositions of small molecule GLP-1 agonists and GIP/GLP-1 dual receptor agonists and uses thereof.

[Continued on next page]

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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— *with sequence listing part of description (Rule 5.2(a))*

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. 63/490,512 filed March 15, 2023, 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.025PR.xml created on March 14, 2023, which is 40,752 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] 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.

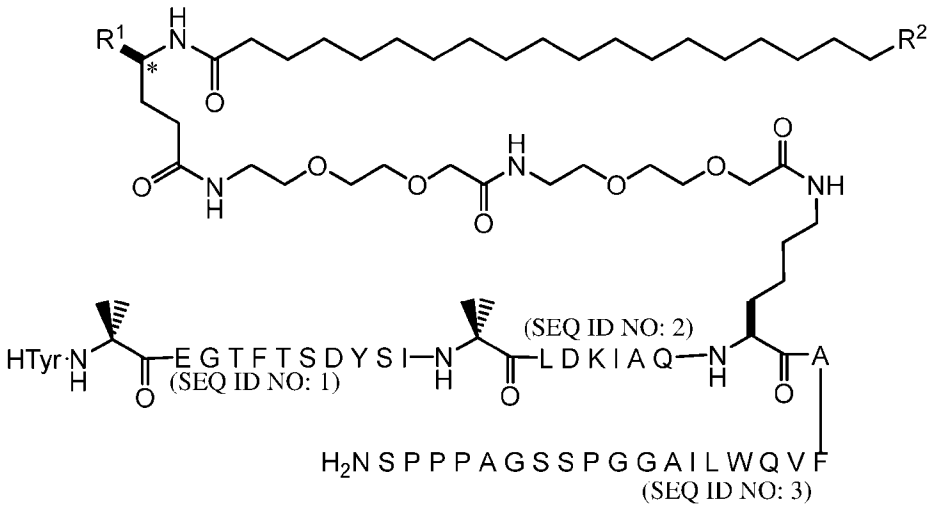
[0005] Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and is the most common cause of chronic liver disease. NAFLD may progress to liver inflammation, fibrosis, cirrhosis and even hepatocellular carcinoma. GLP-1 agonists and GIP/GLP-1 dual receptor agonists have been developed for treating NAFLD, non-alcoholic steatohepatitis (NASH), diabetes, obesity, and other diseases. However, the use of GLP-1 agonists and 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. Therefore, a need exists for GLP-1 agonist and GIP/GLP1 dual agonist compounds that can be used to treat fatty liver diseases and other diseases and disorders.

[0006] Peptide compounds show some promise as GLP-1 agonists and GIP/GLP-1 dual agonists that can be used to treat metabolic disorders such as NAFLD. However, there are many difficulties in preparing oral compositions of peptides. Such oral compositions have varying bioavailabilities of the active agent. Accordingly, there is a need for suitable pharmaceutical compositions of such peptide-based dual agonist compounds.

SUMMARY

[0007] In one aspect of the present disclosure, provided herein is a pharmaceutical composition comprising: a permeability enhancer; and a therapeutically effective amount of a compound, wherein the compound is a GLP-1 agonist or a GLP/GIP dual agonist; wherein the mass of the permeability enhancer is greater than 300 mg.

[0008] In some embodiments of the first aspect, the compound 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} aryloxy and C_{6-10} aryl alkoxy;

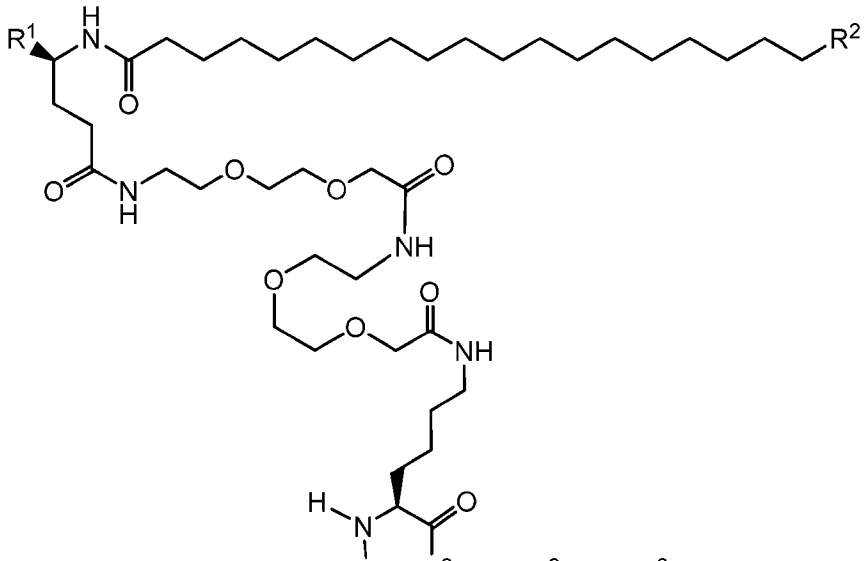
each R^5 may be independently hydrogen or C_{1-6} alkyl;

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, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl.

[0009] In some embodiments of the compound of Formula (I), at least one of Z^1 and Z^2 is not hydrogen.

[0010] In other embodiments of the first aspect, the compound 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) (SEQ ID NO: 5)

(II)

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;

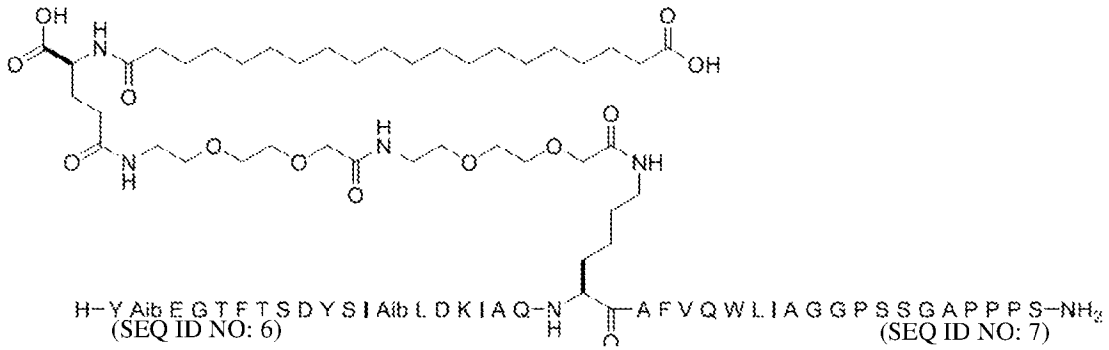
each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

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.

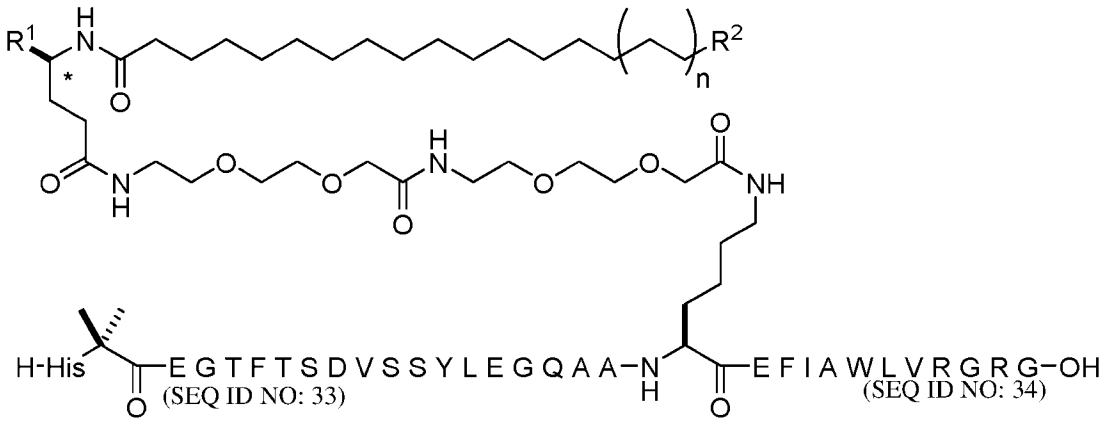
[0011] In some embodiments, the compound is not:



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

[0012] In some embodiments of the compound of Formula (II), at least one of Z^1 and Z^2 is not hydrogen.

[0013] In yet other embodiments of the first aspect, the compound is a compound having the structure of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, 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 1-4 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 $-C(=O)(OZ^2)$, $-(CH_2CH_2)_nP(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-4 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 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} aryloxy and C_{6-10} aryl alkoxy;

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

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

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; and

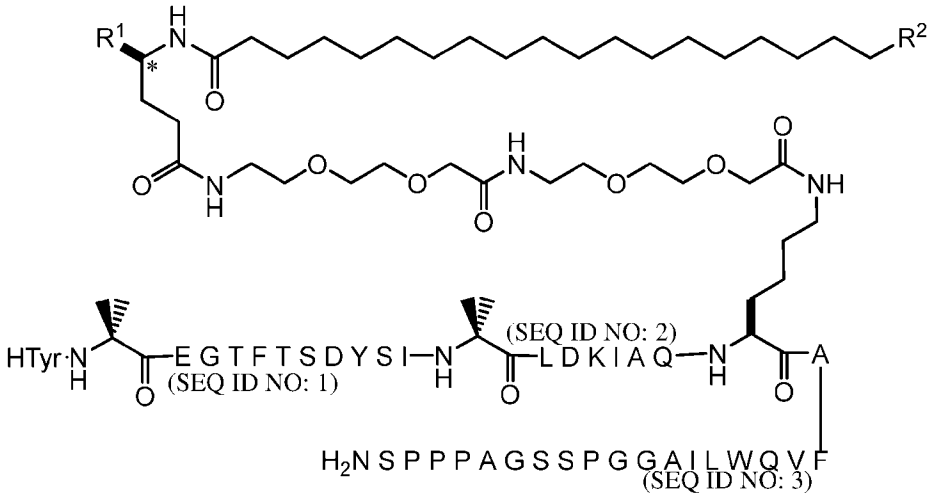
n is 0, 1, 2, 3 or 4.

[0014] In some embodiments of the first aspect, the permeability enhancer is salcaprozate sodium (SNAC), sodium caprate (C10), or a combination thereof.

[0015] In a second aspect of the present disclosure, provided herein is a pharmaceutical composition, comprising:

salcaprozate sodium; and

a therapeutically effective amount of a compound having the structure of Formula I, or a pharmaceutically acceptable salt thereof:



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 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_{6-10} 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; and

wherein the mass of salcaprozate is greater than about 300 mg.

[0016] In some embodiments of the second aspect, at least one of Z^1 and Z^2 is not hydrogen.

[0017] In some embodiments of the aspects of the present disclosure, the pharmaceutical composition is formulated for oral administration. In some such embodiments, the pharmaceutical composition is enterically coated.

[0018] In a third aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating one or more fatty liver diseases in a subject, comprising administering a pharmaceutical composition disclosed herein to a subject in need thereof.

[0019] In a fourth aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating one or disease or disorders in a subject, comprising administering a pharmaceutical composition disclosed herein to a subject in need thereof, 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.

[0020] In a fifth aspect of the present disclosure, provided herein is a method of preventing, treating, or ameliorating a metabolic disorder or metabolic syndrome. 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.

[0021] In a sixth aspect of the present disclosure, provided herein is a method of preparing a pharmaceutical composition. In some embodiments, the method comprises the steps of:

(i) combining a permeability enhancer and magnesium stearate to form first granules;

(ii) combining microcrystalline cellulose, a compound disclosed herein, and polyvinylpyrrolidinone to form second granules

(iii) combining the first granules and the second granules to form a mixture;

(iv) adding magnesium stearate to the mixture to form third granules;

(v) pressing the third granules into tablets.

[0022] In other embodiments, the method comprising the steps of:

(i) combining salcaprozate sodium (SNAC) and magnesium stearate to form first granules;

(ii) combining microcrystalline cellulose, a compound disclosed herein, and polyvinylpyrrolidinone to form second granules

(iii) combining the first granules and the second granules to form a mixture;

(iv) adding magnesium stearate to the mixture to form third granules;

(v) pressing the third granules into tablets.

[0023] In other embodiments, the method comprising the steps of:

(i) combining C10 and magnesium stearate to form first granules;

(ii) combining microcrystalline cellulose, a compound disclosed herein, and polyvinylpyrrolidinone to form second granules

(iii) combining the first granules and the second granules to form a mixture;

(iv) adding magnesium stearate to the mixture to form third granules;

(v) pressing the third granules into tablets.

[0024] In some embodiments, provided herein is a method of preparing a pharmaceutical composition, the method comprising the steps of:

(i) combining microcrystalline cellulose and compound disclosed therein in a first vessel;

(ii) combining polyvinylpyrrolidinone and water in a second vessel;

(iii) adding the contents of the first vessel to the second vessel to form wet granules;

(iv) drying the wet granules to form dry granules;

(v) combining the dry granules with magnesium stearate; and

(vi) pressing the resulting mixture of step (v) into granules.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 is a graph depicting the mean plasma concentration versus time profile following administration of an oral dose of various compounds to male beagle dogs.

[0026] FIG. 2 is a graph showing a comparison of AUC values for dosing groups of dogs administered formulations of Compound 4 with varying quantities of salcaprozate sodium (SNAC).

[0027] FIG. 3 is a graph depicting the mean plasma concentration versus time profile following administration of an oral dose of various compounds to male beagle dogs.

[0028] FIG. 4 is a graph depicting the mean plasma concentration versus time profile following administration of various formulations of Compound 4 to male cynomolgus monkeys.

[0029] FIG. 5A is a graph depicting the mean plasma concentration versus time profile following administration of Compound 24 in various excipients to male Sprague Dawley rats.

[0030] FIG. 5B is a graph depicting the mean plasma concentration versus time profile following administration of Compound 27 in various excipients to male Sprague Dawley rats.

[0031] FIG. 5C is a graph depicting the mean plasma concentration versus time profile following administration of Compound 4 in various excipients to male Sprague Dawley rats.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0032] In some embodiments, pharmaceutical compositions are provided for administration to a subject in need thereof. 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

[0033] 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.

[0034] "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.

[0035] 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).

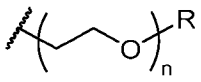
[0036] As used herein, "C_a to C_b" or "C_{a-b}" in which "a" and "b" are integers refer to the number of carbon atoms in the specified group. That is, the group can contain from "a" to "b", inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" or "C_{1-4} alkyl" group refers to all alkyl 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 $(CH_3)_3C$-.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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.

[0041] 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.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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).

[0047] 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.

[0048] 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).

[0049] 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.

[0050] 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.

[0051] As used herein, "cycloalkyl" means a fully saturated carbocyclyl ring or ring system. Examples include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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).

[0059] A "cyano" group refers to a "-CN" group.

[0060] A "cyanato" group refers to an "-OCN" group.

[0061] An "isocyanato" group refers to a "-NCO" group.

[0062] A "thiocyanato" group refers to a "-SCN" group.

[0063] An "isothiocyanato" group refers to an " -NCS" group.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] An "aminoalkyl" group refers to an amino group connected via an alkylene group.

[0076] An "alkoxyalkyl" group refers to an alkoxy group connected via an alkylene group, such as a "C_{2-8} alkoxyalkyl" and the like.

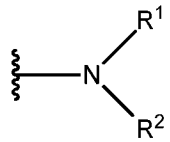
[0077] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be "substituted," it is meant that the group is substituted with 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.

[0078] 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.

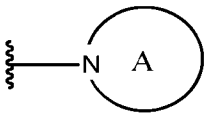
[0079] It is to be understood that certain radical naming conventions can include either a mono-radical or a di-radical, depending on the context. For example, where a substituent requires two points of attachment to the rest of the molecule, it is understood that the substituent is a di-radical. For 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."

[0080] 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:

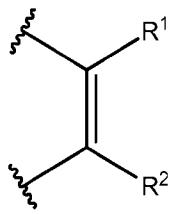


[0081] and R^1 and R^2 are defined as selected from the group consisting of hydrogen and alkyl, or R^1 and R^2 together with the nitrogen to which they are attached form a heterocyclyl, it is meant that R^1 and R^2 can be selected from hydrogen or alkyl, or alternatively, the substructure has structure:

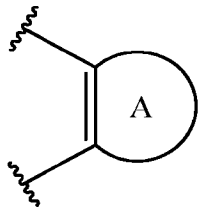


[0082] where ring A is a heterocyclyl ring containing the depicted nitrogen.

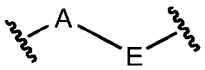
[0083] Similarly, when two "adjacent" R groups are said to form a ring "together with the atoms to which they are attached," it is meant that the collective unit of the atoms, intervening bonds, and the two R groups are the recited ring. For example, when the following substructure is present:



[0084] 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:



[0085] where A is an aryl ring or a carbocyclyl containing the depicted double bond.

[0086] 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.

[0087] 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.

[0088] "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.

[0089] 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).

[0090] "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.

Compounds

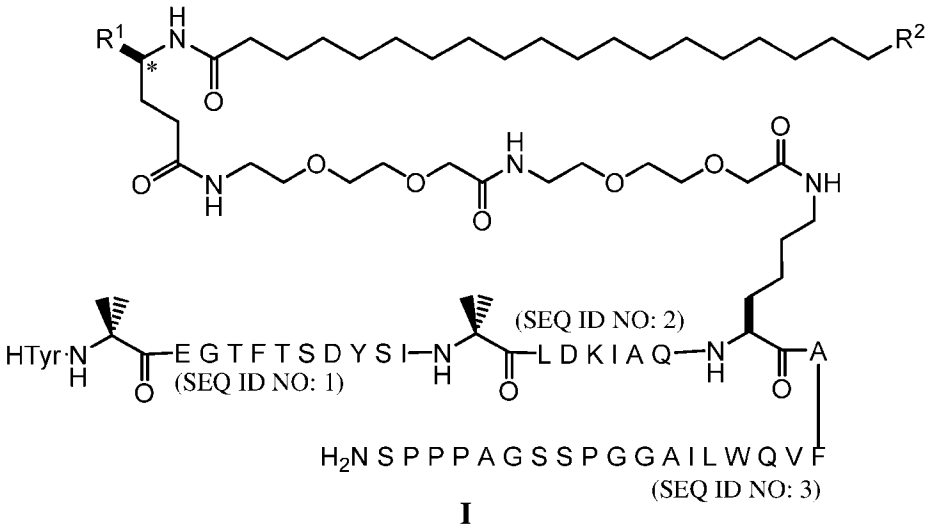
[0091] In some embodiments, the pharmaceutical compositions include compounds that are non-macrocyclic functionalized peptides that act as GIP/GLP-1 dual receptor agonists. In other embodiments, the pharmaceutical compositions include compounds that are non-macrocyclic functionalized peptides that act as GLP-1 receptor monoagonists.

[0092] 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.

[0093] 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.

Compounds of Formula (I)

[0094] Various embodiments of these 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

[0095] In some embodiments of compounds of Formula (I):

[0096] 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;

[0097] 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;

[0098] 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;

[0099] 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;

[0100] 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;

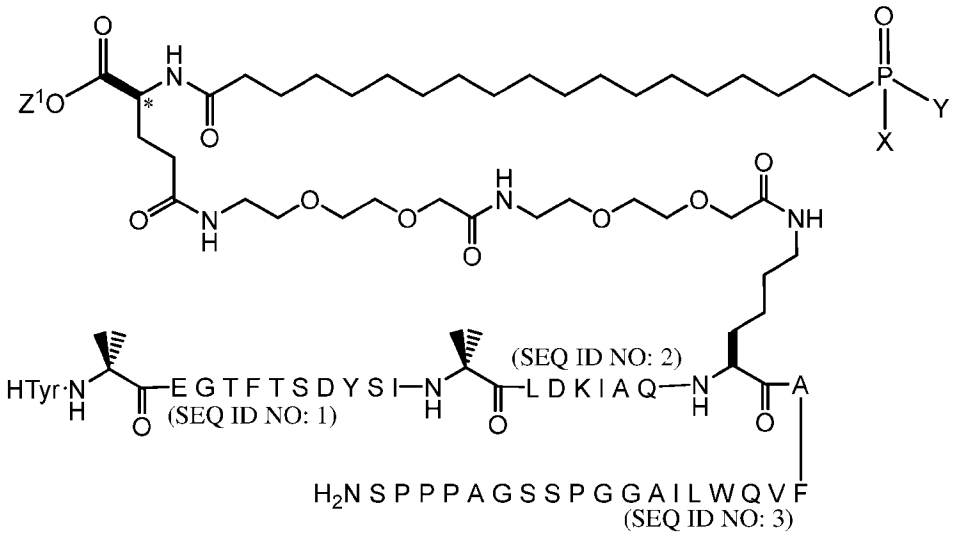
[0101] each R^5 may be independently hydrogen or C_{1-6} alkyl;

[0102] each R^6 may be independently hydrogen or C_{1-6} alkyl; and

[0103] Z^1 and Z^2 may each be 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.

[0104] In some embodiments, at least one of Z^1 and Z^2 is not hydrogen.

[0105] Some embodiments of compounds of Formula I include compounds having the structure of Formula (I-a):



I-a

or pharmaceutically acceptable salts thereof.

[0106] 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, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

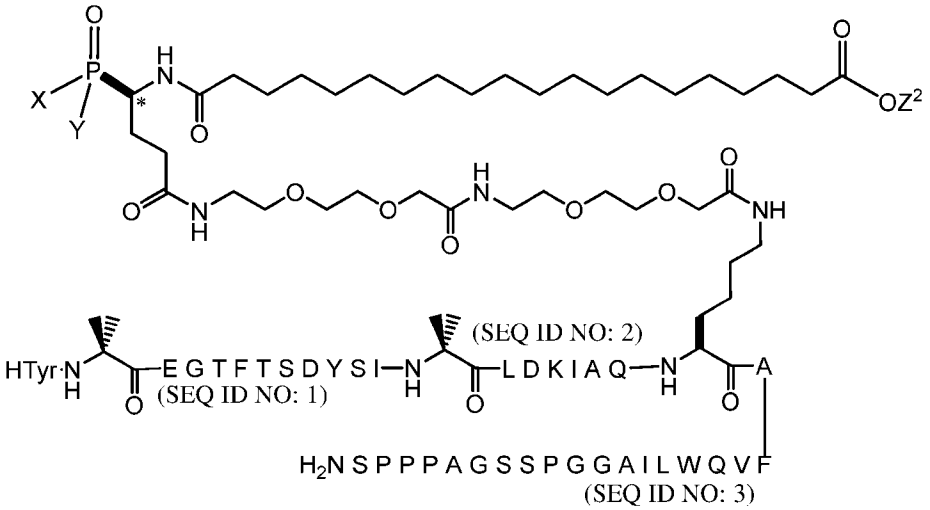
[0107] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is selected from hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

[0108] 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.

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

[0110] In some embodiments of compounds of Formula (I-a) or their pharmaceutically acceptable salts; Z^1 is hydrogen and each R^4 is hydrogen.

[0111] Some embodiments of compounds of Formula (I) include compounds having the structure of Formula (I-b):



I-b

or pharmaceutically acceptable salts thereof.

[0112] 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, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

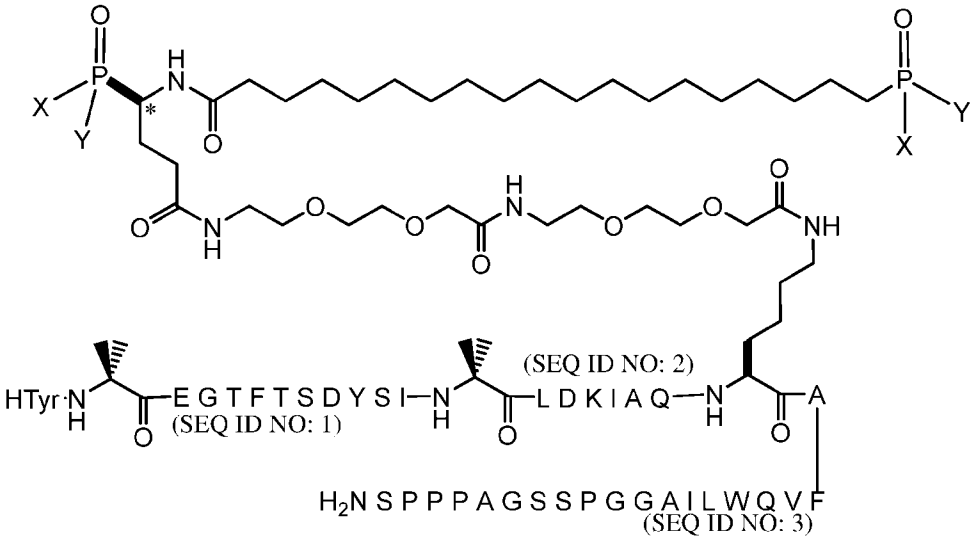
[0113] In some embodiments of compounds of Formula (I-b) or their pharmaceutically acceptable salts; Z^2 is selected from hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

[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

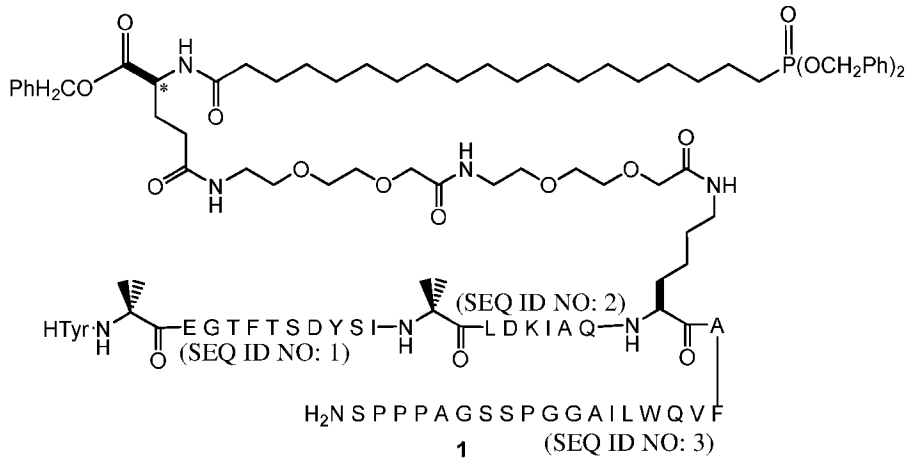
or pharmaceutically acceptable salts thereof.

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

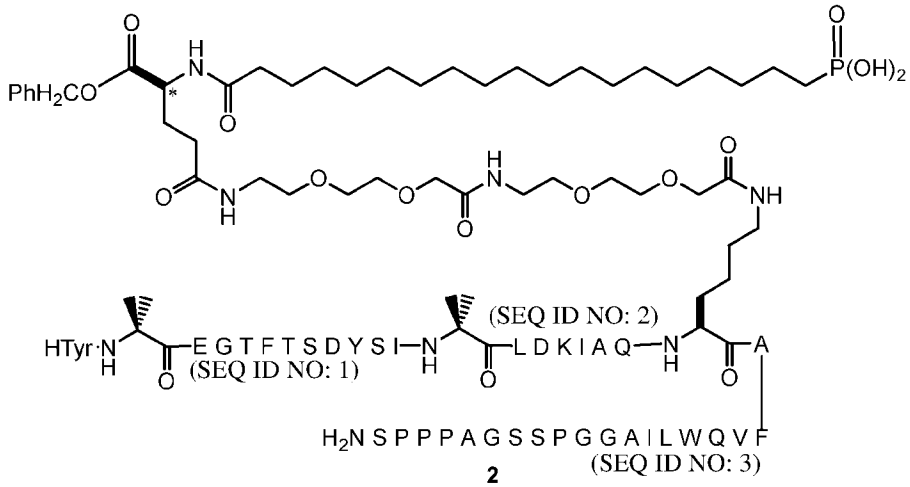
[0119] In some embodiments of compounds of Formula (I-c) or their pharmaceutically acceptable salts; each R^4 may be independently selected from hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

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

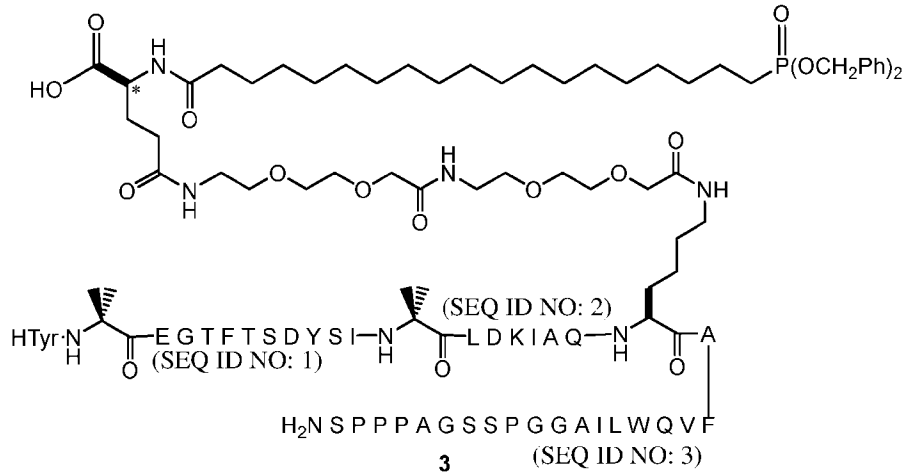
[0121] Some embodiments include a compound having the structure selected from the group consisting of:


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)

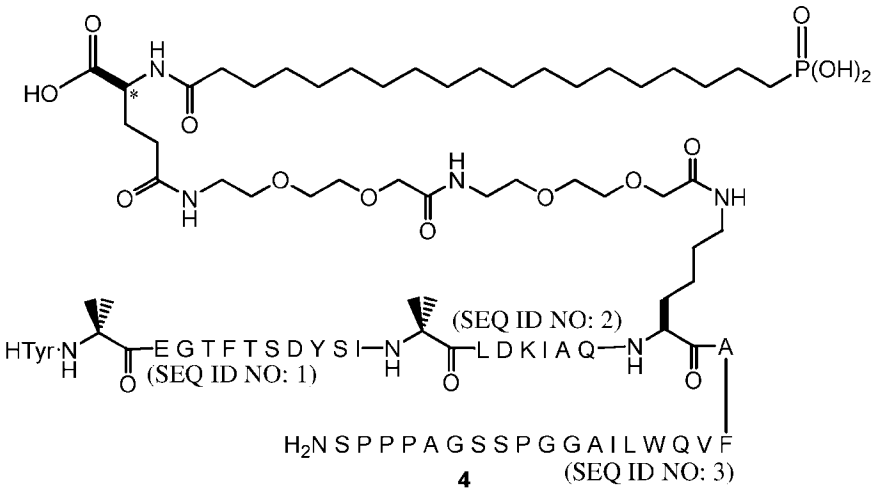
1


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)

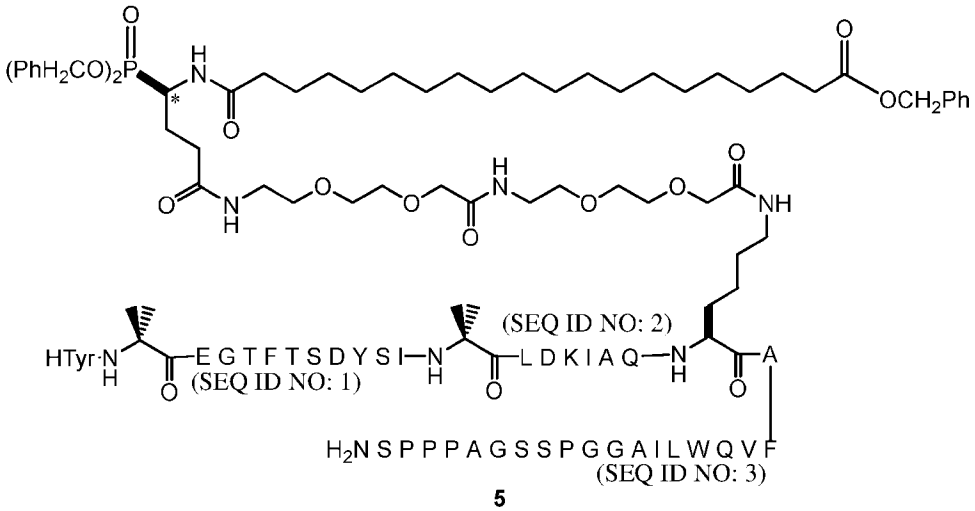
2


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)

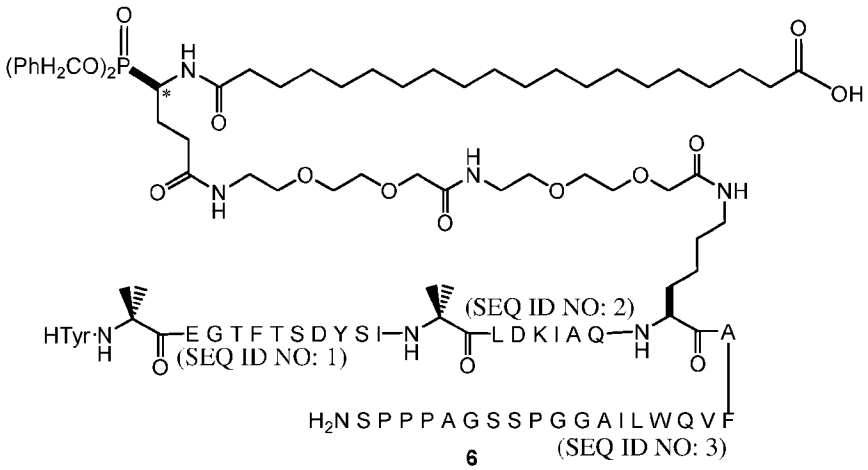
3


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

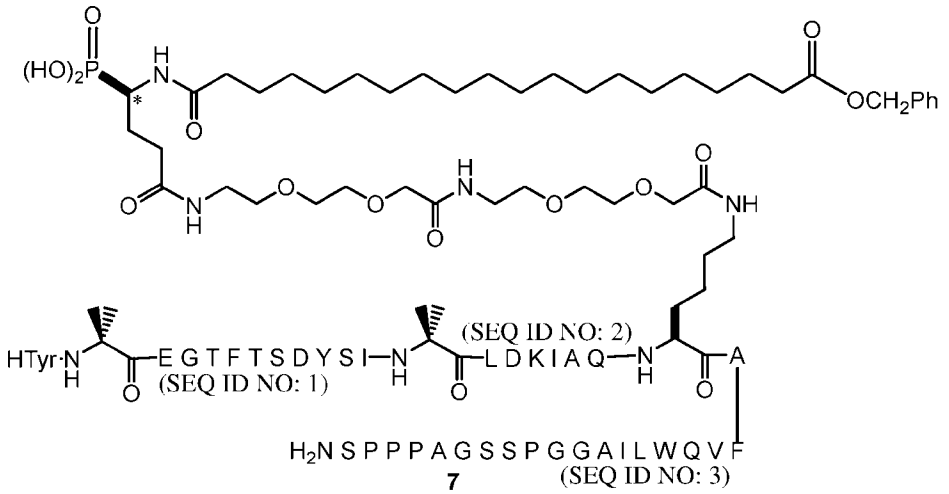
4


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

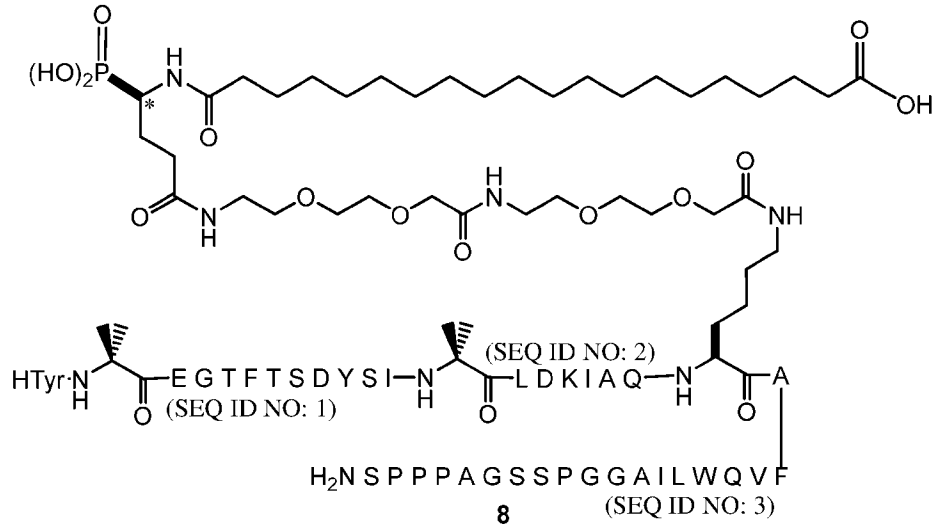
5


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

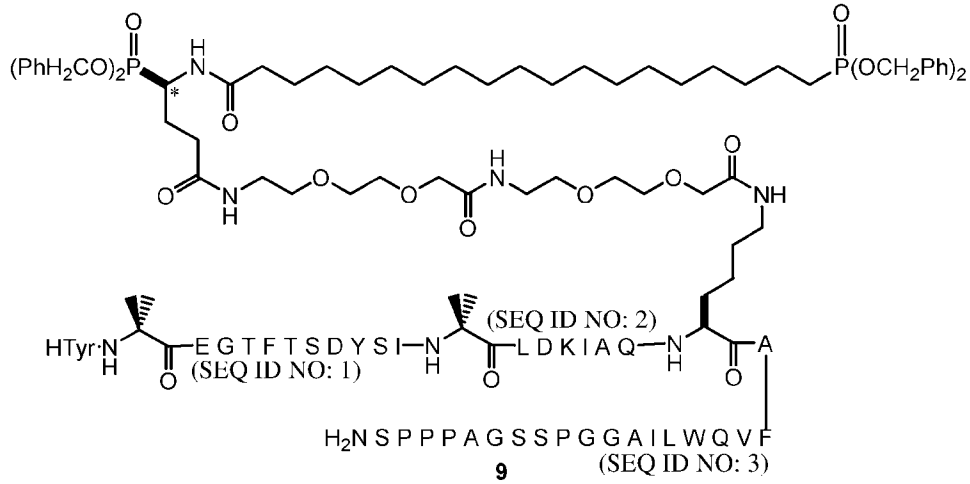
6


(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)

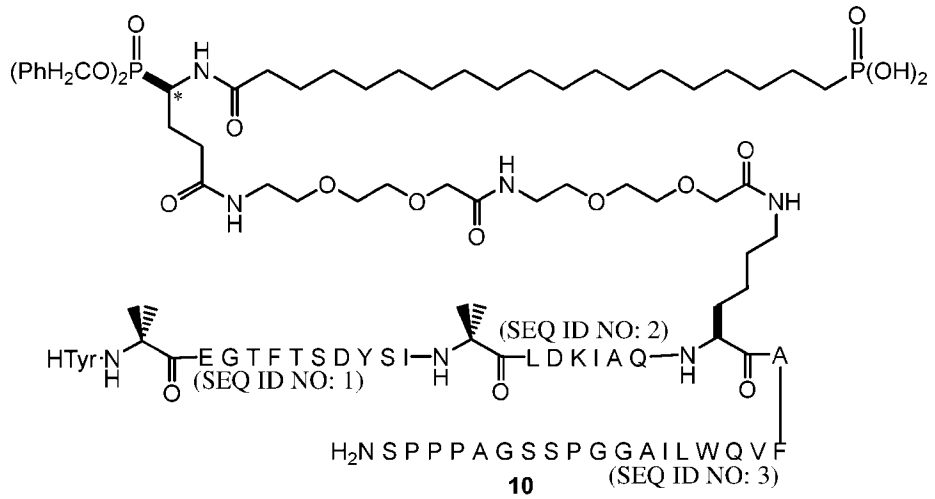
7


(HO)2P
OH
HTyr·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)

8


(PhH2CO)2P
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)

9



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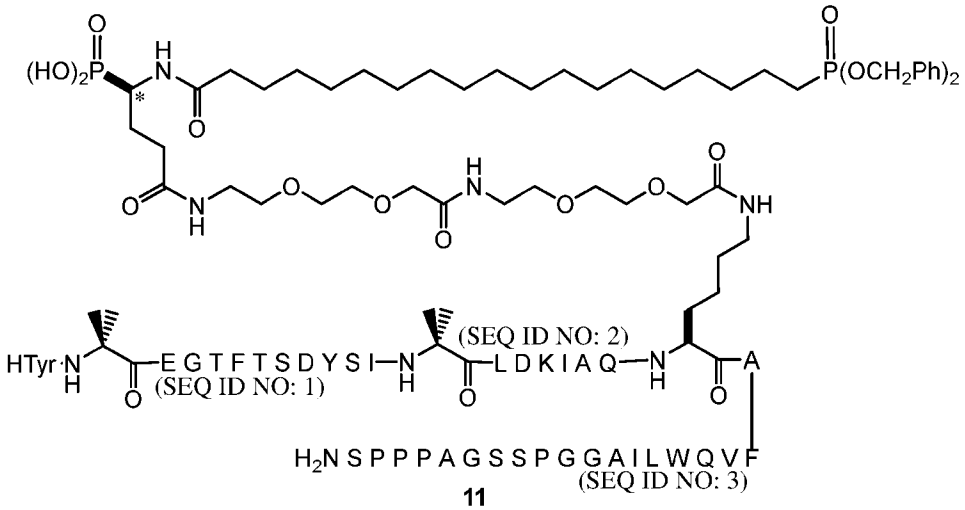

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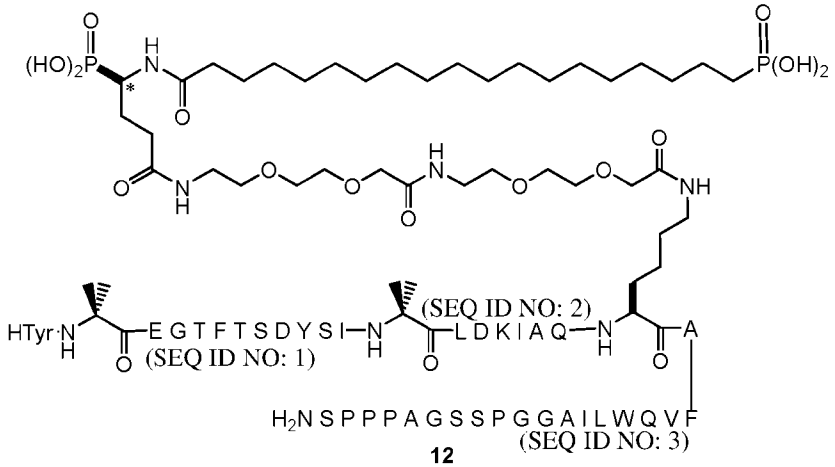


12

and pharmaceutically acceptable salts thereof.

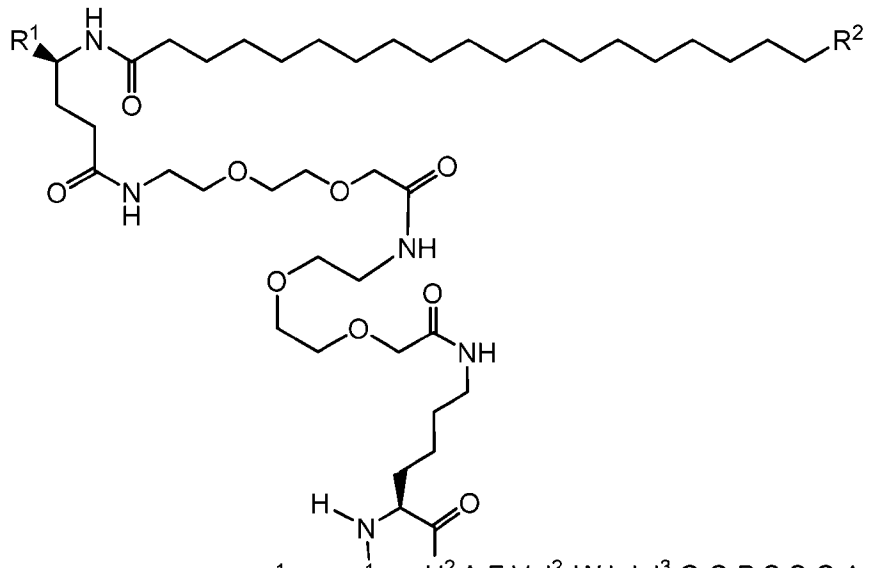
[0122] Some embodiments include a compound wherein "*" indicates a chiral carbon with "S" configuration.

[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.

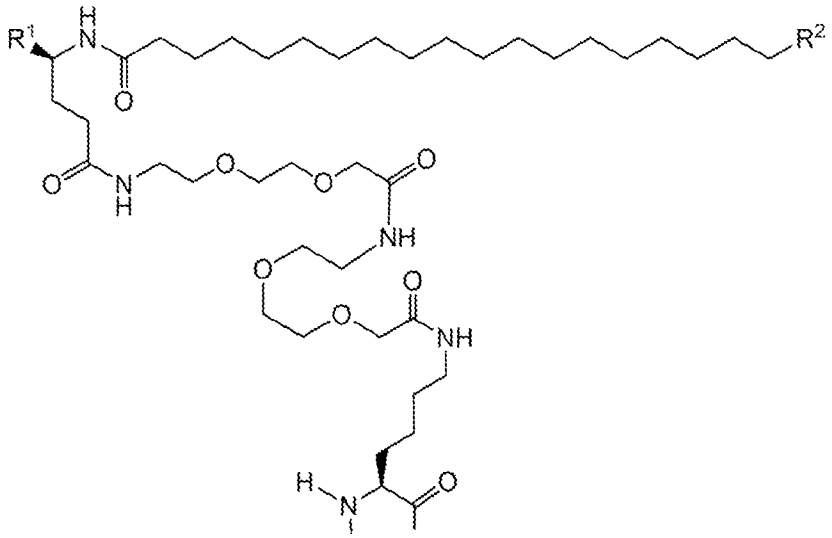
Compounds Formula (II)

[0125] Various embodiments of these 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:



(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;

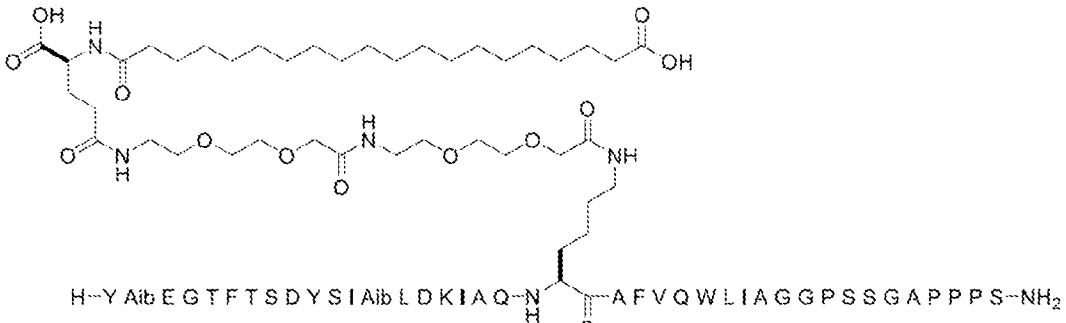
each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

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.

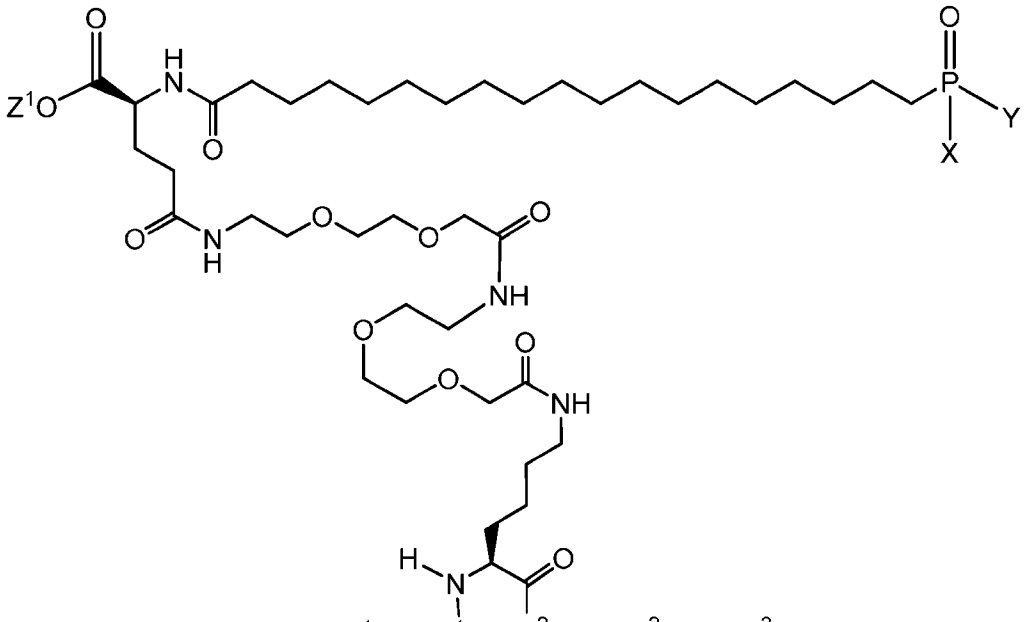
[0132] In some embodiments of compounds of Formula (II), each instance of J^8, J^9, J^{10}, and J^{11} is independently an amino acid selected from A, I, and Q. In some embodiments, J^8 is I or Q. In some embodiments, J^9 is A or Q. In some embodiments, J^{10} is Q. In some embodiments, J^{11} is Q.

[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):



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-a

or a pharmaceutically acceptable salt thereof.

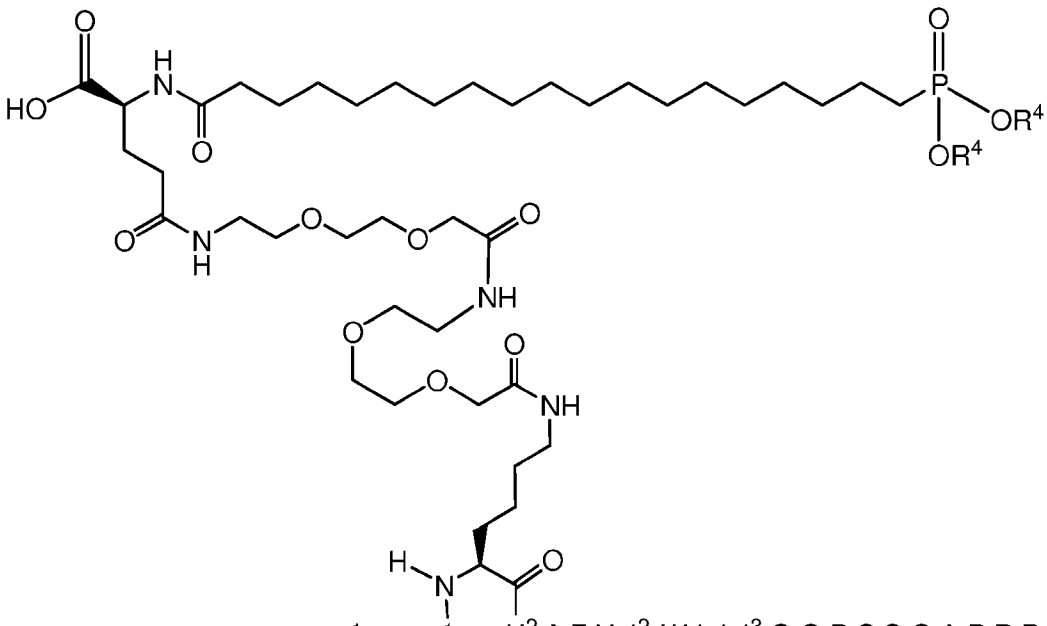
[0137] In some embodiments of compounds of Formula (II-a) or their pharmaceutically acceptable salts, Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

[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):



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

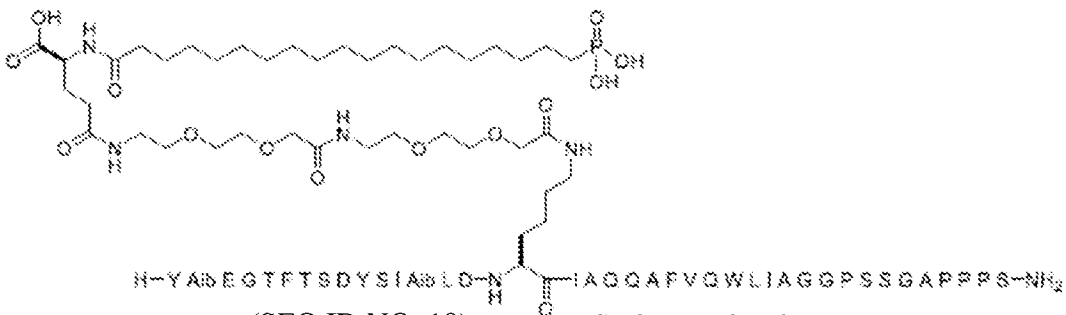
II-b

or a pharmaceutically acceptable salt thereof.

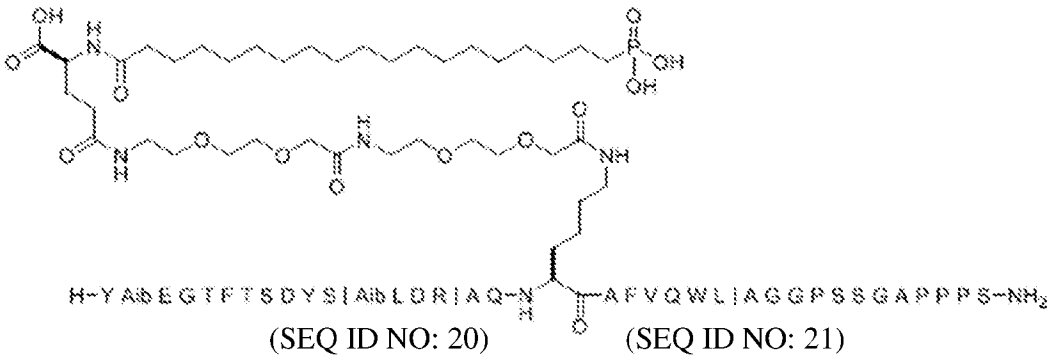
[0142] In some embodiments of compounds of Formula (II-b) or their pharmaceutically acceptable salts, each R^4 is independently selected from the group consisting of hydrogen, C_{6-10} aryl and C_{7-11} arylalkyl.

[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:



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



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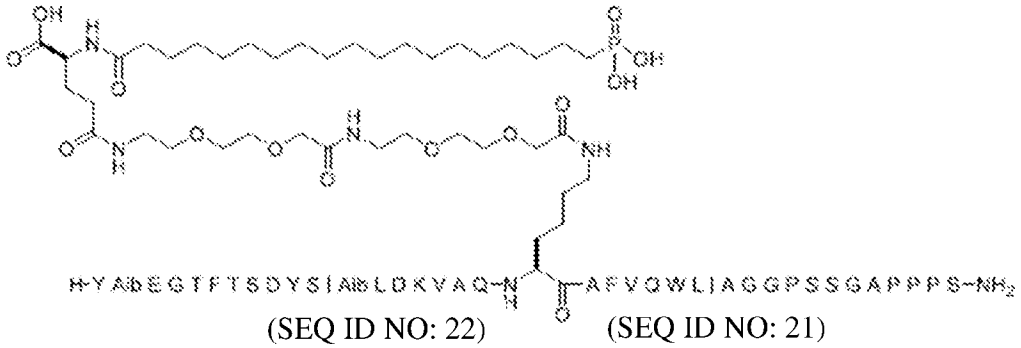

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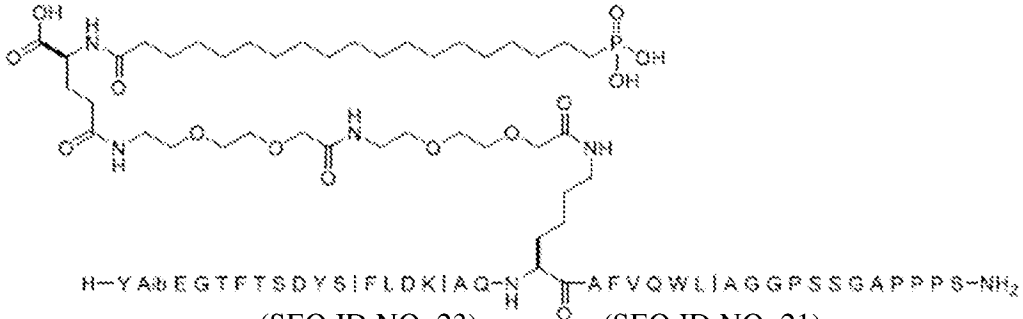

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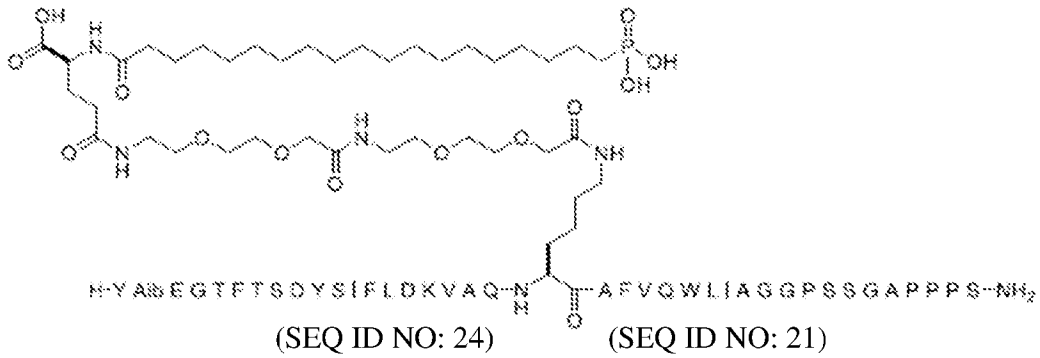

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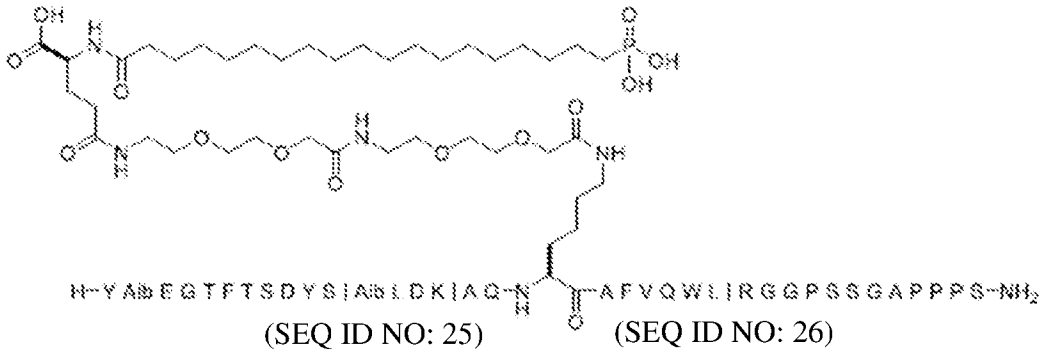

(SEQ ID NO: 25) (SEQ ID NO: 26)

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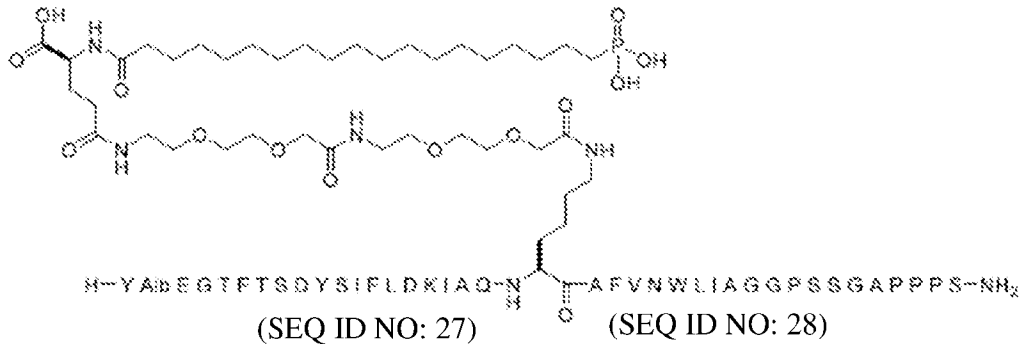

(SEQ ID NO: 27) (SEQ ID NO: 28)

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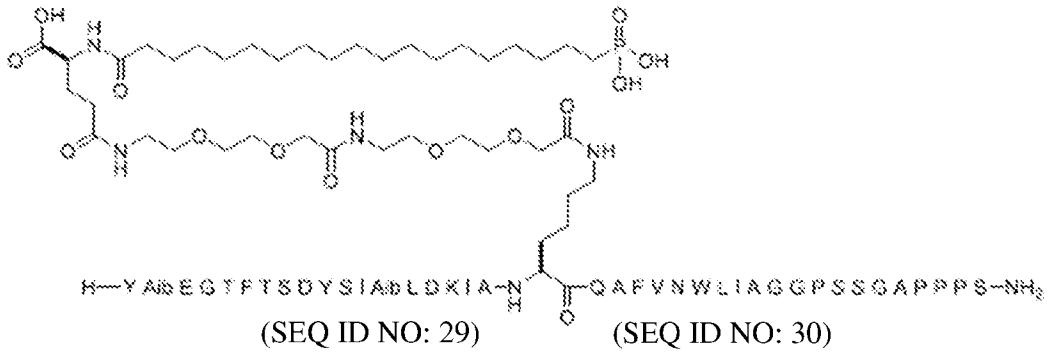

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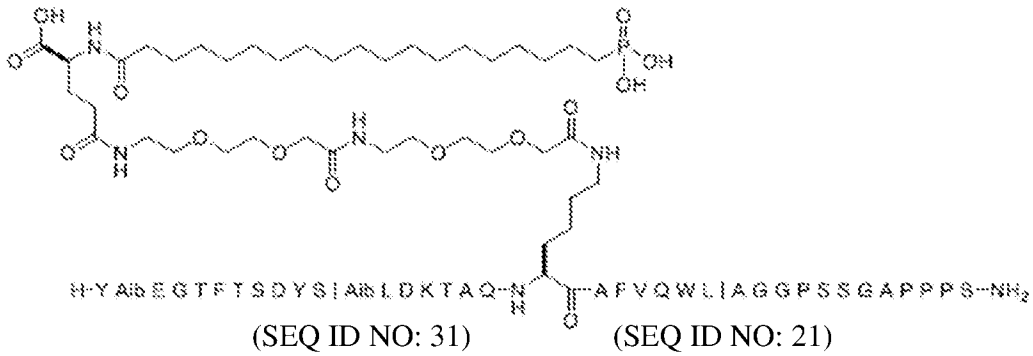

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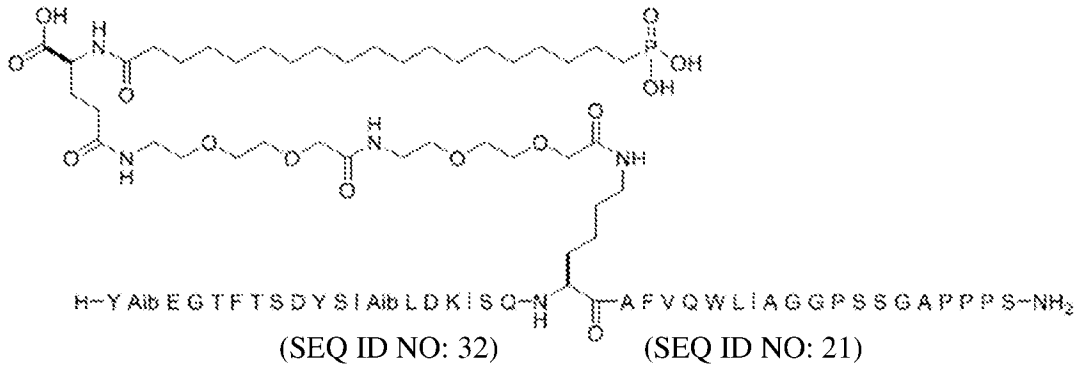

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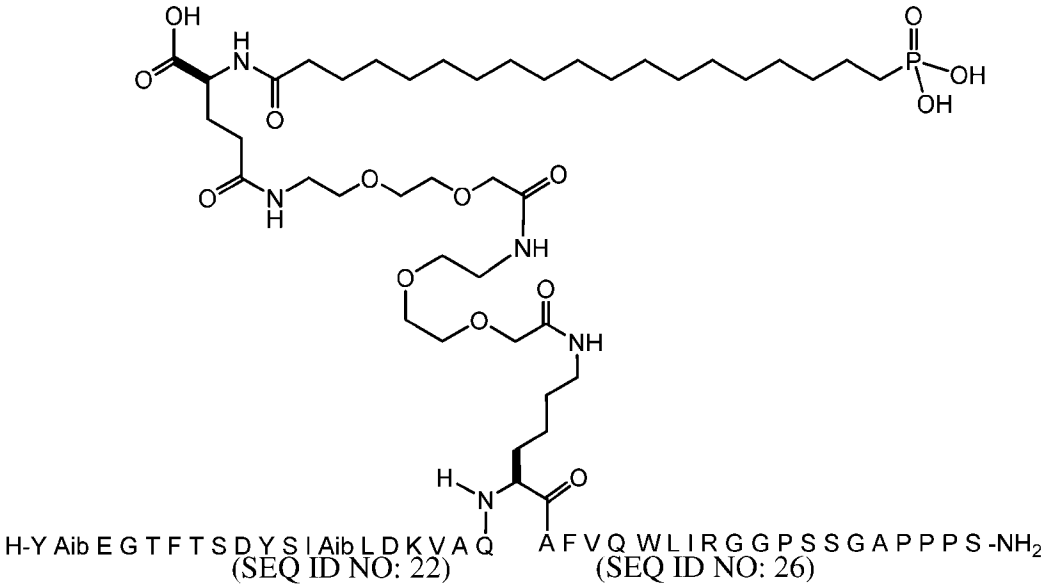

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or pharmaceutically acceptable salts thereof.

[0145] The compounds of Formula (II) disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie, Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include e.g. those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, **1989**, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, **1995**, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize

modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

[0146] In the following scheme, protecting groups for oxygen atoms are selected for their compatibility with the requisite synthetic steps as well as compatibility of the introduction and deprotection steps with the overall synthetic schemes (P.G.M. Green, T.W. Wutts, Protecting Groups in Organic Synthesis (3rd ed.) Wiley, New York (1999)).

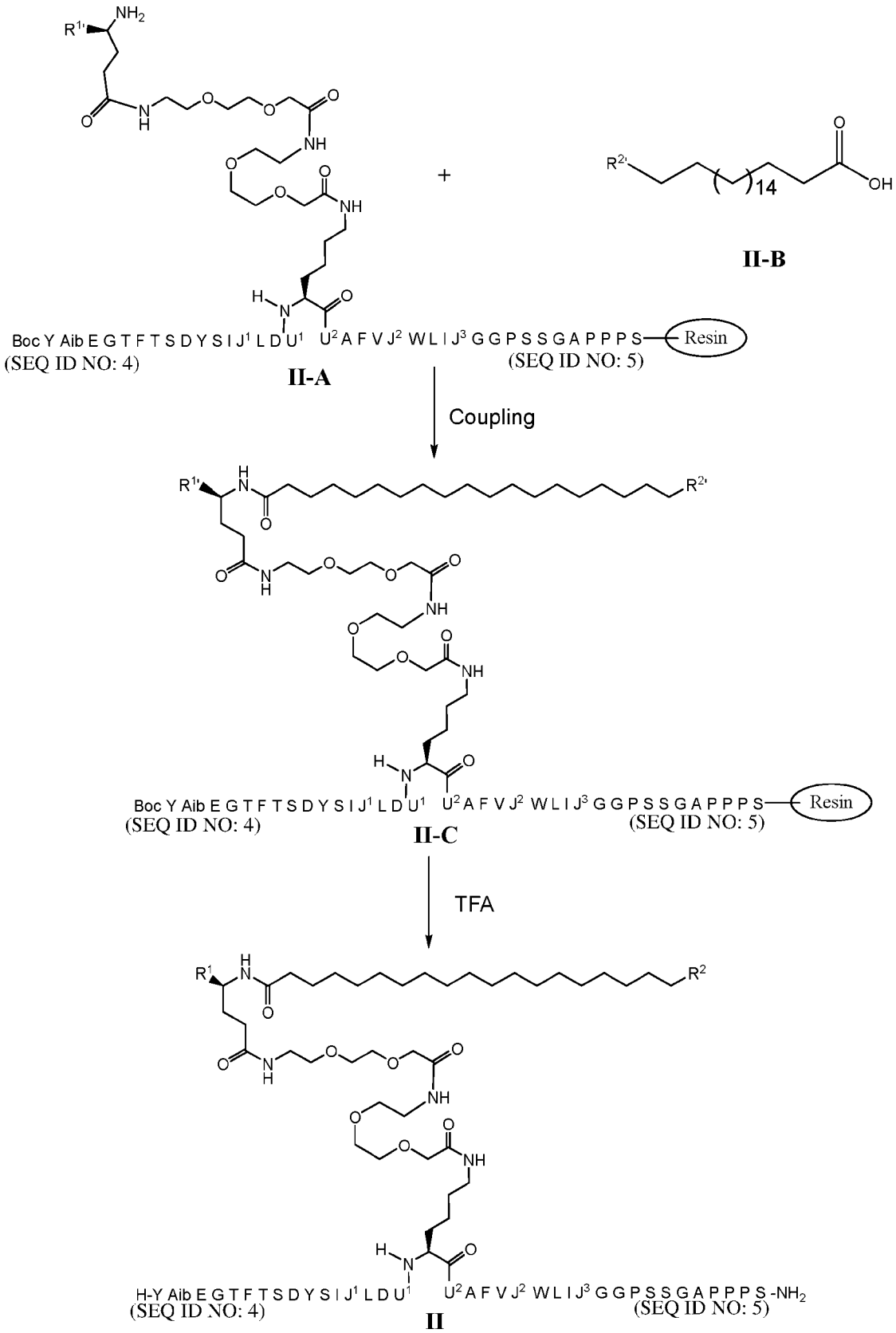
[0147] If the compounds of the present technology contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or d(l) stereoisomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the present technology, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

[0148] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California , USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[0149] **Scheme 1** depicts one method for making compounds according to Formula (**II**). The method may include constructing a peptide backbone using solid-phase peptide synthesis techniques to provide a resin-bound peptide. The side chain of a central lysine containing a Dde group may then be expanded with a linker comprising two PEG_2 amide linkers and a isoglutamic acid (or related analog) linker to provide intermediate (**II-A**). The method includes a coupling reaction between the amine of the isoglutamic acid (or related

analog) of intermediate (**II-A**) and intermediate (**II-B**) to provide the resin-bound intermediate (**II-C**). In formulas (**II-A**) – (**II-C**), $R^{1'}$ and $R^{2'}$ are protected versions of the R^1 and R^2 groups described herein. In one embodiment, the method involves subjecting intermediate (**II-C**) to hydrolysis under acidic conditions to remove the resin and protecting groups, followed by purification to yield the final product (**I**). The peptide backbones disclosed herein may be synthesized by solid-phase peptide synthesis techniques, or obvious modifications thereof, described in *Methods in Molecular Biology, 298, Peptide Synthesis and Applications,* (ed. J. Howl, Humana Press, 2005); and *Amino Acids, Peptides and Proteins in Organic Chemistry, Volume 3, Building Blocks, Catalysts and Coupling Chemistry,* (ed. A. B. Hughs, Wiley-VCH, 2011) which are both hereby incorporated herein by reference in their entirety.

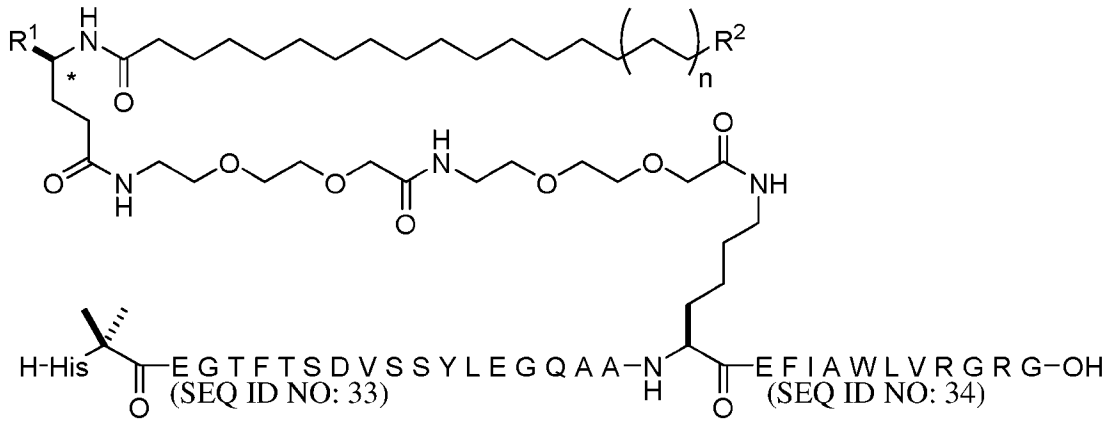
Scheme 1:


Boc Y Aib E G T F T S D Y S I J1 L D U1 U2 A F V J2 W L I J3 G G P S S G A P P P S
(SEQ ID NO: 4)
(SEQ ID NO: 5)
Resin
II-A
II-B
Coupling
II-C
TFA
H-Y Aib E G T F T S D Y S I J1 L D U1 U2 A F V J2 W L I J3 G G P S S G A P P P S-NH2
II

[0150] The above example scheme is provided for the guidance of the reader, and collectively represent an example method for making the compounds encompassed herein. Furthermore, other methods for preparing compounds 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.

Compounds of Formula (III)

[0151] Various embodiments of these compounds include compounds having the structure of Formula (III) as described herein or pharmaceutically acceptable salts thereof. The structure of Formula (III) encompasses all stereoisomers.



(III)

[0152] In some embodiments of compounds of Formula (III):

R^1 is selected from the group consisting of $-C(=O)(OZ^1)$, $-P(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-4 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 1-4 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} aryloxy and C_{6-10} aryl alkoxy;

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

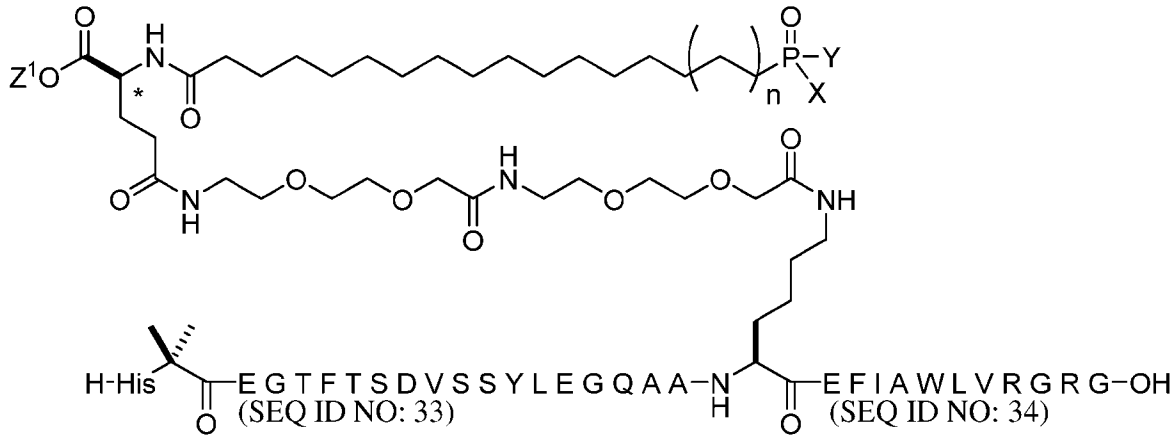
each R^6 may be independently hydrogen or C_{1-6} alkyl;

Z^1 and Z^2 may each be 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

n is 0, 1, 2, 3, or 4.

[0153] In some embodiments, at least one of Z^1 and Z^2 is not hydrogen.

[0154] Some embodiments of compounds of Formula (III) include compounds having the structure of Formula (III-a):



(III-a)

or pharmaceutically acceptable salts thereof.

[0155] 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, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

[0156] In some embodiments of compounds of Formula (III-a) or their pharmaceutically acceptable salts, Z^1 is selected from hydrogen, haloC_{1-6} alkoxy and C_{1-6}

alkoxy; and each R^4 may be independently selected from hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

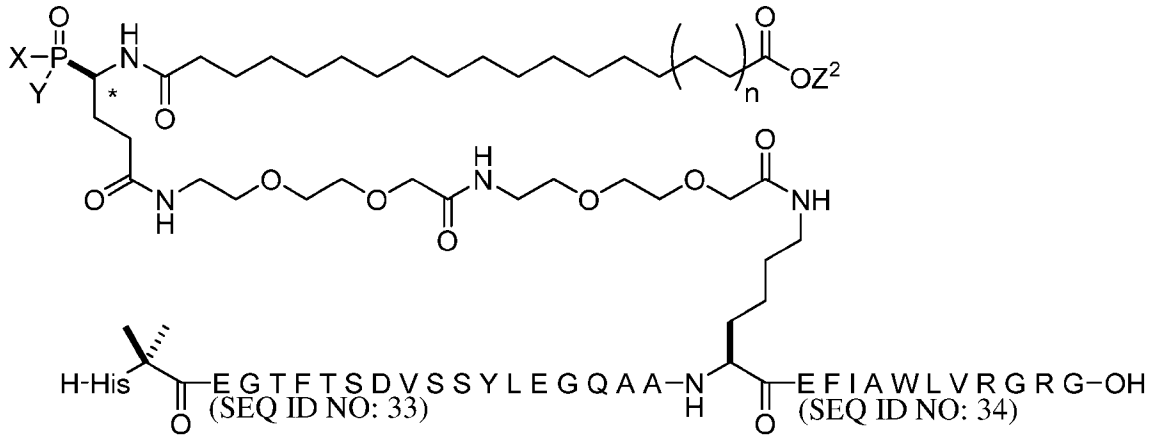
[0157] In some embodiments of compounds of Formula (III-a) or their pharmaceutically acceptable salts; Z^1 is hydrogen and each R^4 may be independently hydrogen or C_{6-10} aryl alkoxy.

[0158] In some embodiments of compounds of Formula (III-a) or their pharmaceutically acceptable salts, each R^4 is hydrogen.

[0159] In some embodiments of compounds of Formula (III-a) or their pharmaceutically acceptable salts, Z^1 is hydrogen and each R^4 is hydrogen.

[0160] In some embodiments of compounds of Formula (III-a) or their pharmaceutically acceptable salts, n is 0. In other embodiments, n is 1. In yet other embodiments, n is 2. In still yet other embodiments, n is 3. In some embodiments, n is 4.

[0161] Some embodiments of compounds of Formula (III) include compounds having the structure of Formula (III-b):



(III-b)

or pharmaceutically acceptable salts thereof.

[0162] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts; Z^2 is selected from 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 $-OR^4$.

[0163] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts; Z^2 is selected from hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 may be independently selected from hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

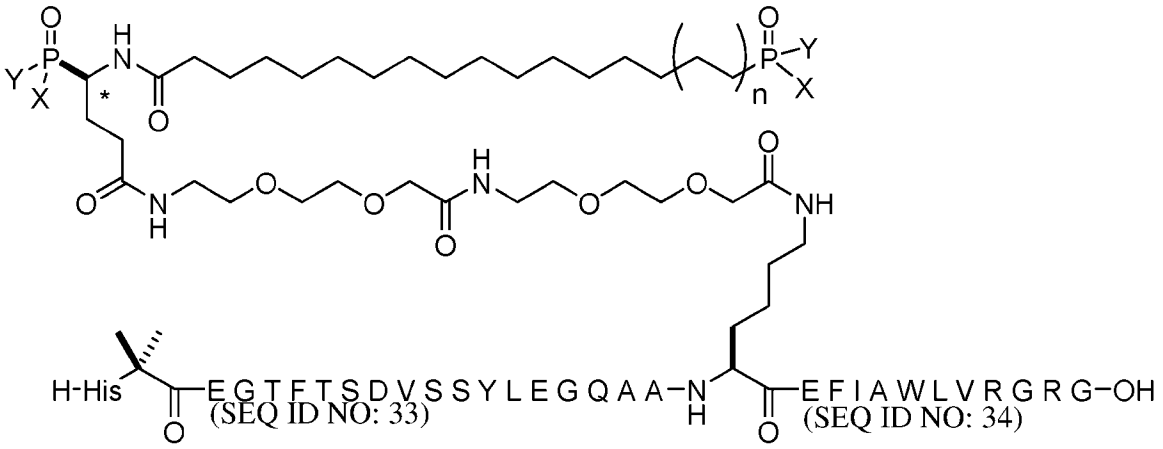
[0164] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts; Z^2 is hydrogen and each R^4 may be independently hydrogen or C_{6-10} aryl alkoxy.

[0165] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts; each R^4 is hydrogen.

[0166] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts; Z^2 is hydrogen and each R^4 is hydrogen.

[0167] In some embodiments of compounds of Formula (III-b) or their pharmaceutically acceptable salts, n is 0. In other embodiments, n is 1. In yet other embodiments, n is 2. In still yet other embodiments, n is 3. In some embodiments, n is 4.

[0168] Some embodiments of compounds of Formula (III) include compounds having the structure of Formula (III-c):



(III-c)

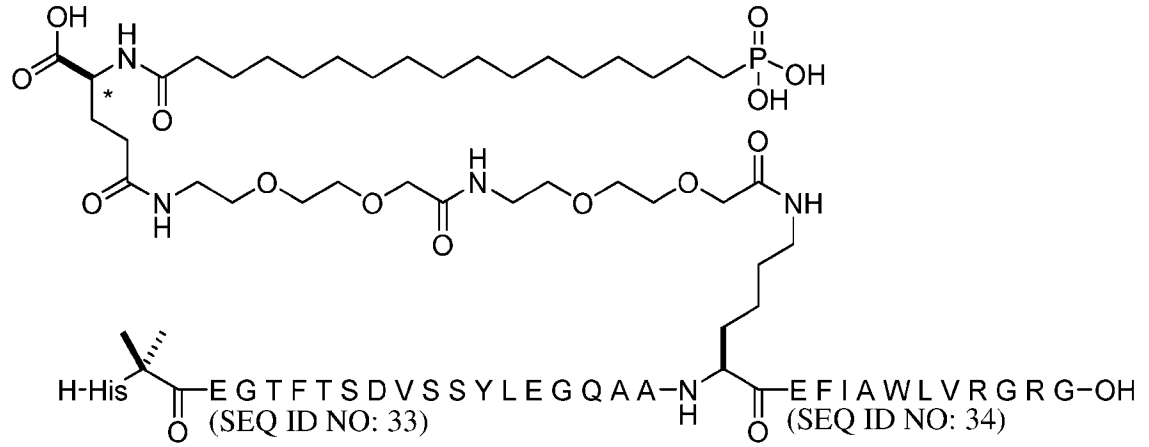
or pharmaceutically acceptable salts thereof.

[0169] In some embodiments of compounds of Formula (III-c) or their pharmaceutically acceptable salts, X and Y each are $-OR^4$.

[0170] In some embodiments of compounds of Formula (III-c) or their pharmaceutically acceptable salts, each R^4 may be independently selected from hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy. In some embodiments of compounds of Formula (III-c) or their pharmaceutically acceptable salts, each R^4 is hydrogen.

[0171] In some embodiments of compounds of Formula (III-c) or their pharmaceutically acceptable salts, n is 0. In other embodiments, n is 1. In yet other embodiments, n is 2. In still yet other embodiments, n is 3. In some embodiments, n is 4.

[0172] Some embodiments include a compound having the structure selected from the group consisting of:



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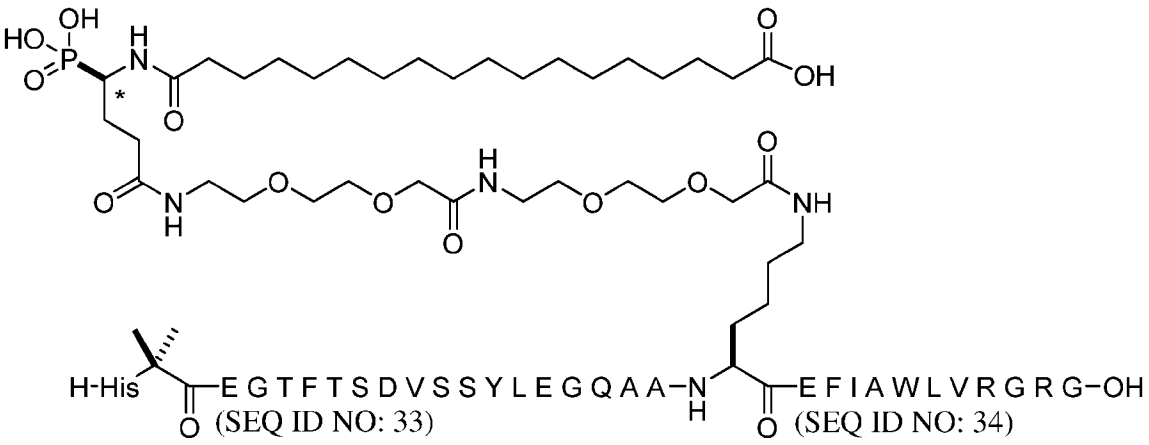

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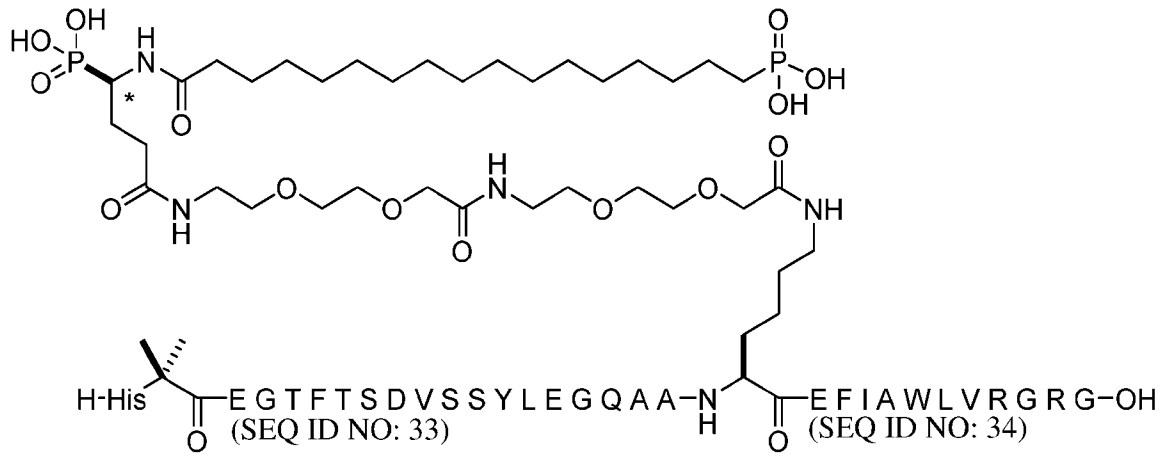

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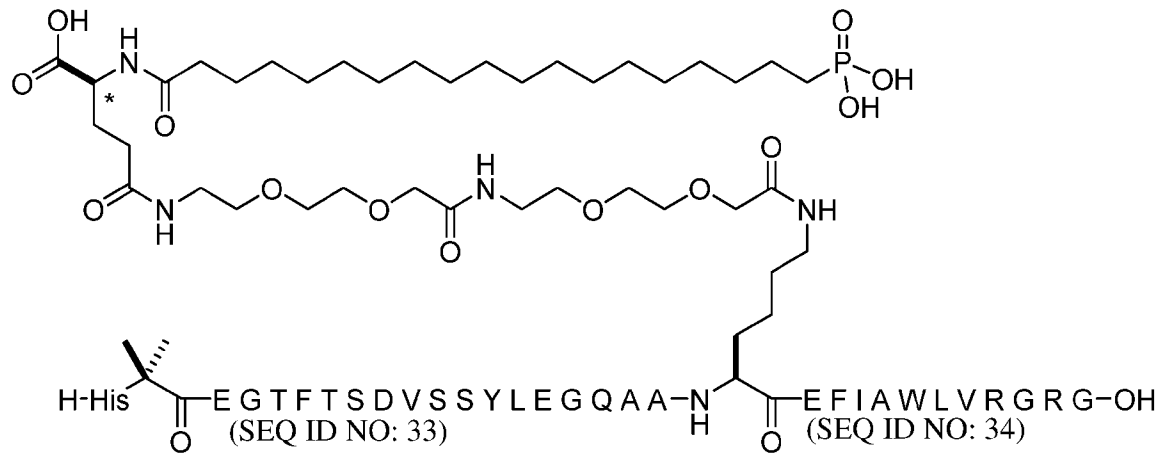

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and pharmaceutically acceptable salts thereof.

[0173] Some embodiments include a compound wherein "*" indicates a chiral carbon with "S" configuration.

[0174] Some embodiments include a compound wherein "*" indicates a chiral carbon with "R" configuration.

[0175] The compounds of Formula (III) disclosed herein may be synthesized by methods described below, or by modification of these methods. Ways of modifying the methodology include, among others, temperature, solvent, reagents etc., known to those skilled in the art. In general, during any of the processes for preparation of the compounds disclosed herein, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry* (ed. J.F.W. McOmie,

Plenum Press, 1973); and P.G.M. Green, T.W. Wutts, *Protecting Groups in Organic Synthesis* (3rd ed.) Wiley, New York (1999), which are both hereby incorporated herein by reference in their entirety. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. Synthetic chemistry transformations useful in synthesizing applicable compounds are known in the art and include e.g. those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers, 1989, or L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, 1995, which are both hereby incorporated herein by reference in their entirety. The routes shown and described herein are illustrative only and are not intended, nor are they to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

[0176] In the following scheme, protecting groups for oxygen atoms are selected for their compatibility with the requisite synthetic steps as well as compatibility of the introduction and deprotection steps with the overall synthetic schemes (P.G.M. Green, T.W. Wutts, Protecting Groups in Organic Synthesis (3rd ed.) Wiley, New York (1999)).

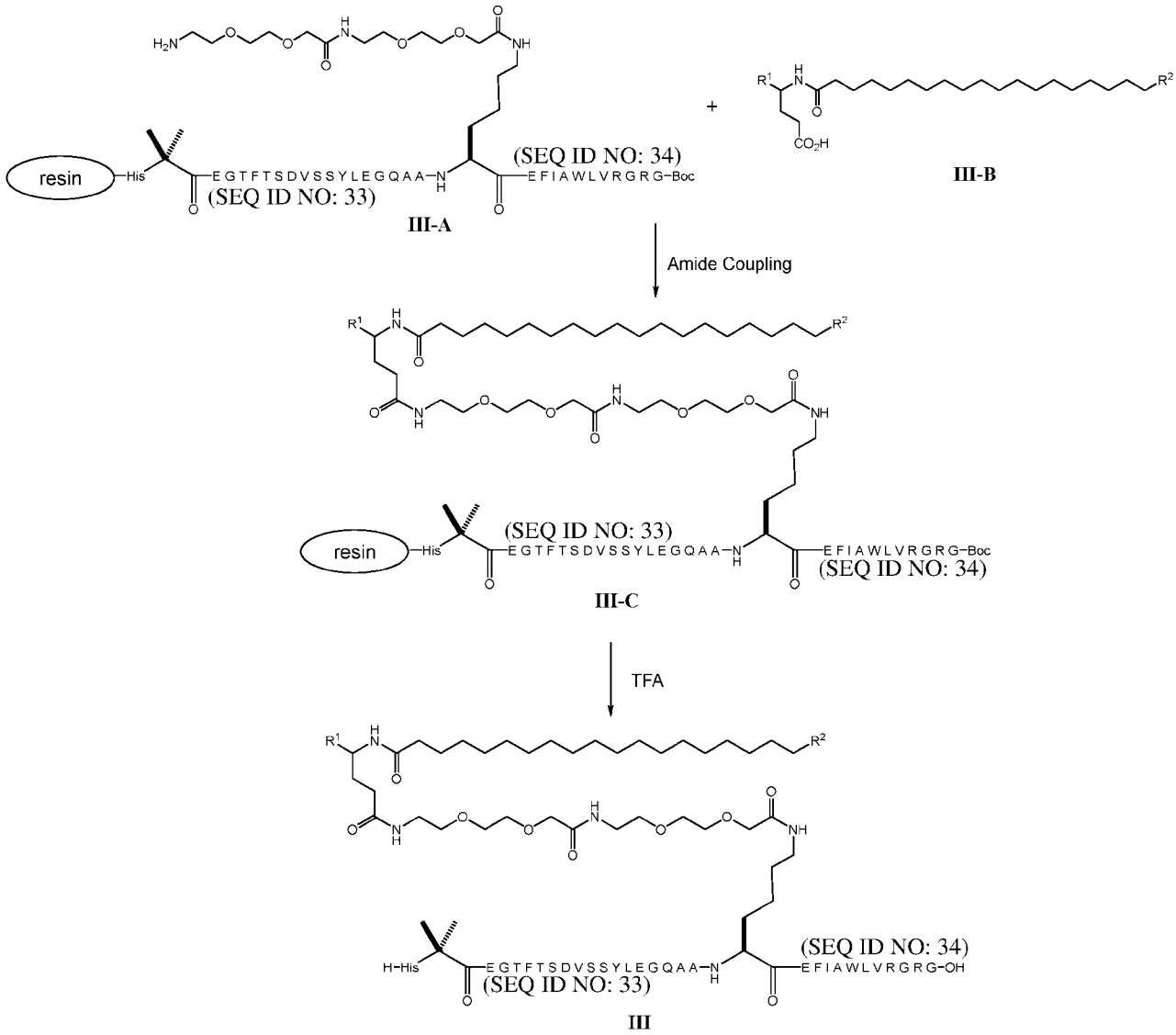
[0177] If the compounds of the present technology contain one or more chiral centers, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or d(l) stereoisomers, or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of the present technology, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

[0178] The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA), Bachem (Torrance, California , USA), Emka-Chemce or Sigma (St. Louis, Missouri, USA). Others may be prepared by procedures, or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's

Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[0179] In one embodiment, the methods disclosed herein may include constructing a 31-amino acid peptide backbone using solid-phase peptide synthesis techniques to provide intermediate (**III-A**). The peptide backbone includes two PEG_2 amide linkers. The method includes an amide coupling reaction between the amine of the terminal PEG_2 amide of intermediate (**III-A**) and an appropriately substituted carboxylic acid (**III-B**) to provide the resin-bound intermediate (**III-C**). In one embodiment, the method involves subjecting intermediate (**III-C**) to hydrolysis under acidic conditions followed by purification to yield the final product (**III**). (**Scheme 2**).

Scheme 2:



[0180] The above example scheme is provided for the guidance of the reader, and collectively represent an example method for making the compounds encompassed herein. Furthermore, other methods for preparing compounds 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.

Pharmaceutical Compositions

[0181] Some embodiments include pharmaceutical compositions comprising a compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c), 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 an excipient. In some embodiments, the pharmaceutical composition is suitable for use as an oral dosage form.

[0182] 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 examples, 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 50% to about 80%, from about 50% to about 75%, from about 60% to about 75%, or from about 70% to about 75% percent. 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. In some embodiments, the permeability enhancer is lauroyl-L-carnitine chloride (LCC). In some embodiments, the permeability enhancer is Labrasol®. Labrasol® contains PEG-8 mono- and diesters of caprylic (C8) and capric (C10) acids with a small fraction of mono-, di- and triglycerides.

[0183] 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.

[0184] In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c), 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), (II-b), (III), (III-a), (III-b), or (III-c) 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 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), (II-b), (III), (III-a), (III-b), or (III-c) in the pharmaceutical composition is about 3.6% by weight.

[0185] In some embodiments, the amount of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c), 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), (II-b), (III), (III-a), (III-b), or (III-c), 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.

[0186] In some embodiments, the amount of Compound 4 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 4 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.

[0187] 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.

[0188] 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), (II-b), (III), (III-a), (III-b), or (III-c) 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, 20.5:1,, 21:1, 21.5:1, 22:1, 22.5:1, 23:1, 23.5:1, 24:1, 24.5:1, 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), (II-b), (III), (III-a), (III-b), or (III-c) 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.

[0189] In some embodiments, the pharmaceutical compositions described herein include one or more additional pharmaceutically-acceptable excipient(s). 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.

[0190] In some embodiments, the pharmaceutical compositions described herein may comprise the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c) and SNAC. In some such embodiments, the pharmaceutical compositions may further comprise microcrystalline cellulose, polyvinylpyrrolidinone (PVP), polyvinylpyrrolidinone-vinyl acetate copolymer (PVP-VA), magnesium stearate, or a combination thereof.

[0191] In some embodiments, the pharmaceutical compositions described herein may comprise the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c) and C10. In some such embodiments, the pharmaceutical compositions may further comprise microcrystalline cellulose, polyvinylpyrrolidinone (PVP), polyvinylpyrrolidinone-vinyl acetate copolymer (PVP-VA), magnesium stearate, or a combination thereof.

[0192] In some embodiments, the pharmaceutical compositions described herein may comprise the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c) and a combination of SNAC and C10. In some such embodiments, the pharmaceutical compositions may further comprise microcrystalline cellulose,

polyvinylpyrrolidinone (PVP), polyvinylpyrrolidinone-vinyl acetate copolymer (PVP-VA), magnesium stearate, or a combination thereof.

[0193] In some embodiments, the pharmaceutical compositions described herein 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 pharmaceutical compositions described herein 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 pharmaceutical compositions described herein comprised about 19.4% microcrystalline cellulose by weight.

[0194] In some embodiments, the pharmaceutical compositions described herein may comprise polyvinylpyrrolidinone 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 pharmaceutical compositions described herein 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 polyvinylpyrrolidinone. In some embodiments, the pharmaceutical compositions described herein comprised about 1.9% polyvinylpyrrolidinone by weight.

[0195] In some embodiments, the pharmaceutical compositions described herein 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 pharmaceutical compositions described herein 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 pharmaceutical compositions described herein comprised about 2.3% magnesium stearate by weight.

[0196] In some embodiments, the pharmaceutical compositions described herein may comprise a disintegrant. In some embodiments, the pharmaceutical composition may comprise a disintegrant in an amount of 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 pharmaceutical compositions described herein 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 disintegrant. In some embodiments, the pharmaceutical compositions described herein comprised about 1.9% disintegrant by weight. In some embodiments, the disintegrant may be croscarmellose sodium (e.g., primellose, AcDiSol)). In some embodiments, the disintegrant may be sodium alginate. In some embodiments, the disintegrant may be crospovidone. In some embodiments, the disintegrant may be sodium starch glycolate.

[0197] In some embodiments, the pharmaceutical compositions described herein 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), (II-b), (III), (III-a), (III-b), or (III-c); 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 3.0% by weight polyvinylpyrrolidinone; and from about 1.0% to about 3.0% by weight magnesium stearate. In some such embodiments, pharmaceutical composition comprises: about 3.6% by weight of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c); about 72.7% by weight salcaprozate sodium; about 19.4% by weight microcrystalline cellulose; about 1.9% by weight polyvinylpyrrolidinone; and about 2.3% by weight magnesium stearate. In other such embodiments, pharmaceutical composition comprises: about 3.2% by weight of the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c); about 71.1% by weight salcaprozate sodium; about 21.1% by weight microcrystalline cellulose; about 2.1% by weight polyvinylpyrrolidinone; and about 2.6% by weight magnesium stearate.

[0198] The pharmaceutical compositions include a therapeutically effective dosage or amount of a compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c). The term "therapeutically effective dosage" or "therapeutically effective

amount," as used herein, is dependent on the subject and disease state being treated, the severity of the affliction, the manner and schedule of administration and the judgment of the prescribing physician. In some embodiments, the therapeutically effective dosage may be a daily dosage from about 0.0125 mg/kg to about 120 mg/kg or more of body weight, from about 0.025 mg/kg or less to about 70 mg/kg, from about 0.05 mg/kg to about 50 mg/kg of body weight, or from about 0.075 mg/kg to about 10 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 0.88 mg per day to about 8000 mg per day, from about 1.8 mg per day or less to about 7000 mg per day or more, from about 3.6 mg per day to about 6000 mg per day, from about 5.3 mg per day to about 5000 mg per day, or from about 11 mg to about 3000 mg per day. In some embodiments, the therapeutically effective dosage is from about 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.12 mg/kg, 0.14 mg/kg, 0.15 mg/kg, 0.16 mg/kg, 0.18 mg/kg, 0.19 mg/kg, 0.20 mg/kg, 0.21 mg/kg, 0.22 mg/kg, 0.24 mg/kg, 0.25 mg/kg, 0.26 mg/kg, 0.28 mg/kg, 0.3 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 5 mg/kg, 10 mg/kg, 25 mg/kg, 50 mg/kg, 100v, 200 mg/kg, 500 mg/kg, or ranges including and/or spanning the aforementioned values. In some embodiments, the therapeutically effective dosage is from about 0.01 mg/kg to about 5 mg/kg. In some embodiments, the therapeutically effective dosage is from about 0.05 mg/kg to about 1 mg/kg. In some embodiments, the therapeutically effective dosage is from about 0.15 mg/kg to about 0.25 mg/kg.

[0199] 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.

[0200] The pharmaceutical compositions can be provided in a dosage form. In some embodiments, the dosage form is a solid. The solid dosage forms include tablets, capsules, granules and bulk powders. In some embodiments, the solid dosage form is a tablet.

[0201] 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 Preparing Dosage Forms

[0202] The pharmaceutical compositions may be formulated into an oral dosage form. In some embodiments, the oral dosage form may be a tablet. In some such embodiments, the tablet may be enterically coated.

[0203] In some embodiments, tablets may be prepared using a dry granulation method. In some embodiments, the method comprises the steps of: (i) combining the permeability enhancer and magnesium stearate to form first granules; (ii) combining microcrystalline cellulose, the compound of Formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c), and polyvinylpyrrolidinone to form second granules; (iii) combining the first granules and the second granules to form a mixture; (iv) adding magnesium stearate to the mixture to form third granules; and (v) pressing the third granules into tablets. In some embodiments, the permeability enhancer is SNAC. In some embodiments, the compound is Compound 4.

[0204] In some embodiments, tablets may be prepared using a wet granulation method. In some embodiments, the method comprises the steps of: (i) combining microcrystalline cellulose and compound disclosed therein in a first vessel; (ii) combining polyvinylpyrrolidinone and water in a second vessel;(iii) adding the contents of the first vessel to the second vessel to form wet granules; (iv) drying the wet granules to form dry granules; (v) combining the dry granules with magnesium stearate; and (vi) pressing the resulting mixture of step (v) into granules.

[0205] In some embodiments, tablets may be prepared by a spray-dried dispersion method. For example, in some embodiments, the compound disclosed herein may be combined with a polymer including but not limited to hydroxypropylmethylcellulose acetate succinate type M (HPMCAS-M); hydroxypropylmethylcellulose acetate succinate type L (HPMCAS-L); (polyvinylpyrrolidinone-vinyl acetate copolymer (PVP-VA64); Eudragit ® L100, or any combination thereof, in a solvent to form a solution for spray drying. The solutions are then dried with a heated nitrogen stream and collected using a cyclone. The spray dried matier is

then combined with microcrystalline cellulose, magnesium stearate, and additional fillers and disintegrants, and pressed into tablets.

[0206] In some embodiments, tablets may be prepared by a wet granulation method. In some embodiments, the compound disclosed herein is combined with microcrystalline cellulose and hydroxypropyl cellulose. In some embodiments, the mixture of materials is wet granulated using purified water as the granulation liquid and then dried. Thereafter, the dried granulate is milled and blended. A lubricant (e.g., magnesium stearate) may then be added to the blended mixture, and the resulting mixture compressed into tablets.

Methods of Treatment

[0207] 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. The pharmaceutical compositions further comprise one or more pharmaceutically acceptable carriers and one or more pharmaceutically acceptable diluents.

[0208] 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.

[0209] 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.

[0210] 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.

[0211] 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.

[0212] 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.

[0213] 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.

[0214] 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.

[0215] 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.

[0216] 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.

[0217] 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.

[0218] In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the activation of a glucose-dependent insulinotropic polypeptide (GIP) receptor. In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the activation of a glucagon-like peptide-1 (GLP-1) receptor. In some embodiments, the method of administering one or more of the pharmaceutical compositions disclosed herein results in the activation of the GIP receptor and the GLP-1 receptor.

[0219] 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.

[0220] 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

[0221] It will be apparent to the skilled artisan that methods for preparing precursors and functionality related to the compounds claimed herein are generally described in the literature. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The skilled artisan given the literature and this disclosure is well equipped to prepare any of the compounds.

[0222] It is recognized that the skilled artisan in the art of organic chemistry can readily carry out manipulations without further direction, that is, it is well within the scope and practice of the skilled artisan to carry out these manipulations. These include reduction of carbonyl compounds to their corresponding alcohols, oxidations, acylations, aromatic substitutions, both electrophilic and nucleophilic, etherifications, esterification and saponification and the like. These manipulations are discussed in standard texts such as March Advanced Organic Chemistry (Wiley), Carey and Sundberg, Advanced Organic Chemistry (incorporated herein by reference in their entirety) and the like. All the intermediate compounds of the present disclosure were used without further purification unless otherwise specified.

[0223] The skilled artisan will readily appreciate that certain reactions are best carried out when other functionality is masked or protected in the molecule, thus avoiding any undesirable side reactions and/or increasing the yield of the reaction. Often the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many of these manipulations can be found for example in T. Greene and P. Wuts Protecting Groups in Organic Synthesis, 4th Ed., John Wiley & Sons (2007), incorporated herein by reference in its entirety.

[0224] The following example schemes are provided for the guidance of the reader, and represent preferred methods for making the compounds exemplified herein. These methods are not limiting, and it will be apparent that other routes may be employed to prepare these compounds. Such methods specifically include solid phase based chemistries, including combinatorial chemistry. The skilled artisan is thoroughly equipped to prepare these compounds by those methods given the literature and this disclosure. The compound numberings used in the synthetic schemes depicted below are meant for those specific schemes only, and should not be construed as or confused with same numberings in other sections of the application.

[0225] 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.

[0226] 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

PVP-VA = polyvinylpyrrolidinone-vinyl acetate copolymer

R^2 = correlation coefficient of regression

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

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

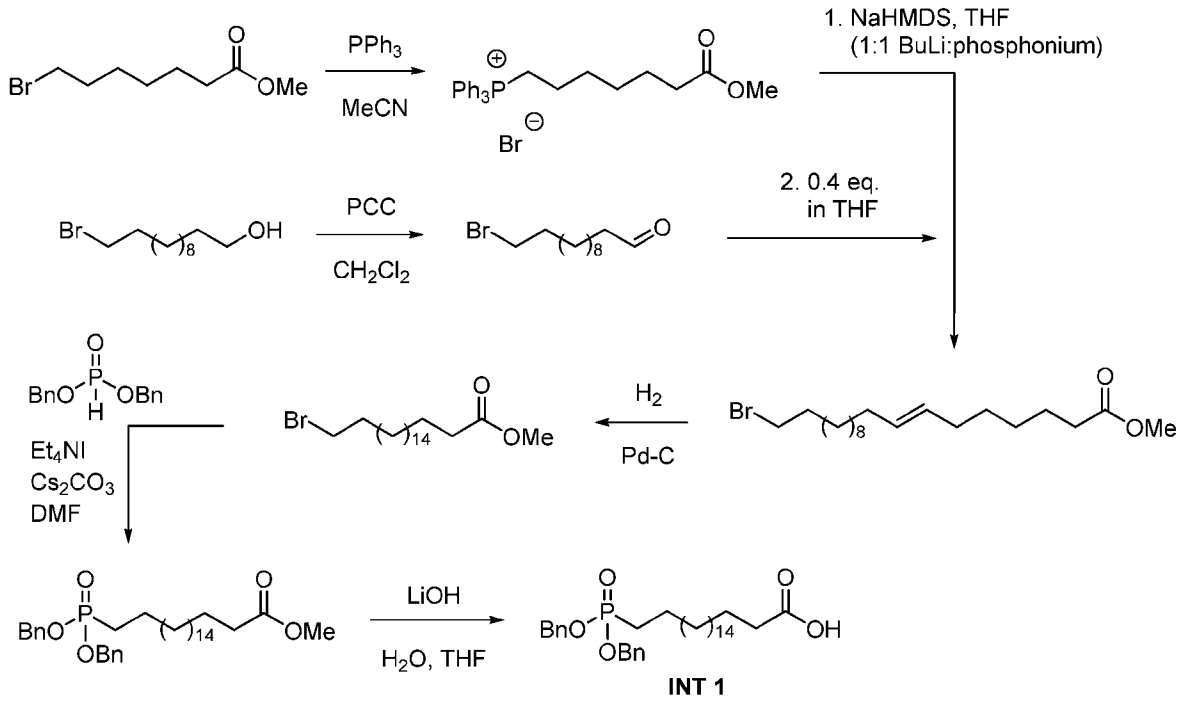
V_z/F = volume of distribution following extravascular administration

[0227] 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 compositons 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

Synthesis of Intermediate 1 (INT 1)

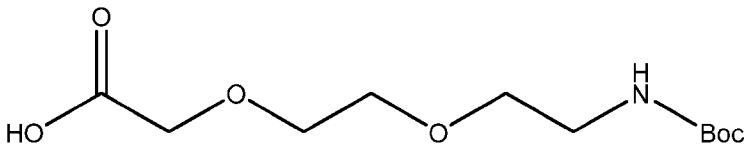
[0228] Methyl 7-bromoheptanoate was reacted with triphenylphosphine to form the corresponding phosphonium bromide salt. The thoroughly dried salt was treated with one equivalent of NaHMDS to make an ylide, which was reacted immediately in a Wittig reaction with the aldehyde from PCC oxidation of 12-bromo-1-dodecanol. The resulting alkene was purified by silica gel chromatography to give a pale yellow oil. The alkene was hydrogenated, and the bromoester could be trituated with methanol to afford an off-white solid. The bromide was displaced dibenzyl phosphite in weak base to afford a phosphonate ester, which was purified by chromatography. Hydrolysis of the methyl ester in LiOH provided desired **INT-1**, which could be precipitated from aqueous HCl at pH 2. The final product could be obtained in 10-100-gram batches with >99% purity by HPLC with satisfactory MS (*m/z* 559.3) and NMR data. The key ^{31}P signal for the phosphonate ester of **INT-1** appears at 33.3 ppm in DMSO-d_6.



EXAMPLE 2

Synthesis of Peptide Backbones

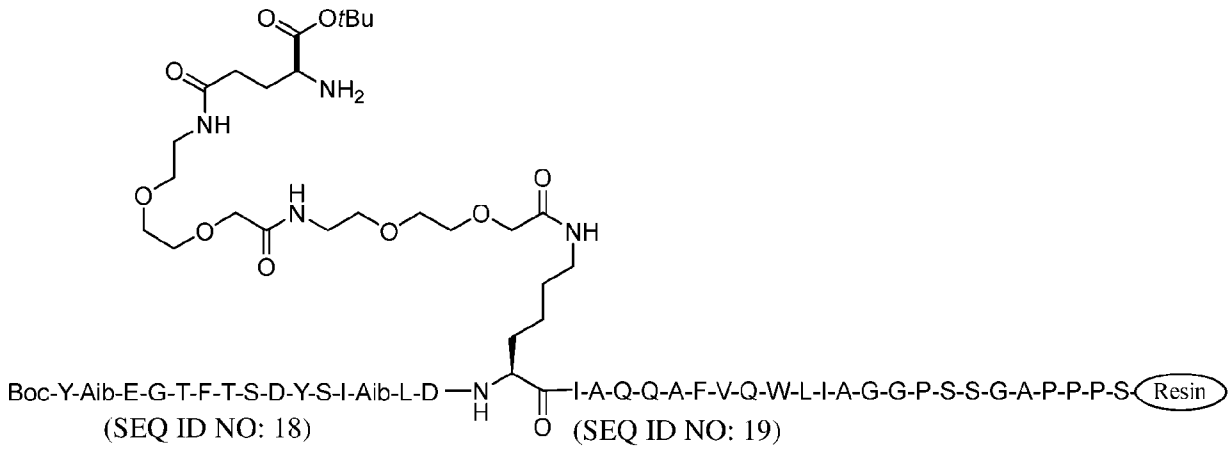
[0229] Each 39-amino acid peptide backbone was constructed using Fmoc solid phase peptide synthesis techniques with diimide, HATU, or HBTU activation for amide linkage synthesis on a Rink resin. Reagent selection varied based on the identity of the amino acids being connected. The lysine at lysine-16, lysine-19, or lysine-20 was protected with a Dde protecting group. Upon completion of the complete backbone, the aminoalkyl sidechain of lysine-16, lysine-19, or lysine-20 was extended with two PEG_2 amide linkers followed by an isoglutamic acid residue. Specifically, the Dde group on the lysine was cleaved. The deprotected amino group on the lysine was then coupled to a Boc-protected PEG_2 group having the following structure:



[0230] After removing the Boc group, a second PEG_2 was added. Finally, after removing the second PEG_2 Boc group, Fmoc-protected isoglutamate was coupled to the second PEG_2. The Fmoc group was then removed.

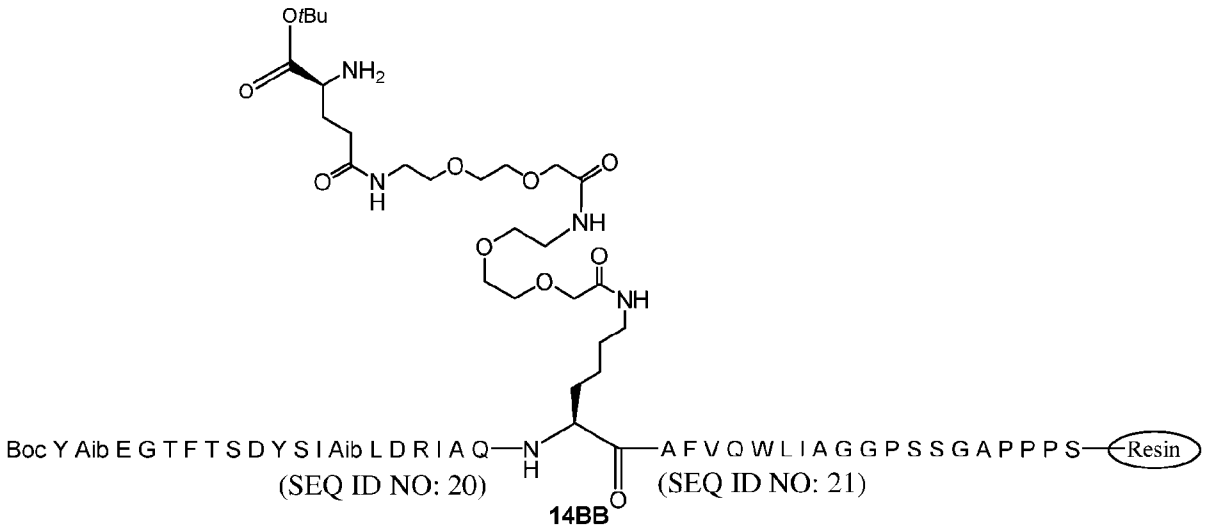
[0231] The entire backbone and sidechain on lysine-16, lysine-19, or lysine-20 was synthesized before coupling to **INT-1**. Accordingly, prior to **INT-1** coupling, the following intermediates were obtained.

[0232] The aminoalkyl sidechain of lysine-16 was extended as noted above to prepare peptide **13BB**.

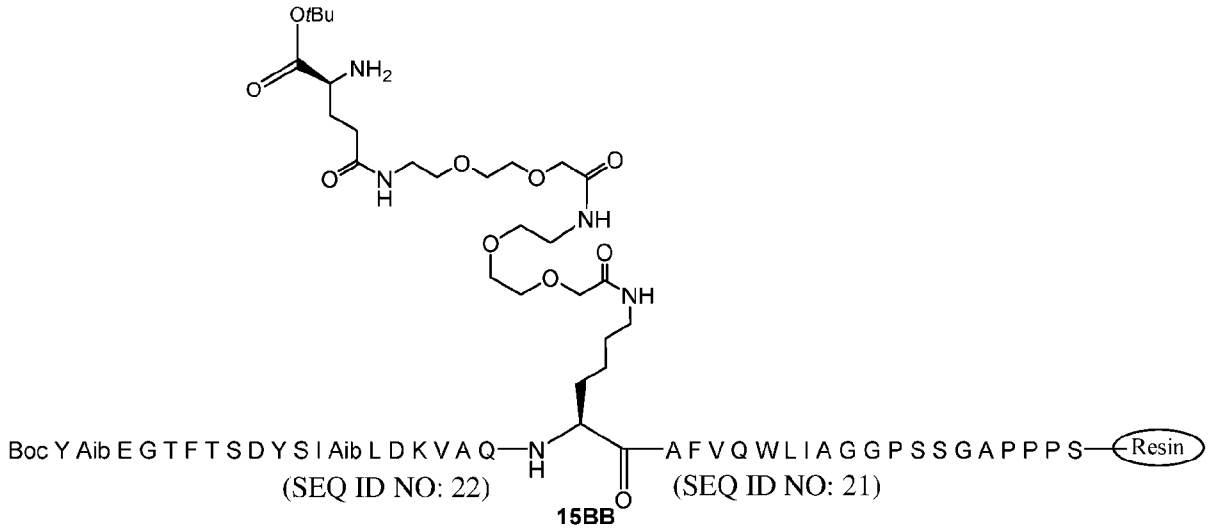


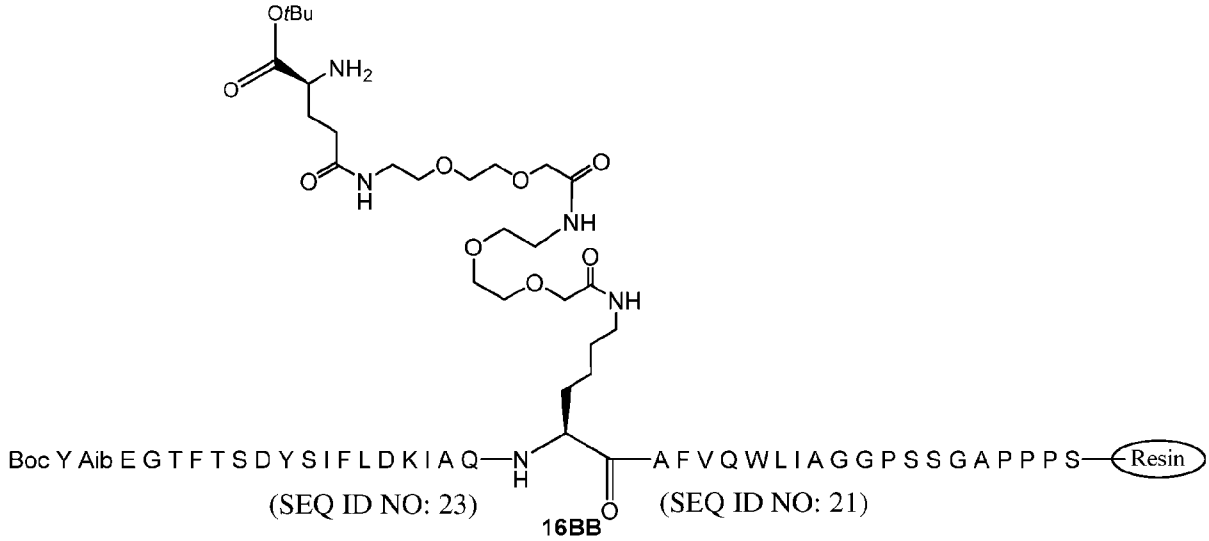
13BB

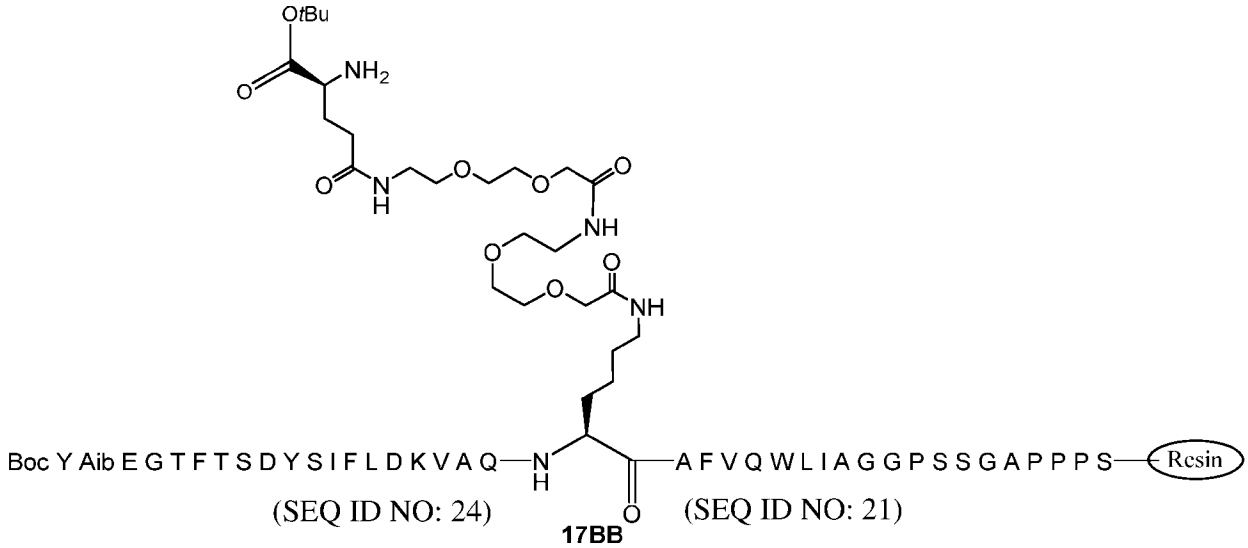
[0233] The aminoalkyl sidechain of side-chain of lysine-20 was extended to prepare peptides **14BB, 15BB, 16BB, 17BB, 18BB, 19BB, 21BB, and 22BB**.



14BB

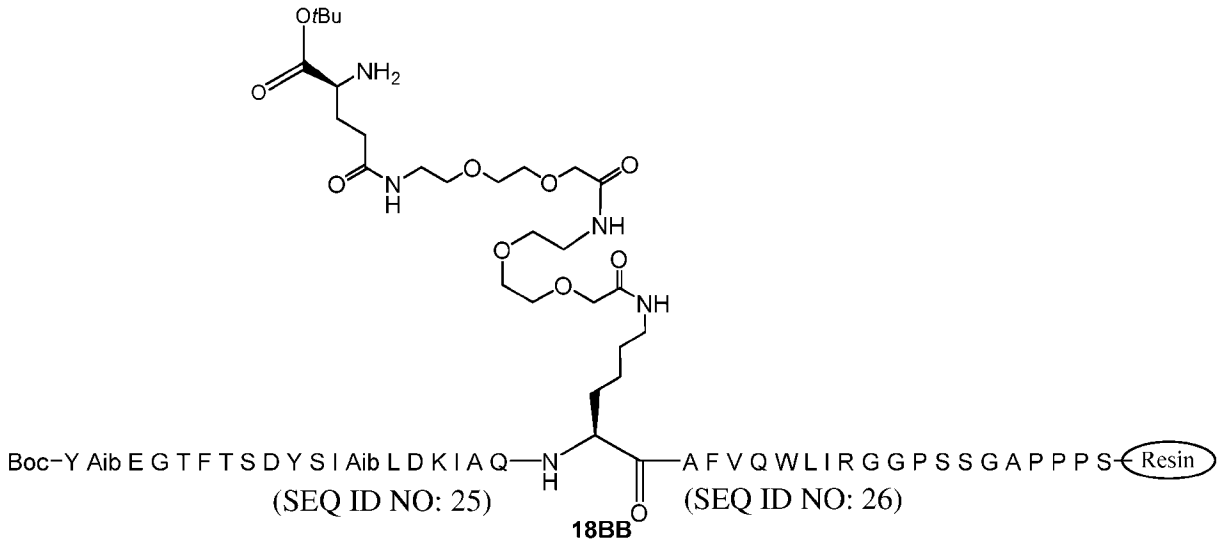

OtBu
NH2
O
N
H
O
O
O
NH
O
O
O
NH
Boc Y Aib E G T F T S D Y S I Aib L D K V A Q
N
H
A F V Q W L I A G G P S S G A P P P S
Resin
(SEQ ID NO: 22)
(SEQ ID NO: 21)
15BB


OtBu
NH2
O
N
H
O
O
O
NH
O
O
O
NH
Boc Y Aib E G T F T S D Y S I F L D K I A Q
N
H
A F V Q W L I A G G P S S G A P P P S
Resin
(SEQ ID NO: 23)
(SEQ ID NO: 21)
16BB



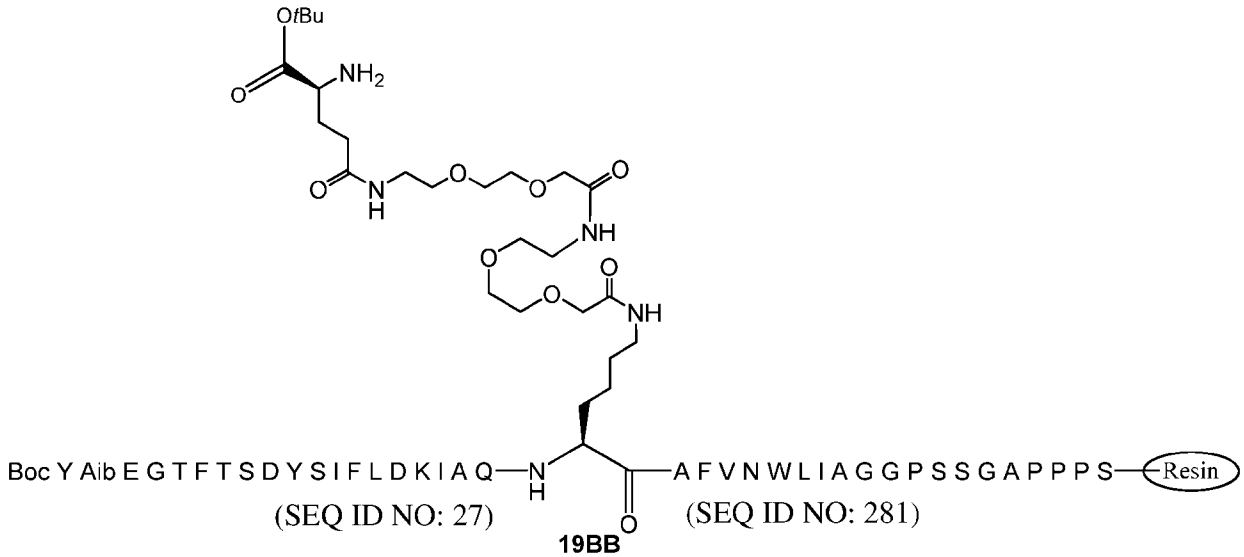
(SEQ ID NO: 24) (SEQ ID NO: 21)

17BB



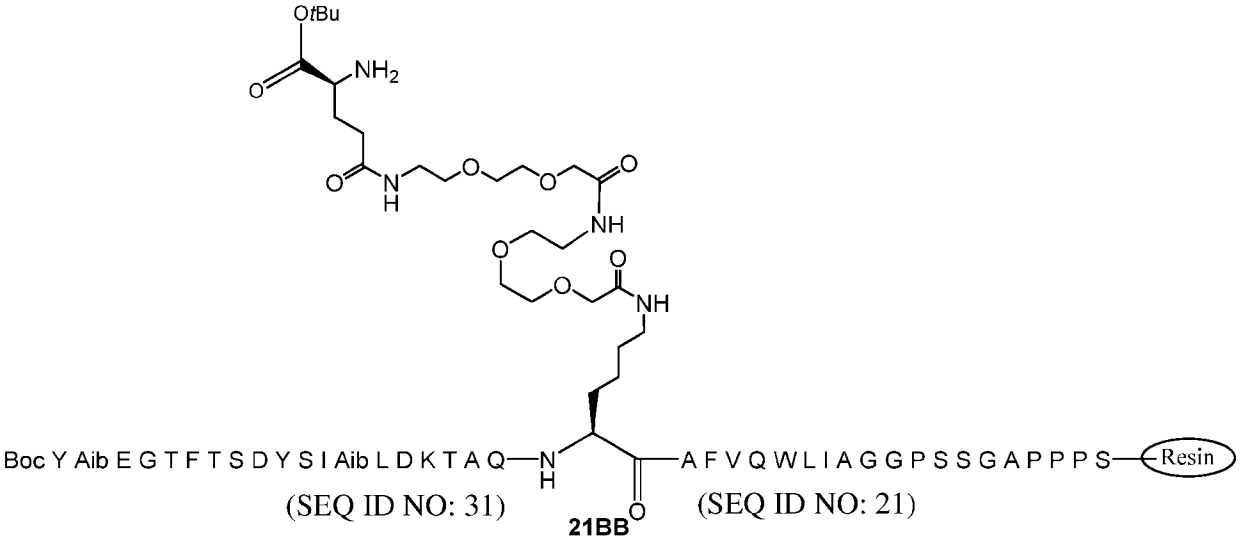
(SEQ ID NO: 25) (SEQ ID NO: 26)

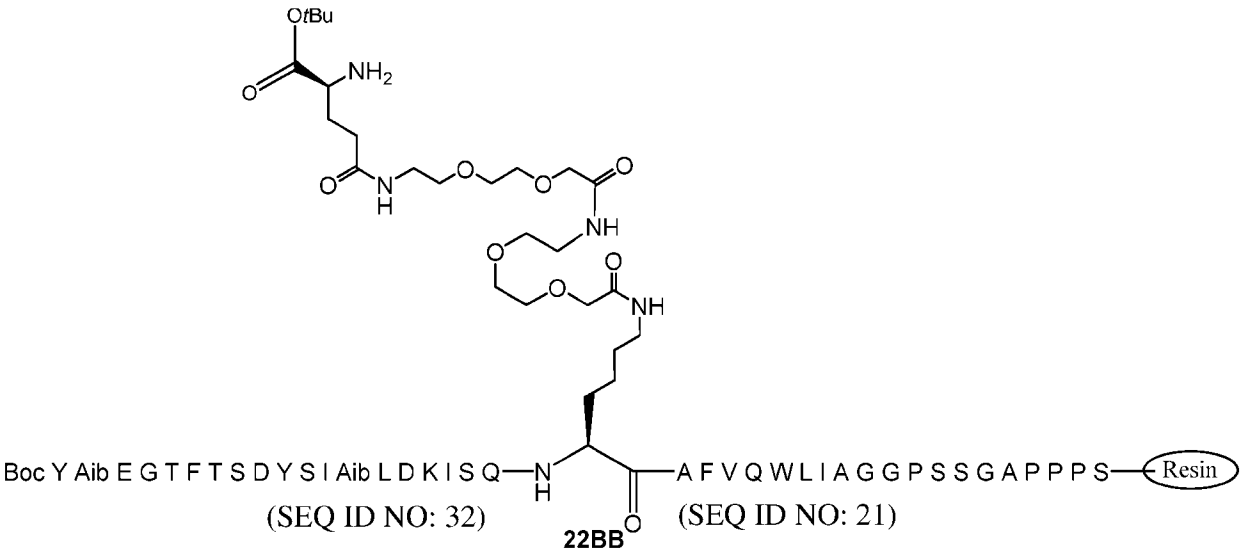
18BB



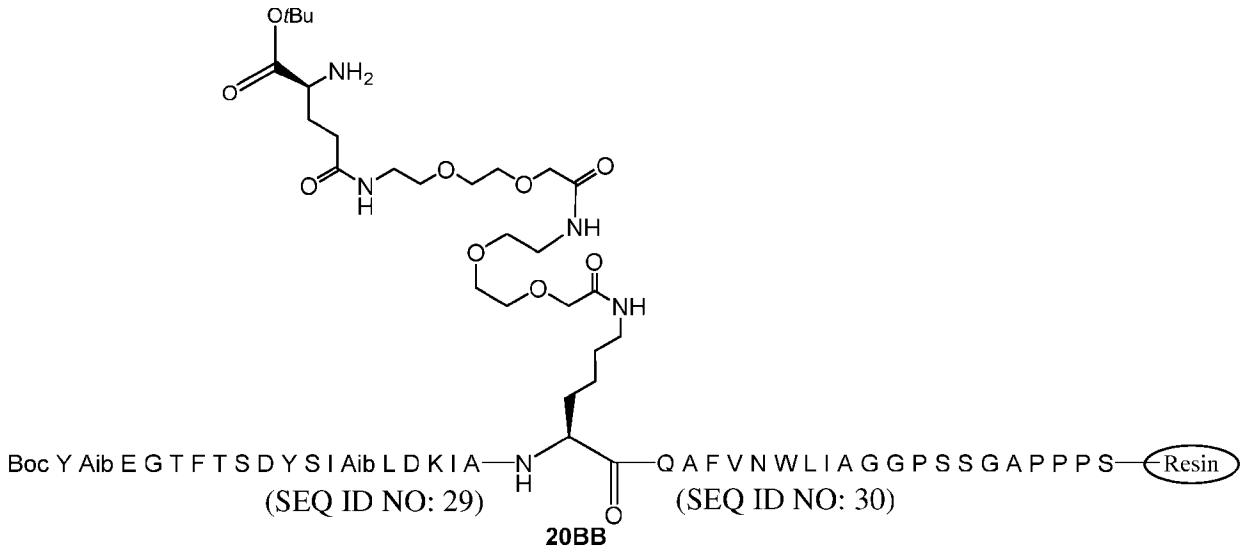
(SEQ ID NO: 27) (SEQ ID NO: 281)

19BB





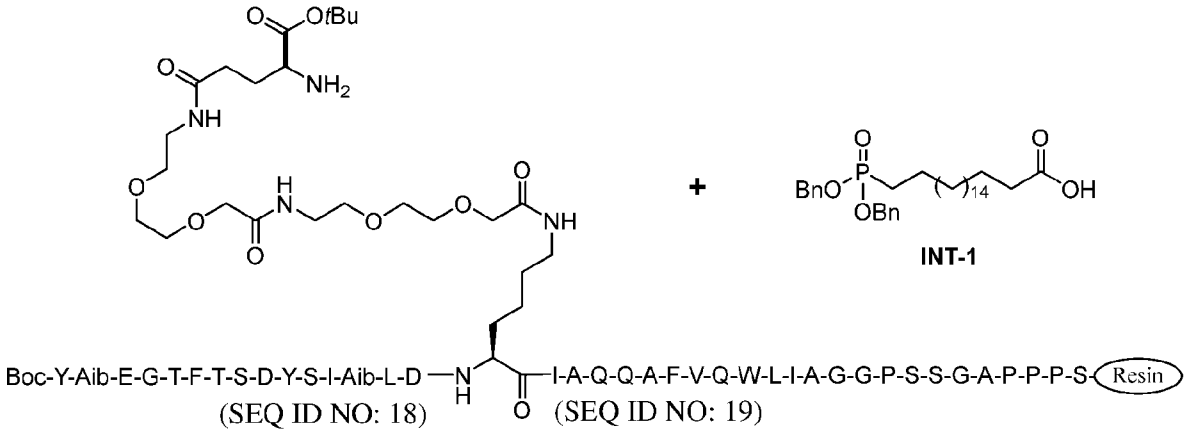
[0234] The side-chain of lysine-19 was extended to prepare peptide **20BB**.



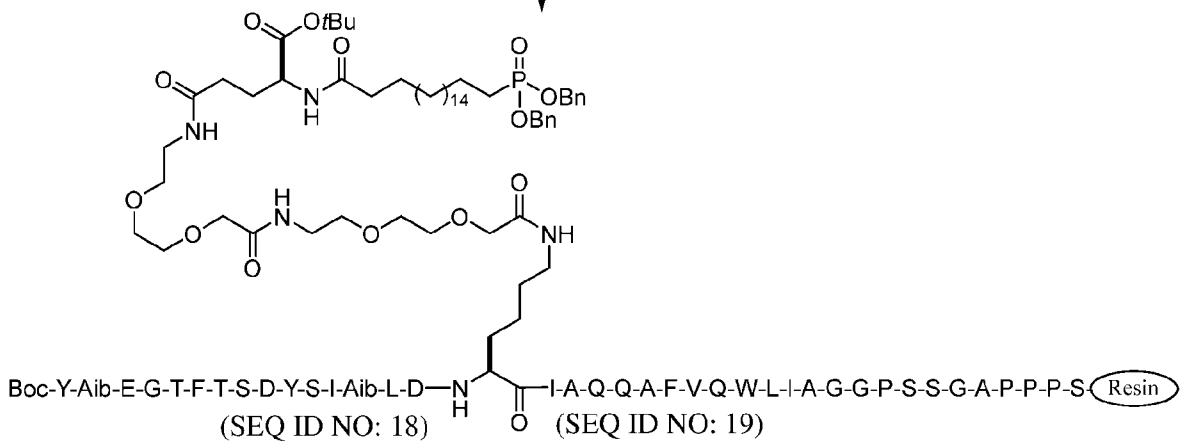
EXAMPLE 3

Synthesis of Compound 13

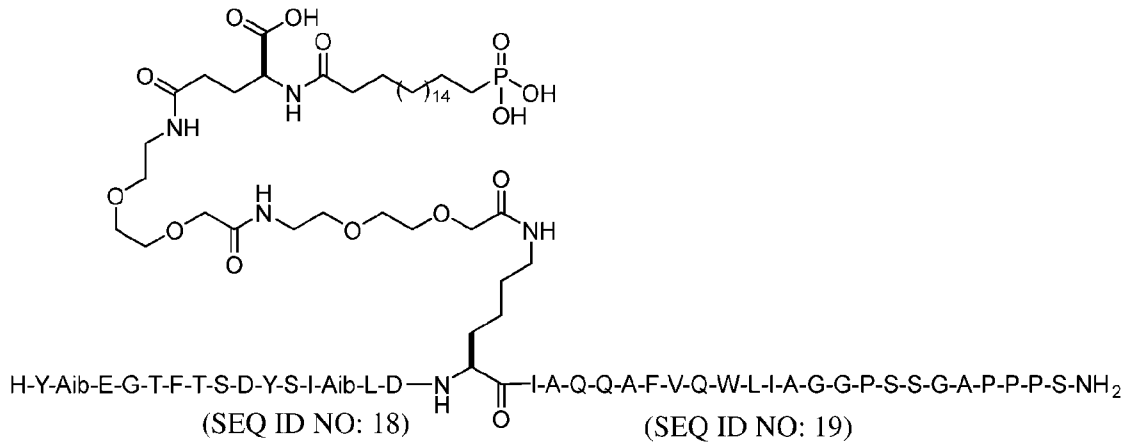
[0235] The peptide **13BB** was coupled to **INT-1** to give resin-bound, protected Compound **13**. Coupling to **INT-1** was achieved by using amide coupling conditions to couple **INT-1** to the NH_2 group of the isoglutamic acid off lysine-16 in peptide **13BB**. Cleavage of the resin, protecting groups on the peptide chain, and benzyl esters was conducted with TFA to provide Compound , which is then purified through reverse-phase HPLC. By RP-HPLC, the purity was 95.0%. The peptide content was 96.0% and gave satisfactory amino acid analysis results. LCMS analysis showed a molecular weight of 4849.4 g/mol.


OtBu
NH2
NH
O
H
N
NH
+
BnO
P
OBn
14
OH
INT-1
Boc-Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D
N
H
I-A-Q-Q-A-F-V-Q-W-L-I-A-G-G-P-S-S-G-A-P-P-P-S-
Resin
(SEQ ID NO: 18)
(SEQ ID NO: 19)

13BB


OtBu
OBn
OBn
14
NH
Boc-Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D
N
H
I-A-Q-Q-A-F-V-Q-W-L-I-A-G-G-P-S-S-G-A-P-P-P-S-
Resin
(SEQ ID NO: 18)
(SEQ ID NO: 19)

TFA

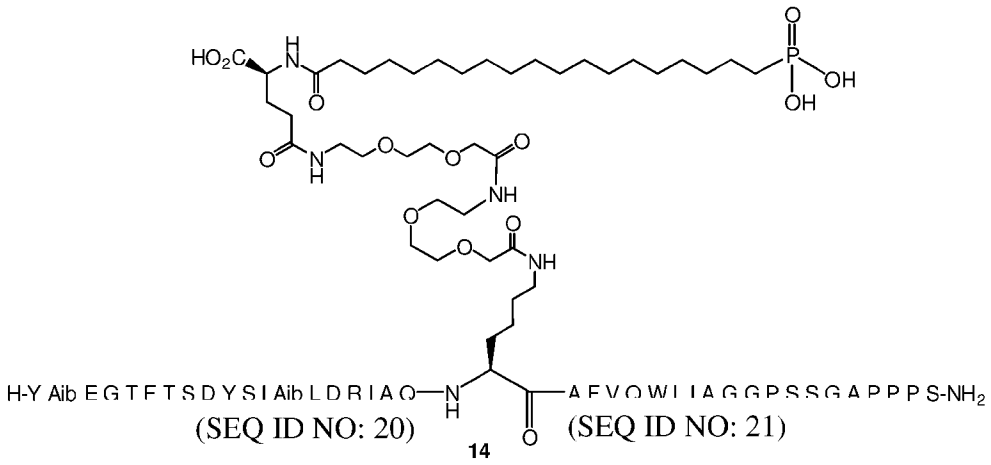

OH
OH
OH
14
NH
H-Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D
N
H
I-A-Q-Q-A-F-V-Q-W-L-I-A-G-G-P-S-S-G-A-P-P-P-S-NH2
(SEQ ID NO: 18)
(SEQ ID NO: 19)

13

EXAMPLE 4

Synthesis of Compound 14

[0236] Compound **14** was prepared from peptide **14BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



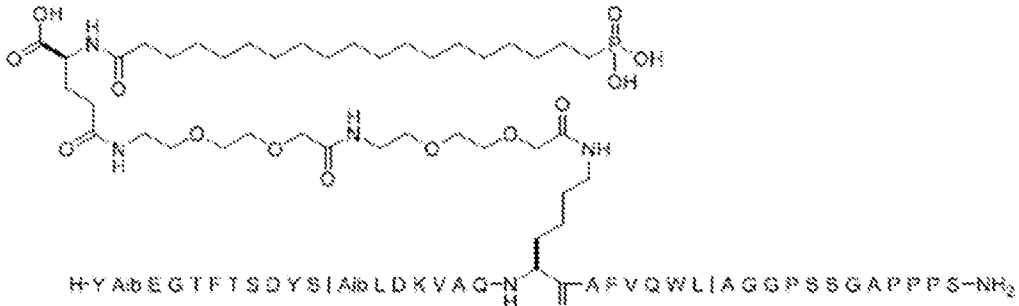
(SEQ ID NO: 20) (SEQ ID NO: 21)

14

EXAMPLE 5

Synthesis of Compound 15

[0237] Compound **15** was prepared from peptide **15BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



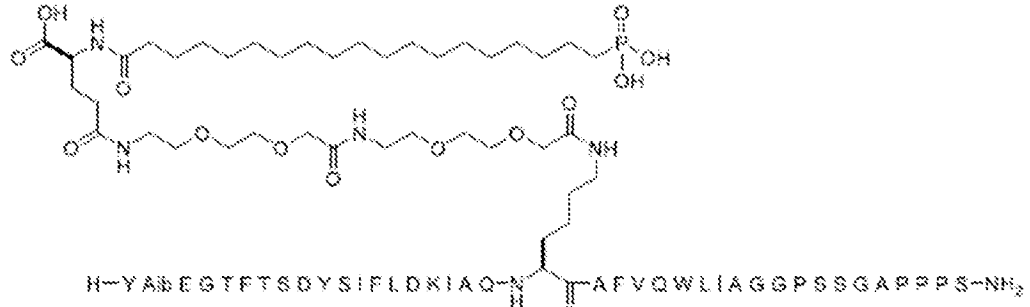
(SEQ ID NO: 22) (SEQ ID NO: 21)

15

EXAMPLE 6

Synthesis of Compound 16

[0238] Compound **16** was prepared from peptide **16BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



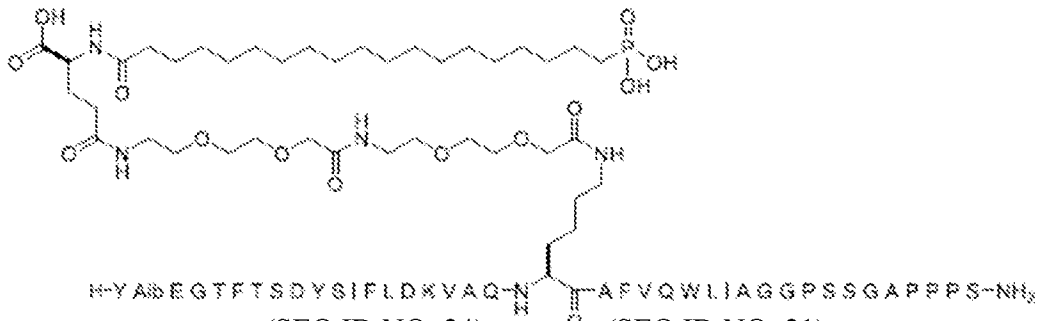
(SEQ ID NO: 23) (SEQ ID NO: 21)

16

EXAMPLE 7

Synthesis of Compound 17

[0239] Compound **17** was prepared from peptide **17BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



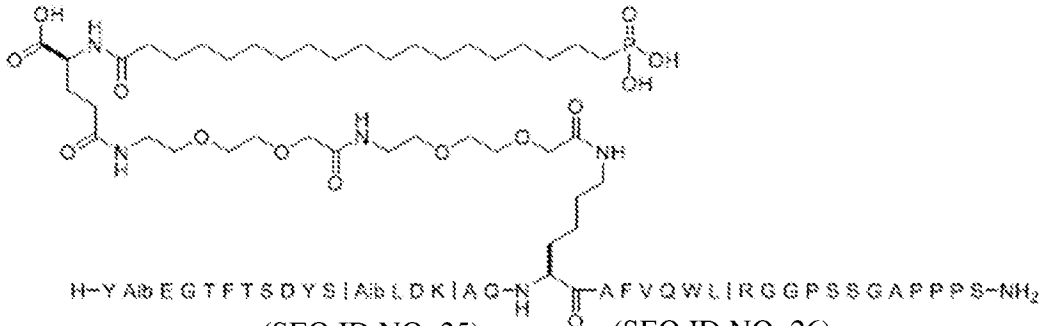
(SEQ ID NO: 24) (SEQ ID NO: 21)

17

EXAMPLE 8

Synthesis of Compound 18

[0240] Compound **18** was prepared from peptide **18BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



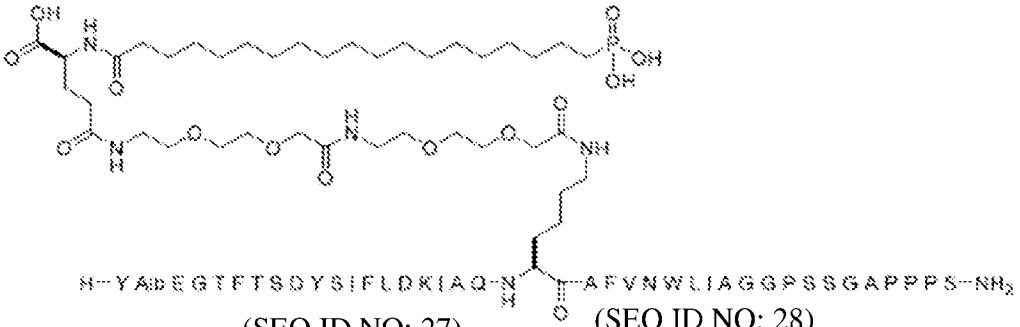
(SEQ ID NO: 25) (SEQ ID NO: 26)

18

EXAMPLE 9

Synthesis of Compound 19

[0241] Compound **19** was prepared from peptide **19BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



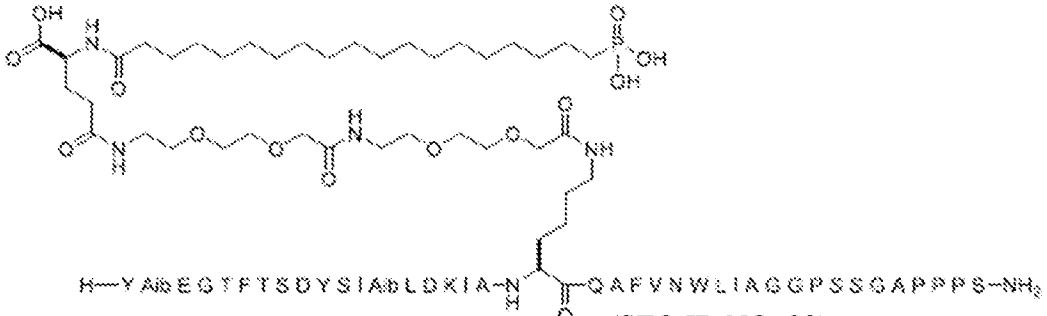
(SEQ ID NO: 27) (SEQ ID NO: 28)

19

EXAMPLE 10

Synthesis of Compound 20

[0242] Compound **20** was prepared from a peptide **20BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



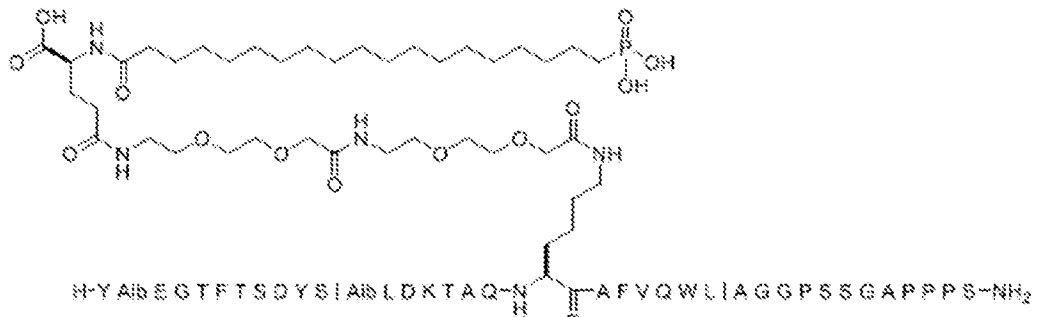
(SEQ ID NO: 29) (SEQ ID NO: 30)

20

EXAMPLE 11

Synthesis of Compound 21

[0243] Compound **21** was prepared from peptide **21BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



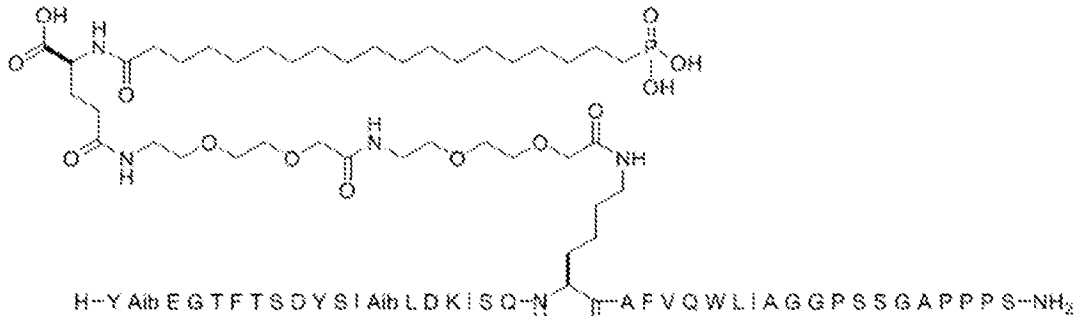
(SEQ ID NO: 31) (SEQ ID NO: 21)

21

EXAMPLE 12

Synthesis of Compound 22

[0244] Compound **22** was prepared from peptide **22BB** and **INT-1** in a manner analogous to the preparation of Compound **13**.



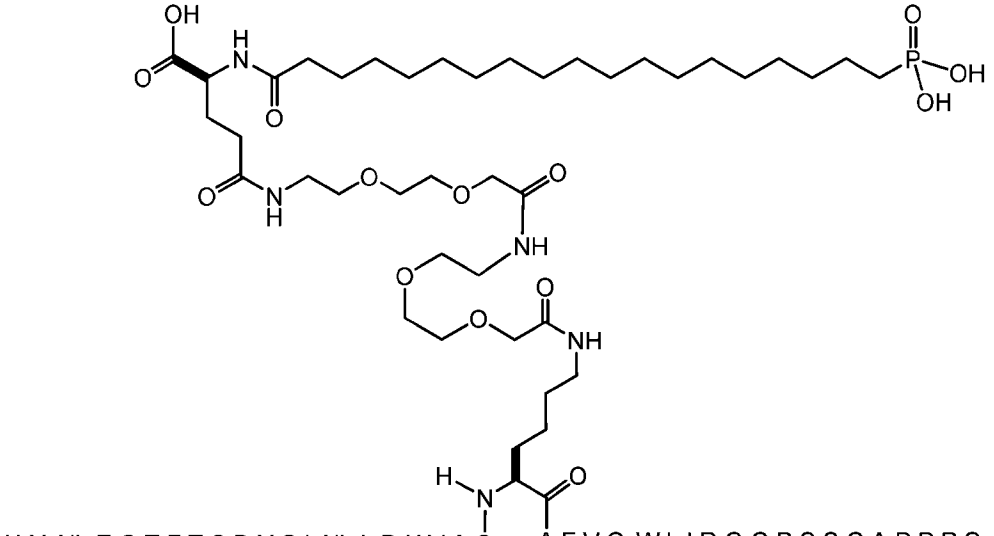
(SEQ ID NO: 32) (SEQ ID NO: 21)

22

EXAMPLE 13

Synthesis of Compound 23

[0245] Compound **23** was prepared from a peptide backbone analogous to that described herein and **INT-1** in a manner analogous to the preparation of Compound **13**.

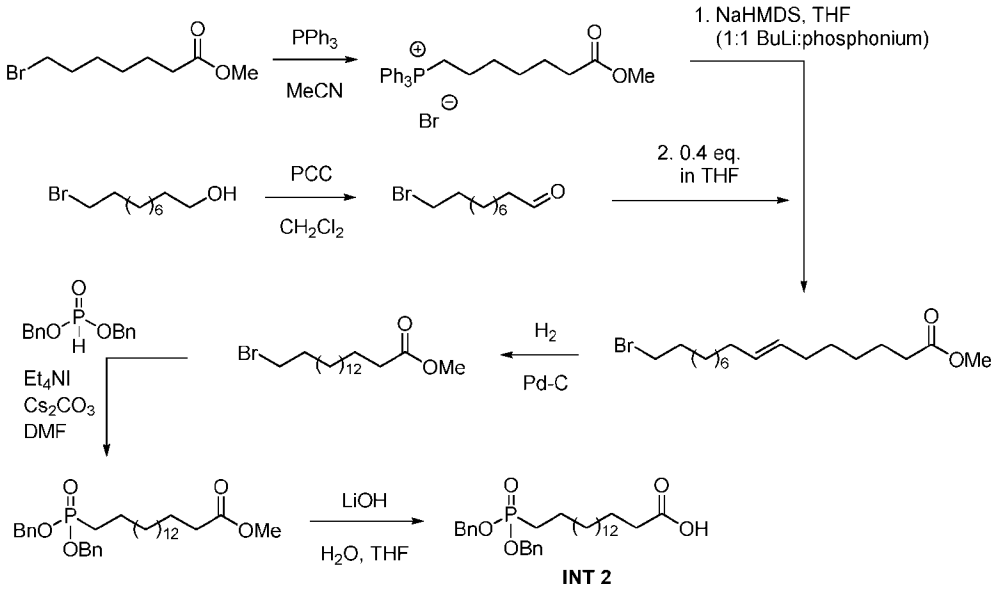


23

EXAMPLE 14

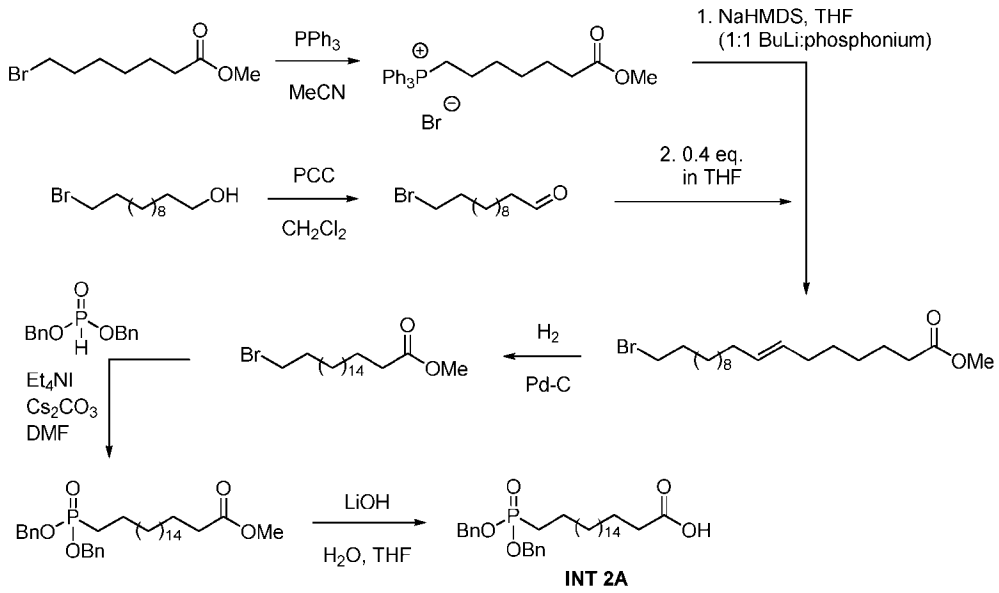
Synthesis of Intermediate 2 (INT 2)

[0246] Methyl 7-bromoheptanoate is treated with triphenylphosphine to form the corresponding phosphonium salt. The salt is treated with one equivalent of NaHMDS to make an ylide, which is reacted immediately in a Wittig reaction with the aldehyde from PCC oxidation of 10-bromo-1-decanol. The resulting bromo alkene is hydrogenated, and treated with dibenzyl phosphite in weak base to form a phosphonate ester. Hydrolysis of the methyl carboxylate provides desired **INT 2** having a terminal carboxylic acid and a dibenzyl phosphonate.



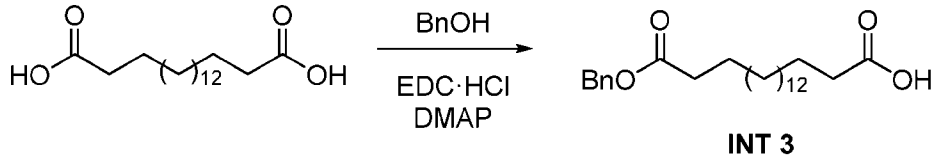
Synthesis of Intermediate 2A (INT 2A)

[0247] Methyl 7-bromoheptanoate is treated with triphenylphosphine to form the corresponding phosphonium salt. The salt is treated with one equivalent of NaHMDS to make an ylide, which is reacted immediately in a Wittig reaction with the aldehyde from PCC oxidation of 12-bromo-1-dodecanol. The resulting bromo alkene is hydrogenated, and treated with dibenzyl phosphite in weak base to form a phosphonate ester. Hydrolysis of the methyl carboxylate provides desired **INT 2A** having a terminal carboxylic acid and a dibenzyl phosphonate.



Synthesis of Intermediate 3 (INT 3)

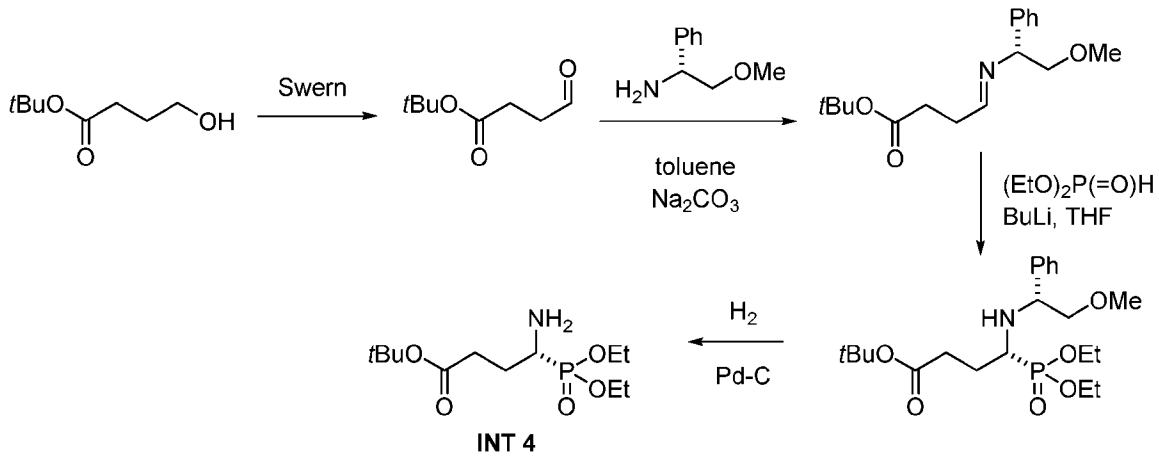
[0248] Octadecanedioic acid is coupled to benzyl alcohol with EDC·HCl and DMAP in THF to give **INT 3** as the monobenzyl ester.



INT 3

Synthesis of Intermediate 4 (INT 4)

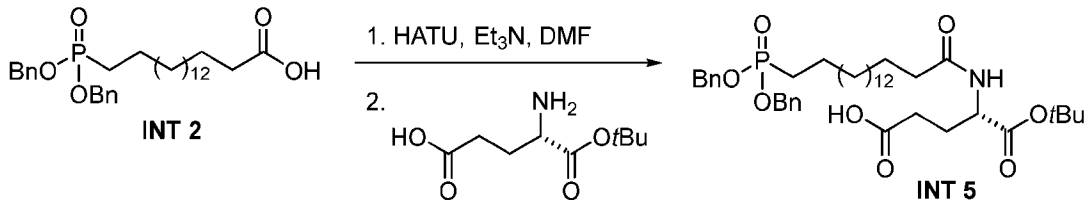
[0249] t-Butyl 4-hydroxybutanoate undergoes a Swern oxidation to give an aldehyde. The aldehyde is condensed with (R)-1-amino-2-methoxy-1-phenylethane to form an imine. Addition of the lithium salt of diethyl phosphite in THF generates an α-aminophosphonate, which undergoes hydrogenolysis to cleave the N-alkyl group and provide **INT 4** with a free primary amine, a t-butyl ester, and a diethyl phosphonate ester. The optical purity of **INT 4** was confirmed to be at least 96% by ^{1}H-NMR through Mosher's amide analysis.



INT 4

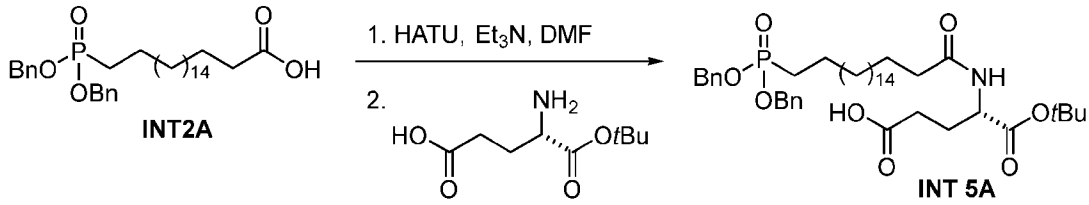
Synthesis of Intermediate 5 (INT 5)

[0250] **INT 2** is coupled with the 1-t-butyl ester of D-glutamic acid in the presence of HATU and triethylamine in DMF to provide **INT 5**.



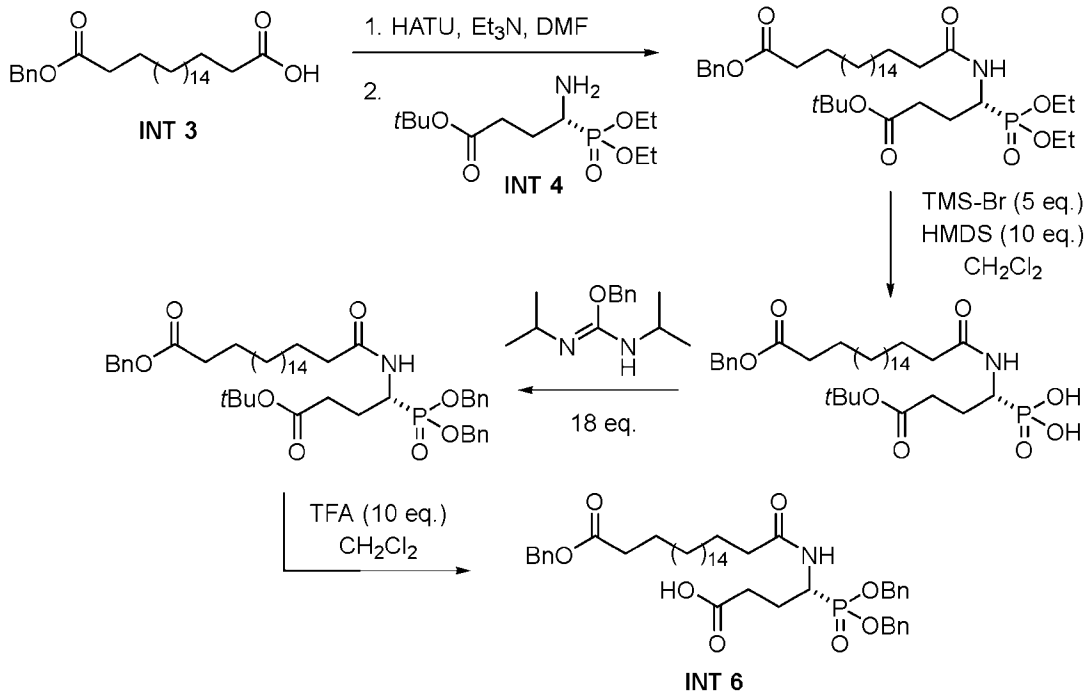
Synthesis of Intermediate 5A (INT 5A)

[0251] **INT 2A** is coupled with the 1-t-butyl ester of D-glutamic acid in the presence of HATU and triethylamine in DMF to provide **INT 5A**.



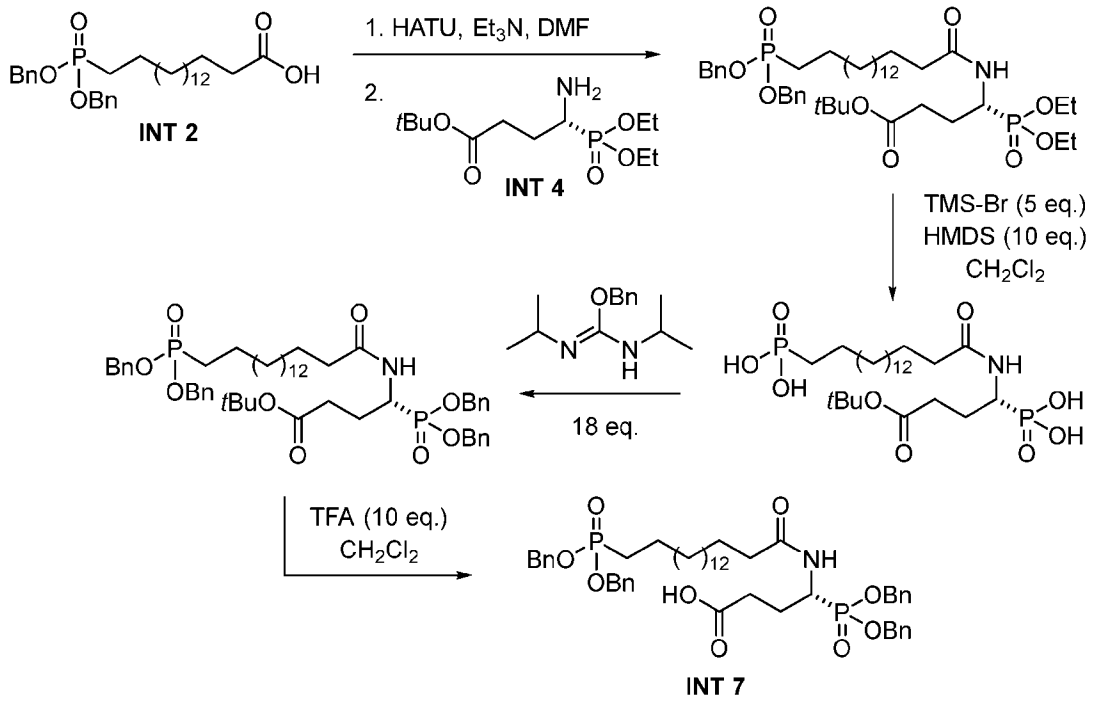
Synthesis of Intermediate 5 (INT 5)

[0252] **INT 3** is coupled with **INT 4** in the presence of HATU and triethylamine in DMF to prepare a new amide linkage. Cleavage of the ethyl phosphonate esters with TMS-Br gives the free phosphonic acid. Re-esterification with a large excess of the benzyl ester of N,N'-diisopropylcarbamimidic acid provides the corresponding dibenzyl phosphonate. The t-butyl ester is cleaved with TFA to provide **INT 6**.



Synthesis of Intermediate 7 (INT 7)

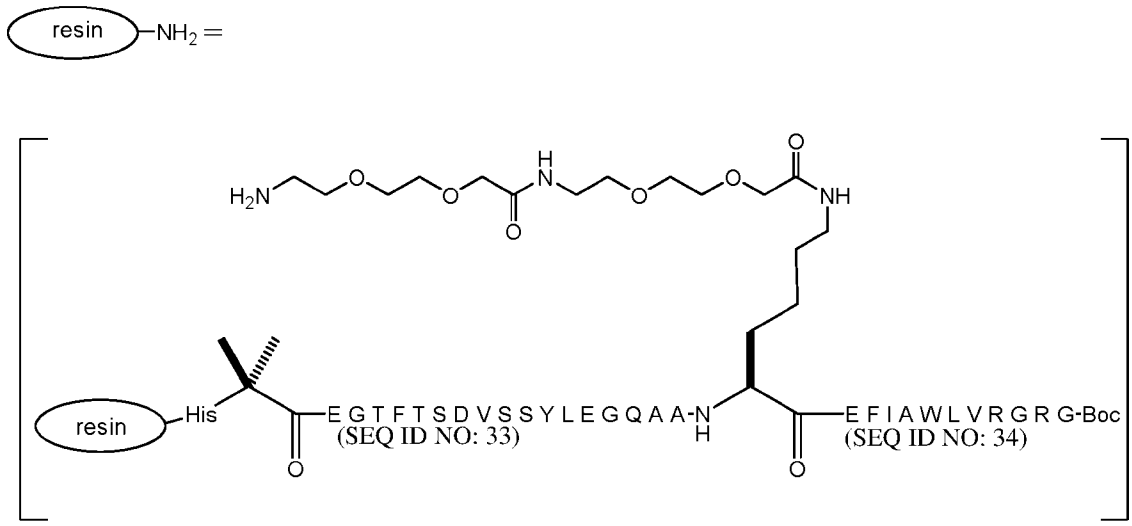
[0253] **INT 2** is coupled with **INT 4** in the presence of HATU and triethylamine in DMF to provide a new amide linkage. Cleavage of the benzyl and ethyl phosphonate esters with TMS-Br gives both free phosphonic acids. Re-esterification with a large excess of the benzyl ester of N,N'-diisopropylcarbamimidic acid provides the corresponding tetrabenzyl diphosphonate ester. The t-butyl ester is cleaved with TFA to give **INT 7**.



EXAMPLE 15

Synthesis of Common Peptide Backbone

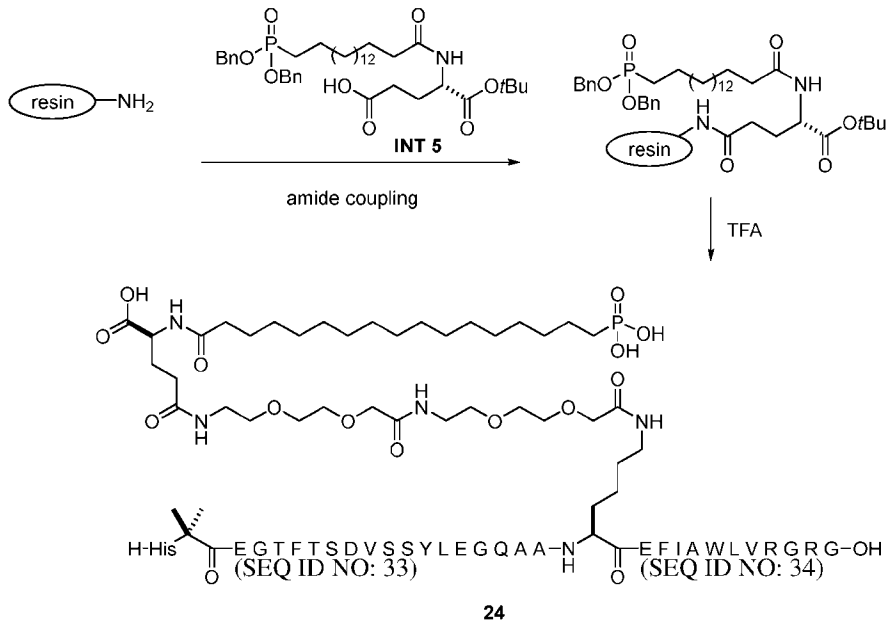
[0254] The 31-amino acid peptide backbone is constructed using solid-phase peptide synthesis techniques with diimide, HATU, or HBTU activation for amide linkage synthesis on a Rink resin. Reagent selection varies based on the identity of the amino acids being connected. The R-group of lysine-20 was extended with two PEG_2 amide linkers. The entire backbone is synthesized on the resin before coupling **INT 5, INT 5A, INT 6,** or **INT 7** to the amino terminus of the lysine-bound linker.



EXAMPLE 16

Synthesis of Compound 24

[0255] The peptide backbone is coupled to **INT 5** to give resin-bound, protected Compound **24**. Cleavage of the resin, protecting groups on the peptide chain, and benzyl esters of **INT 5** with TFA provides Compound **24**, which is purified through HPLC.

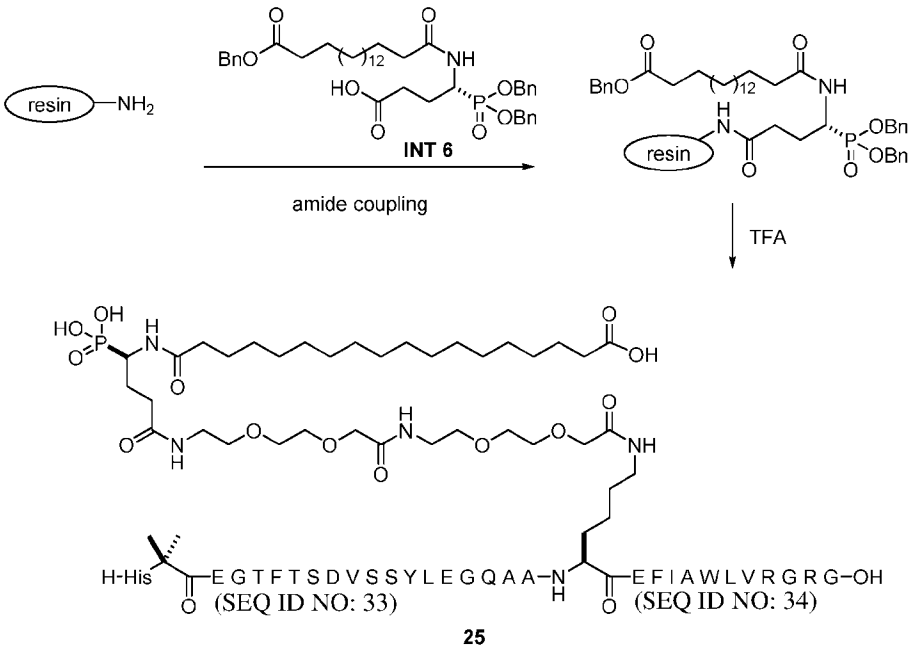


24

EXAMPLE 17

Synthesis of Compound 25

[0256] The peptide backbone is coupled to **INT 6** to give resin-bound, protected Compound **24**. Cleavage of the resin, protecting groups on the peptide chain, and benzyl esters of **INT 6** with TFA provides Compound **24**, which is purified through HPLC.

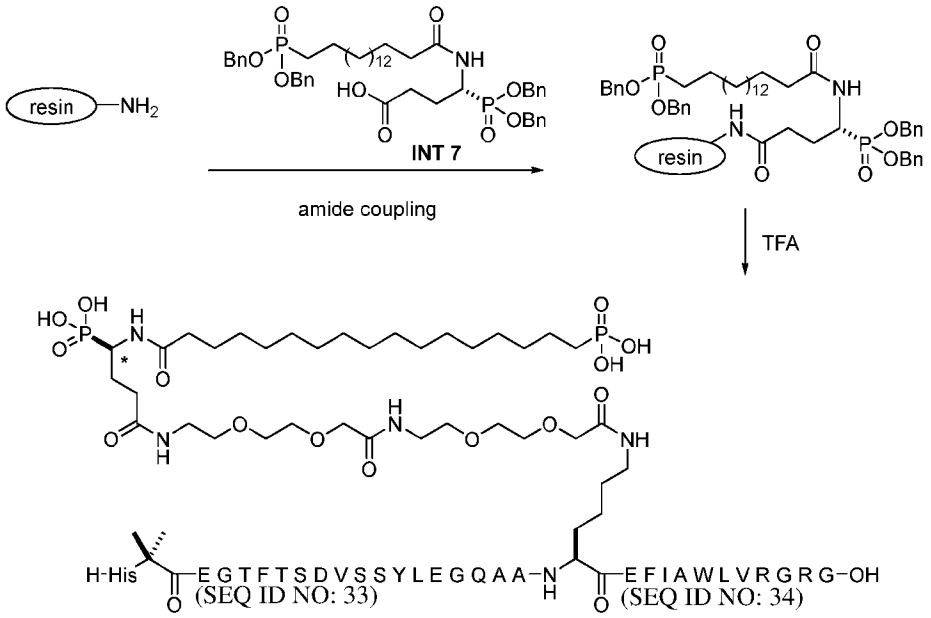


25

EXAMPLE 18

Synthesis of Compound 26

[0257] The peptide backbone is coupled to **INT 7** to give resin-bound, protected Compound **3**. Cleavage of the resin, protecting groups on the peptide chain, and benzyl esters of **INT 7** with TFA provides Compound **26**, which is purified through HPLC.

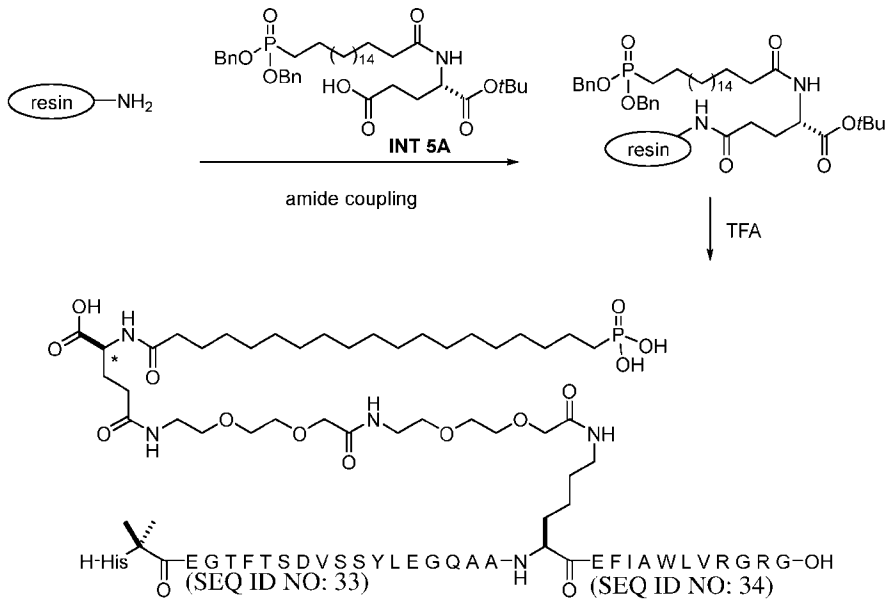


26

EXAMPLE 19

Synthesis of Compound 27

[0258] The peptide backbone is coupled to **INT 5A** to give resin-bound, protected Compound **27**. Cleavage of the resin, protecting groups on the peptide chain, and benzyl esters of **INT 5A** with TFA provides Compound **27**, which is purified through HPLC.



27

EXAMPLE 20

Pharmacokinetic Study in Dogs

[0259] The pharmacokinetic properties of selected compounds disclosed herein were assessed after administration of an oral dosage form (tablet) to male beagle dogs. Animals were acclimated to the study room for a minimum of 3 days prior to initial of dosing. The dogs (N=3) received a single oral tablet dose containing the compound. Plasma samples were collected prior to dosing the dogs and at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours after dosing. The composition provided to the dogs is shown in Table 1.

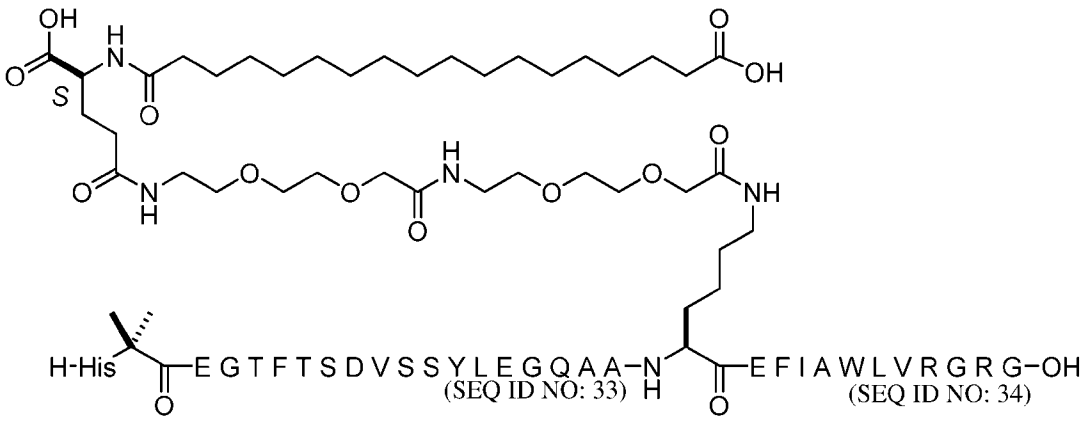
Table 1 – Tablet Formulation for Dog Studies

Component	**Mass (mg)**	**Percent of Total**
Compound	20	3.3
Salcaprozate sodium (SNAC)	300	50
Microcrystalline cellulose	258	43.0
Polyvinylpyrrolidinone K90	10	1.7
Magnesium stearate	12	2.0
Total	600	100%

[0260] Pharmacokinetic analyses were performed on plasma concentration versus time data using Phoenix WinNonlin (v 8.3) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. The C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. As the data permitted, the terminal rate constant (lambda z, λz) was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time where the data points were randomly distributed around a straight line, at least three data points post the C_{max} were used in the regression, the correlation coefficient (R^2) of regression was >0.90, and the period over which the regression is88etermineed (span) was at least 2.0-fold greater than the calculated half-life itself.

[0261] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. The AUC_{INF} value was calculated as: $AUC_{last} + (C_{last} / \lambda z)$. The Cl/F value was calculated as Dose / AUC_{INF} and the Vz/F value was calculated as Dose / ($AUC_{INF} * \lambda z$). If the percent of extrapolated area for AUC_{INF} was >20%,

the AUC_{INF}, Vz/F, and CL/F values were not reported. Terminal half-life ($t_{1/2}$) was calculated as: ln(2) / λz. If the span to define the lambda z line was less than 2-fold of the $t_{1/2}$, the $t_{1/2}$ value was flagged with an asterisk (*) and removed from summary statistics. Administration of Compound 4, Compound Z, and Compound 24) to the beagle dogs provided the plasma concentration versus time profile shown in FIG. 1. The data shows that the mean plasma concentration of Compound 4 and Compound 24 was higher than that of an analogous formulation of peptide Compound Z having the structure:



(**Z**)

with 300 mg SNAC, and that both Compound 4 and Compound 24 was detected in plasma at 144 hours after dosing.

EXAMPLE 21

Pharmacokinetic Assessment After Oral Administration

[0262] The pharmacokinetic properties of various peptide compounds disclosed herein were assessed after administration of an oral dosage form (tablet) to male beagle dogs. The test compounds were formulated with varying quantities of salcaprozate sodium (SNAC). Animals were acclimated to the study room for a minimum of 3 days prior to initial of dosing. The dogs (N=6) received oral tablet doses containing a test compound. Plasma samples were collected on Day 1 prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. On Day 3, samples were collected at pre-dose only. On Day 5, samples were collected prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours after dosing. The formulations provided to the dogs and the dosing groups is shown in Table 2.

Table 2 – Dosing Groups for Dog Studies

Dose Group	Number of Animals	Compound/ SNAC (mg)	Dosage of Compound (mg/tablet)
1	6	Compound Z / 300 mg	20
2	6	Compound 24 /200 mg	20
3	6	Compound 24 /300 mg	20
4	6	Compound 24 / 450 mg	20
5	6	Compound 27 /200 mg	20
6	6	Compound 27 /300 mg	20
7	6	Compound 27 / 450 mg	20
8	6	Compound 4 / 200 mg	20
9	6	Compound 4 / 300 mg	20
10	6	Compound 4 /450 mg	20

[0263] Pharmacokinetic analyses were performed on plasma concentration versus time data using Phoenix WinNonlin (v 8.3) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. The C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. As the data permitted, the terminal rate constant (lambda z, λz) was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time where the data points were randomly distributed around a straight line, at least three data points post the C_{max} were used in the regression, the correlation coefficient (R^2) of regression was >0.90, and the period over which the regression is determined (span) was at least 2.0-fold greater than the calculated half-life itself.

[0264] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. The AUC_{INF} value was calculated as: $AUC_{last} + (C_{last} / \lambda z)$. The Cl/F value was calculated as Dose / AUC_{INF} and the Vz/F value was calculated as Dose / ($AUC_{INF} * \lambda z$). If the percent of extrapolated area for AUC_{INF} was >20%, the AUC_{INF}, Vz/F, and CL/F values were not reported. Terminal half-life ($t_{1/2}$) was calculated as: $\ln(2) / \lambda z$. If the span to define the lambda z line was less than 2-fold of the $t_{1/2}$, the $t_{1/2}$ value was flagged with an asterisk (*) and removed from summary statistics.

[0265] Table 3 below discloses the mean pharmacokinetic data gained from each experiment with each of Groups 1-10. Various ratios of SNAC to peptide compound were

tested. With respect to Compound 24 (Groups 2-4), Compound 27 (Groups 5-7), and Compound 4 (Groups 8-10), exposure was increased with increasing SNAC levels over the range tested from 200 mg to 450 mg.

Table 3 – Pharmacokinetic Data for Dosing Study of Peptide Compounds in Dogs

Group	**Day**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (h*ng/mL)**	**AUC_{INF} (h*ng/mL)**	**$t_{1/2}$ (h)**
1	1	3.13	8.25	222	222	--
	5	0.917	29.5	779	1850	77.0
2	1	0.792	40.2	1080	1080	--
	5	29.1	83.9	2780	7110	66.6
3	1	2.00	315	8350	8350	--
	5	1.63	187	5550	12400	73.6
4	1	1.42	736	20600	20600	--
	5	1.13	408	11800	21700	56.8
5	1	1.46	22.4	775	775	--
	5	1.38	34.3	1230	3980	97.6
6	1	196	66.4	1880	1880	--
	5	2.17	270	8190	17600	69.3
7	1	1.83	804	21900	21900	--
	5	1.13	799	24300	51200	59.6
8	1	1.71	23.0	815	815	--
	5	1.21	41.7	1340	4420	88.6
9	1	1.13	50.1	1550	1550	--
	5	1.17	99.2	3080	8410	92.2
10	1	1.96	57.3	1800	1800	--
	5	0.667	245	6630	15200	86.7

EXAMPLE 22

Pharmacokinetic Assessment After Oral Administration

[0266] The pharmacokinetic properties of various peptide compounds disclosed herein were assessed after administration of an oral dosage form (tablet) to male beagle dogs. The test compounds were formulated with 450 mg of salcaprozate sodium (SNAC). Animals were acclimated to the study room for a minimum of 3 days prior to initial of dosing. The dogs (N=6) received single oral tablet doses containing a test compound. Plasma samples were collected on Day 1 prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. On Day 3, samples were collected at pre-dose only. On Day 5, samples were collected prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours after dosing. The formulations provided to the dogs and the dosing groups is shown in Table 4.

Table 4 – Dosing Groups for Dog Studies

Dose Group	Number of Animals	Compound/ SNAC (mg)	Dosage of Compound (mg/tablet)
1	6	Compound 4 / 450 mg	20
2	6	Compound 15 / 450 mg	20
3	6	Compound 18 / 450 mg	20
4	6	Compound 23 / 450 mg	20

[0267] Pharmacokinetic analyses were performed on plasma concentration versus time data using Phoenix WinNonlin (v 8.3) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. The C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. As the data permitted, the terminal rate constant (lambda z, λz) was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time where the data points were randomly distributed around a straight line, at least three data points post the C_{max} were used in the regression, the correlation coefficient (R^2) of regression was >0.90, and the period over which the regression is determined (span) was at least 2.0-fold greater than the calculated half-life itself.

[0268] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. The AUC_{INF} value was calculated as: $AUC_{last} + (C_{last} / \lambda z)$. The Cl/F value was calculated as Dose / AUC_{INF} and the Vz/F value was calculated as Dose / (AUC_{INF} * λz). If the percent of extrapolated area for AUC_{INF} was >20%, the AUC_{INF}, Vz/F, and CL/F values were not reported. Terminal half-life ($t_{1/2}$) was calculated as: ln(2) / λz. If the span to define the lambda z line was less than 2-fold of the $t_{1/2}$, the $t_{1/2}$ value was flagged with an asterisk (*) and removed from summary statistics.

[0269] Table 5 below discloses the mean pharmacokinetic data gained from each experiment with each of Groups 1-4. Good drug exposure was achieved with all of the tested compounds.

Table 5 – Pharmacokinetic Data for Dosing Study of Peptide Compounds in Dogs

Group	**Day**	**C_{max} (ng/mL)**	**AUC_{last} (h•ng/mL)**	**T_{max} (h)**
1	1	83.4	2840	0.75
	5	103	4360	1.80
2	1	154	4680	0.950
	5	200	11800	2.1
3	1	53.6	1280	1.17
	5	53.3	1610	1.92
4	1	68.2	1990	1.38
	5	131	6200	1.65

EXAMPLE 23

Pharmacokinetic Assessment of Compound 4 After Oral Administration

[0270] The pharmacokinetic properties of Compound 4 was assessed after administration of an oral dosage form (20 mg Compound 4 per tablet) to male beagle dogs. The test compounds were formulated with varying quantities of salcaprozate sodium (SNAC) or C10. Animals were acclimated to the study room for a minimum of 3 days prior to initial of dosing. The dogs (N=5) received oral tablet doses containing a test compound. Plasma samples were collected on Day 1 prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. On Day 3, samples were collected at

pre-dose only. On Day 5, samples were collected prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours after dosing. The formulations provided to the dogs and the dosing groups is shown in Table 6.

Table 6 – Dosing Groups for Oral Administration of Compound 4 in Dogs

Dose Group	Number of Animals	Compound 4 (mg)	SNAC (mg)	C10 (mg)	Enteric Coating
1	5	20	0	0	No
2	5	20	0	75	No
3	5	20	0	75	Yes
4	5	20	0	150	No
5	5	20	0	150	Yes
6	5	20	0	300	No
7	5	20	0	300	Yes
8	5	20	300	0	No
9	5	20	700	0	No
10	5	20	450	0	No
11	5	20	450	0	Yes
12	5	20	450	75	No
13	5	20	450	75	Yes
14	5	20	450	150	No
15	5	20	450	150	Yes
16	5	20	450	300	No
17	5	20	450	300	Yes

[0271] Pharmacokinetic analyses were performed on plasma concentration versus time data using Phoenix WinNonlin (v 8.3) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. The C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. As the data permitted, the terminal rate constant (lambda z, λz) was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time where the data points were randomly distributed around a straight line, at least three data points post the C_{max} were used in the regression, the correlation coefficient (R^2) of regression was >0.90, and the period over which the regression is determined (span) was at least 2.0-fold greater than the calculated half-life itself.

[0272] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. The AUC_{INF} value was calculated as: $AUC_{last} + (C_{last} / \lambda z)$. The Cl/F value was calculated as Dose / AUC_{INF} and the Vz/F value was calculated as Dose / (AUC_{INF} * λz). If the percent of extrapolated area for AUC_{INF} was >20%, the AUC_{INF}, Vz/F, and CL/F values were not reported. Terminal half-life ($t_{1/2}$) was calculated as: ln(2) / λz. If the span to define the lambda z line was less than 2-fold of the $t_{1/2}$, the $t_{1/2}$ value was flagged with an asterisk (*) and removed from summary statistics.

[0273] Table 7 below discloses the mean pharmacokinetic data gained from each experiment with each of Groups 1-17 upon conclusion of the study. Examination of Groups 8, 9, and 10 shows increasing SNAC levels leads to increased, then decreased exposures of Compound 4. The data is also illustrated in FIG. 2, which shows AUC_{INF} values for day 1 and day 5. For both days, doses that include 450 mg SNAC resulted in higher exposure than 300 mg SNAC or 700 mg SNAC. Groups 1-3 showed no measurable plasma level of the drug. Thus, an appropriate mixture of Compound 4 and SNAC in the formulation is important to achieving an effective concentration of the drug in the plasma.

Table 7 – Pharmacokinetic Data for Dosing Study of Peptide Compounds in Dogs

Group	Day	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	AUC_{INF} (h*ng/mL)	$t_{1/2}$ (h)
1	1	--	--	--	--	--
	5	--	--	--	--	--
2	1	--	--	--	--	--
	5	--	--	--	--	--
3	1	--	--	--	--	--
	5	--	--	--	--	--
4	1	2.0	79.8	2398.6	3812	33.2
	5	2.5	50.9	2131.0	2980	42.7
5	1	5.2	39.7	791.5	589	26.3
	5	6.0	139.3	7351.8	8746	67.3
6	1	0.9	194.0	5284.2	8925	36.2
	5	1.7	151.6	8671.8	9967	59.1
7	1	1.9	188.8	6111.6	10773	40.5
	5	3.8	101.2	7233.9	8788	62.6
8	1	1.3	23.7	303.9	1409	42.0
	5	1.1	35.3	1349.8	2575	58.9
9	1	1.5	102.7	2834.5	4895	38.3
	5	1.8	80.6	5432.5	6841	66.9
10	1	0.7	81.9	2052.7	5042	70.2
	5	1.2	181.8	8434.5	9753	56.3
11	1	--	--	--	--	--
	5	3.8	59.8	2814.5	4020	64.7
12	1	0.9	134.2	3249.1	8059	83.8
	5	1.3	102.9	5247.3	6549	62.7
13	1	2.8	318.3	7352.4	12132	31.5
	5	0.6	199.5	13365.2	15052	66.6
14	1	0.9	134	3389.5	6038	36.5
	5	0.9	150.9	9048.2	10539	64.5

15	1	1.2	51.8	1239.5	2118	39.5
	5	2.7	103.8	4724.8	5927	59.0
16	1	1.4	144.2	3710.9	7112	38.7
	5	1.4	189.0	12130.1	13923	178.8
17	1	1.9	83.5	2265.6	3844	36.8
	5	3.7	116.4	7681.2	8698	52.9

EXAMPLE 24

Pharmacokinetic Assessment of Compounds 4, 15, 18, and 23 After Oral Administration

[0274] The pharmacokinetic properties of Compound 15, 18, and 23 was assessed after administration of an oral dosage form (20 mg Compound 15, 18 or 23 and 450 mg salcaprozate sodium (SNAC) per tablet) to male beagle dogs. Animals were acclimated to the study room for a minimum of 3 days prior to initial of dosing. The dogs (N=6) received oral tablet doses containing a test compound. Plasma samples were collected on Day 1 prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 24 hours after dosing. On Day 3, samples were collected at pre-dose only. On Day 5, samples were collected prior to dosing the dogs and then at 15 min, 30 min, 45 min, and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 24, 48, 72, 96, 120, 144, 192 and 240 hours after dosing.

[0275] Pharmacokinetic analyses were performed on plasma concentration versus time data using Phoenix WinNonlin (v 8.3) non-compartmental analysis function (linear trapezoidal rule for AUC calculations). Nominal dose values and sampling times were used for calculations. The C_{max} and the corresponding T_{max} values were determined by direct assessment of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. As the data permitted, the terminal rate constant (lambda z, λz) was determined. The value of λz was calculated by the slope of the regression line of the natural log transformed concentrations vs. time where the data points were randomly distributed around a straight line, at least three data points post the C_{max} were used in the regression, the correlation coefficient (R^2) of regression was >0.90, and the period over which the regression is determined (span) was at least 2.0-fold greater than the calculated half-life itself.

[0276] To optimize the reliability of the identified terminal phase (λz), the data points used to define the λz were manually selected. The AUC_{INF} value was calculated as:

AUC_{last} + (C_{last} / λz). The Cl/F value was calculated as Dose / AUC_{INF} and the Vz/F value was calculated as Dose / (AUC_{INF} * λz). If the percent of extrapolated area for AUC_{INF} was >20%, the AUC_{INF}, Vz/F, and CL/F values were not reported. Terminal half-life ($t_{1/2}$) was calculated as: ln(2) / λz. If the span to define the lambda z line was less than 2-fold of the $t_{1/2}$, the $t_{1/2}$ value was flagged with an asterisk (*) and removed from summary statistics. FIG. 3 shows mean plasma concentration versus time profiles for Compounds 15, 18, and 23, and also includes the profile for Compound 4. The formulations of each of the compounds demonstrated adequate drug exposure at 72 hours.

EXAMPLE 25

Tablet Formulations

Wet Granulation Method – Tablet A

[0277] A batch of tablets (Tablet A) with Compound 4 as the active ingredient were prepared by a wet granulation process. The amounts of each component are found in Table 8 below, shown as mg/tablet and total mg in the 17 gram batch.

Table 8 – Tablet Formulation for Dog Studies

Component	**mg/tablet**	**mg/17 grams**
Compound 4	25	625
Salcaprozate sodium (SNAC)	500	12500
Microcrystalline cellulose	133.3	3332.5
Polyvinylpyrrolidinone K90	13.3	332.5
Magnesium stearate	16.2	405
Total	687.8	17195

[0278] Each ingredient was passed through a #35 mesh sieve. Compound 4 and SNAC were weighed out and blended in a mortar and pestle. Separately, the polyvinylpyrrolidinone was weighted out and dissolved in water at 65 mg/mL, for a total volution of 5.1 mL. The polyvinylpyrrolidinone solution was wet granulated with the blend of Compound 4 and SNAC. The granules were dried in a fluid bed dryer at 30-35 °C to ensure the water content is not more than 4%. The resulting granules were passed through a #35 mesh sieve and then combined with the microcrystalline cellulose and magnesium stearate and mixed in a rotator. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 1 – Tablet B

[0279] A batch of tablets (Tablet B) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Tables 9 and 10 below, shown per tablet and per 17 g batch.

Table 9 - Compounding Table for Tablet B (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	95 mg	38.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.83 mg	--	3.3 mg

Table 10- Compounding Table for Tablet B (per 17 g)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	0.625 g	--
Salcaprozate sodium (SNAC)	12.5 g	--	--
Microcrystalline cellulose	2.375 g	0.958 g	--
Polyvinylpyrrolidinone K90	--	0.333 g	--
Magnesium stearate	0.321 g	--	0.083 g

[0280] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture.

[0281] In a separate stainless-steel bowl, the microcrystalline cellulose was weighed out and then diluted 2x with the final magnesium stearate/SNAC mixture to form the pre-mix. The premix was then added to the remaining final magnesium stearate/SNAC mixture and mixed manually for at least 60 seconds until visually homogenous. The resulting mixture was then mixed in a v-blender for 10 minutes at 25 rpm. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0282] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a

stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0283] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet C

[0284] A batch of tablets (Tablet C) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Tables 11 and 12 below, shown per tablet and per 17 g batch.

Table 11 - Compounding Table for Tablet C (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.83 mg	--	3.3 mg

Table 12 - Compounding Table for Tablet C (per 17 g)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	0.625 g	--
Salcaprozate sodium (SNAC)	12.5 g	--	--
Microcrystalline cellulose	--	3.33 g	--
Polyvinylpyrrolidinone K90	--	0.33 g	--
Magnesium stearate	0.321 g	--	0.083 g

[0285] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0286] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0287] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet D

[0288] A batch of tablets (Tablet D) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 13 below, shown per tablet.

Table 13 - Compounding Table for Tablet D (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	250 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0289] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0290] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The

resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0291] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet E

[0292] A batch of tablets (Tablet E) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 14 below, shown per tablet.

Table 14 - Compounding Table for Tablet E (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	750 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0293] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0294] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0295] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet F

[0296] A batch of tablets (Tablet F) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 15 below, shown per tablet.

Table 15 - Compounding Table for Tablet F (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
PVP-VA	--	90 mg	
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0297] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0298] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, PVP-VA, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0299] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to

resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet G

[0300] A batch of tablets (Tablet G) with Compound 15 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 16 below, shown per tablet.

Table 16 - Compounding Table for Tablet G (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 15	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0301] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0302] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 15, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0303] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet H

[0304] A batch of tablets (Tablet H) with Compound 18 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 17 below, shown per tablet.

Table 17 - Compounding Table for Tablet H (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 18	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0305] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was then added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0306] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 18, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0307] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet J

[0308] A batch of tablets (Tablet J) with Compound 23 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 18 below, shown per tablet.

Table 18 - Compounding Table for Tablet J (per tablet)

Component	1st fraction	2nd fraction	extragranular
Compound 23	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0309] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0310] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 23, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0311] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet K

[0312] A batch of tablets (Tablet K) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 19 below, shown per tablet.

Table 19 - Compounding Table for Tablet K (per tablet)

Component	1st fraction	2nd fraction	extragranular
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--

Microcrystalline cellulose	--	120 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Primellose (croscarmellose sodium)		13.3 mg	
Magnesium stearate	12.85 mg	--	3.34 mg

[0313] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0314] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, primellose, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0315] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet L

[0316] A batch of tablets (Tablet L) with Compound 4 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 19 below, shown per tablet.

Table 20 - Compounding Table for Tablet L (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	120 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0317] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0318] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0319] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet M

[0320] A batch of tablets (Tablet M) with Compound 23 as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 21 below, shown per tablet.

Table 21 - Compounding Table for Tablet M (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 23	--	25 mg	--
Salcaprozate sodium (SNAC)	500 mg	--	--
Microcrystalline cellulose	--	120 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.85 mg	--	3.34 mg

[0321] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The

remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0322] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 23, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0323] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

Dry Granulation Method # 2 – Tablet N

[0324] A batch of tablets (Tablet N) with Compound 4 (20 mg) as the active ingredient were prepared by a dry granulation process. The amounts of each component are found in Table 22 below, shown per tablet.

Table 22 - Compounding Table for Tablet M (per tablet)

Component	**1st fraction**	**2nd fraction**	**extragranular**
Compound 4	--	20 mg	--
Salcaprozate sodium (SNAC)	450 mg	--	--
Microcrystalline cellulose	--	133.3 mg	--
Polyvinylpyrrolidinone K90	--	13.3 mg	--
Magnesium stearate	12.87 mg	--	3.33 mg

[0325] The magnesium stearate was weighed out and passed through a 355 μm sieve. In a stainless-steel bowl, the magnesium stearate was diluted 2x with SNAC. The remaining SNAC was added to a v-blender and mixed for 2 minutes at 25 rpm. The magnesium stearate/SNAC mixture was the added to the v-blender and the contents were mixed for 20 minutes at 25 rpm to form a final magnesium stearate/SNAC mixture. The resulting powder

was pressed into large tablets, broken down in a mortar and pestle, and passed through a 180 μm mesh sieve to form the first fraction granules.

[0326] The second fraction granulation was prepared by weighing the appropriate amounts of microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone into a stainless-steel bowl. The contents of the bowl were mixed manually for 3 minutes until visually homogenous and then transferred to a v-blender and tumbled for 1 minute. The resulting powder was pressed into large tablets, broken down in a mortar and pestle to form the second fraction granules.

[0327] The first fraction granules were added to a v-blender followed by the second fraction granules and mixed for 5 minutes at 32 rpm. Magnesium stearate was then added to resulting mixture and blended at 32 rpm for 30 seconds. The resulting granules were then pressed into a tablet to achieve the desired hardness and thickness.

EXAMPLE 26

Formulation Studies

[0328] The pharmacokinetics of different formulations of Compound 4 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 1 tablet per day in the study. 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.

[0329] The monkeys were administered either Tablet A, Tablet B, or Tablet C described in the previous examples, or an oral solution of Compound 4 (Blend 1) that includes 25 mg of Compound 4 and 500 mg of SNAC.

Table 23 – Formulation Studies for Compound 4

Group	Formulation	Compound 4 (mg)	SNAC (mg)
1	Blend 1	25	500
2	Tablet A	25	500
3	Tablet B	25	500
4	Tablet C	25	500

[0330] The mean plasma concentration versus time data for Compound 4 after repeat oral administration in male cynomolgus monkeys is shown in FIG. 4. Tablet Formulation C results in the highest mean exposure of Compound 4 of Tablet Formulations A, B, C. All of the tablet formulations resulted in a higher mean exposure of Compound 4 as compared to Blend 1.

EXAMPLE 27

Additional Formulation Studies

[0331] The pharmacokinetics of different formulations of various peptide compounds 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 1 tablet per day in the study. Blood samples (0.5 mL) were taken from the monkeys at Day 1, Day 2, 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.

[0332] The monkeys were administered Tablet formulation C described in the previous examples, which includes 25 mg of Compound 4 and 500 mg of SNAC. Compounds 15, 18, and 23 were administered as Formulations G, H, and J, respectively. The mean plasma concentration versus time data and AUC data for Compound 4, Compound 15, Compound 18, and Compound 23 is provided in Table 24. Formulation C provides adequate drug exposure for all four compounds.

Table 24– Pharmacokinetic Data For Various Compounds Formulated as Tablet C

Compound	Formulation	Compound (mg)	SNAC (mg)	C_{max} (ng/mL)	AUC_{inf} h•ng/mL
Compound 4	Tablet C	25	500	4090	399000
Compound 15	Tablet G	25	500	4050	411000
Compound 18	Tablet H	25	500	2140	209000
Compound 23	Tablet J	25	500	5980	690000

EXAMPLE 28

Pharmacokinetic Study Using Permeability Enhancers

[0333] The study in this example was designed to evaluate the pharmacokinetics of compounds of the instant application, with the addition of an absorption enhancer (SNAC, C10, Lauroyl-L-carnitine chloride, and Labrasol) in PBS as an intraduodenal (ID) administration. Male Sprague Dawley rats were socially housed in individual ventilated caging (IVG), three per cage for acclimation for 3-7 days with alpha dri bedding, water ad lib, 2016 Teklad chow ad lib and enrichment. The room temperature was 72 +/- 2° F with a Relative Humidity of 30-70%, and 12 hour light cycle. Animals were individually housed just prior to study initiation with ad lib food and water for the duration of the study. The rats were administered doses of the particular compound on Day 1 of the study at a dose level of 5 mg/kg. Blood samples (0.5 mL) were taken from the rats at pre-dose and at 0.25, 0.6, 1, 2, 4, 8, 12, 24, 36, and 48 hours after administration). Groups 1-4 were administered Compound 24 with SNAC, C10, lauroyl-L-carnitine chloride, and Labrasol, respectively; Groups 5-8 were administered 27 with SNAC, C10, lauroyl-L-carnitine chloride, and Labrasol, respectively; Groups 9-12 were administered Compound 4 with SNAC, C10, lauroyl-L-carnitine chloride (LCC), and Labrasol, respectively. There were three rats per test group.

[0334] Sample analysis was measured with a LC-MS/MS method based on multiple reaction monitoring (MRM) of fragment ions for the rat pharmacokinetic study. All samples from the study were stored at -80 ℃ until ready for analysis.

Excipient stock solutions

[0335] Phosphate buffered saline (PBS): a solution was prepared at pH 7.4 (no calcium, no magnesium). For Labrasol, an 80 mg/mL stock solution was prepared on the day of dosing by weighing out 800 mg of Labrasol into a vial, adding 9.2 ml of PBS and vortexing.

[0336] C10: a 200 mM solution of C10 in PBS was prepared. The solution was warmed in a water bath to 37 °C prior to use until the solution became clear. The solution was allowed to cool back to room temperature before any test compound was added.

[0337] SNAC: a 200 mM solution was prepared in PBS. The solution was prepared on the day of dosing.

[0338] Lauroyl carnitine chloride (LCC): a 100 mM solution of LCC in PBS solution (15 ml). The LCC solution was made in advance and frozen in 5 mL aliquots.

Compound Dosing Solutions

[0339] Labrasol® and Test Compound: The doses were prepared at a concentration of 1 mg/mL of compound (6 mL total). 3 mL of PBS was added into an appropriately sized glass container. 6 mg of compound (corrected for purity) was then added into the 3 mL of PBS and vortexed. 3 mL of Labrasol® stock solution to the compound solution above and vortexed. Animals were dosed with 5 mL/kg of the formulation.

[0340] C10 and Test Compound: 1 mg/mL solutions of test compound were prepared by warming 3 mL of the C10 stock solution 37°C until the solution was clear. The solution returned to room temperature before test compound was added. In an appropriately sized glass container, 3 mL PBS was added, followed by 6 mg of the test compound (corrected for purity). Subsequently, 3 mL of the room temperature C10 stock solution to the test compound solution and vortexed.

[0341] SNAC and Test Compound: 1 mg/mL solutions of test compound were prepared by adding 3 mL PBS to an appropriately sized glass container, followed by 6 mg of the test compound (corrected for purity). Subsequently, 3 mL of the room temperature SNAC stock solution to the test compound solution and vortexed.

[0342] LCC and Test Compound: 1 mg/mL solutions of test ompound were prepared by adding 3 mL PBS to an appropriately sized glass container, followed by 6 mg of the test compound (corrected for purity). Subsequently, 3 mL of the room temperature LCC stock solution to the test compound solution and vortexed.

[0343] The plasma concentration of each compound with each excipient is shown in FIGS. 5A-5C. Plasma concentration of Compound 24 after administration in various excipients shows that highest initial concentration with C10, while no trace is shown for Compound 24 with SNAC as plasma levels of Compound 24 were below the limit of quantitation (FIG. 5A). A similar phenomenon is observed with Compound 27 and C10 (FIG. 5B) and Compound 4 and SNAC (FIG. 5C). However, for the combination of Compound 4 and SNAC, the plasma levels of Compound 4 were above the limit of quantitation.

EXAMPLE 29

Additional Tablet Formulations

Spray Dried Dispersion Method – Tablet O

[0344] A batch of tablets (Tablet O) with a compound disclosed herein as the active ingredient is prepared by a spray-dried dispersion method. The compound disclosed herein is combined with either (a) hydroxypropylmethylcellulose acetate succinate type M (HPMCAS-M); (b) hydroxypropylmethylcellulose acetate succinate type L (HPMCAS-L); (c) polyvinylpyrrolidinone-vinyl acetate copolymer (PVP-VA64); or (d) Eudragit ® L100 in a solvent to form a solution for spray drying. The solutions are then dried with a heated nitrogen stream and collected using a cyclone. The spray dried matier is then combined with microcrystalline cellulose, magnesium stearate, and additional fillers and disintegrants, and pressed into tablets.

Wet Granulation Method # 2– Tablet P

[0345] A batch of tablets (Tablet P) with a compound disclosed herein as the active ingredient is prepared by a wet granulation method. The compound disclosed herein is combined with microcrystalline cellulose and hydroxypropyl cellulose. The mixture of materials is wet granulated using purified water as the granulation liquid. The wet granulate is dried in a fluid bed dryer. Thereafter, the dried granulate is milled and blended for 10 minutes. Magnesium stearate is sieved and added to the blended mixture and blended for an additional 5 minutes. Thereafter, the mixture is compressed into tablets.

[0346] 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.

[0347] 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.

[0348] 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.

[0349] 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.

[0350] 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.

[0351] Other embodiments are set forth in the following claims, along with the full scope of equivalents to which such claims are entitled.

[0352] 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.

[0353] 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.

[0354] 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:

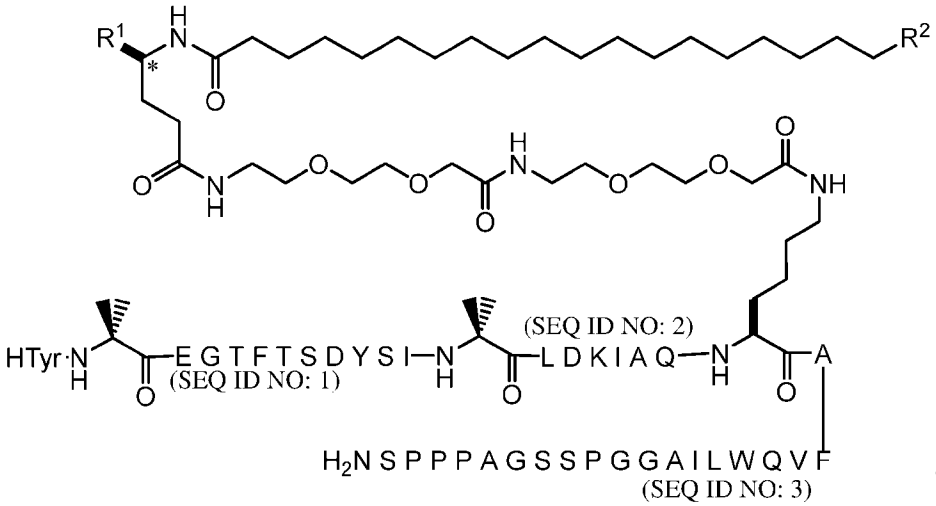
1. A pharmaceutical composition, comprising:

a permeability enhancer; and

a therapeutically effective amount of a compound, wherein the compound is a GLP-1 agonist or a GLP/GIP dual agonist;

wherein the mass of the permeability enhancer is greater than 300 mg.

2. The pharmaceutical composition of claim 1, wherein the compound 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} aryloxy and C_{6-10} aryl alkoxy;

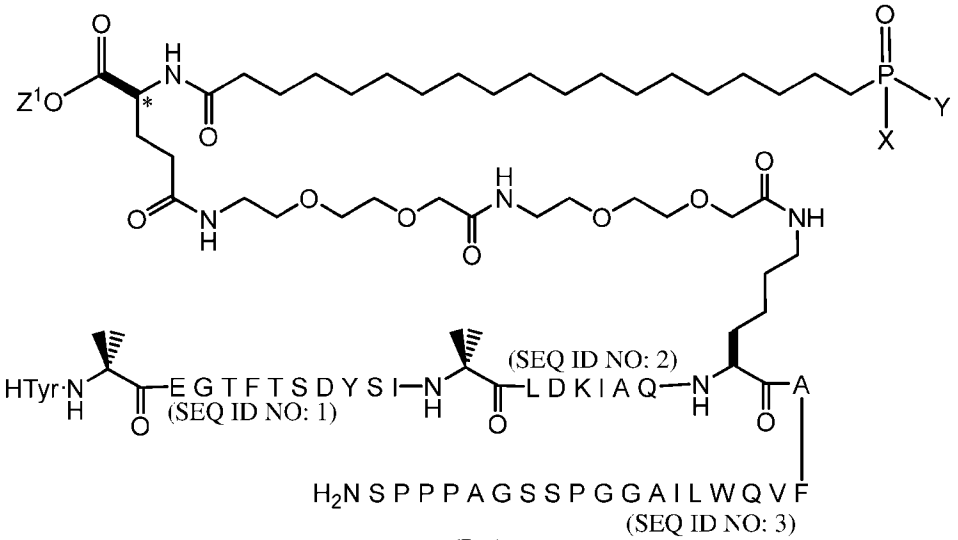
each R^5 may be independently hydrogen or C_{1-6} alkyl;

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, haloC_{1-6} alkoxy, 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 compound 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, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

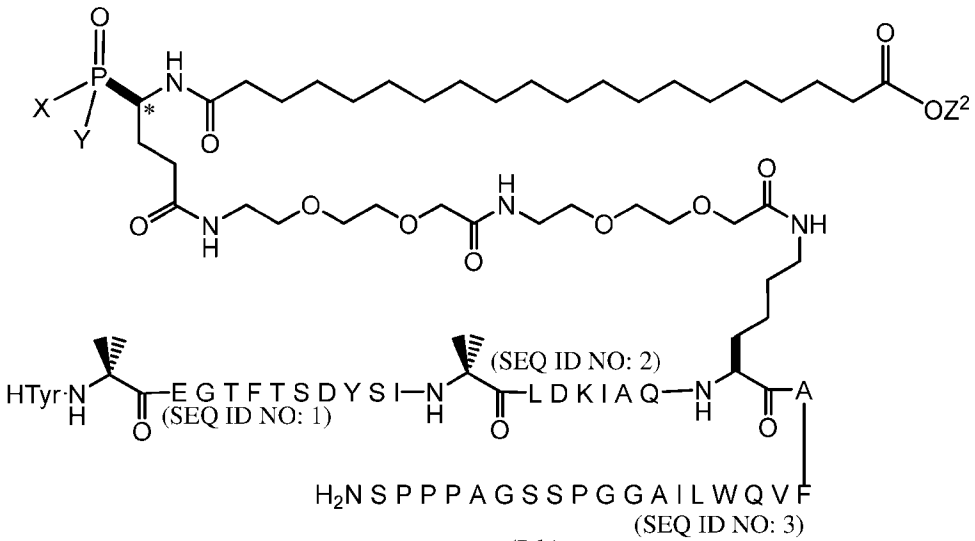
6. The pharmaceutical composition of claim 4 or 5, wherein Z^1 is selected from the group consisting of hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

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 alkoxy.

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 compound 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, 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 $-OR^4$.

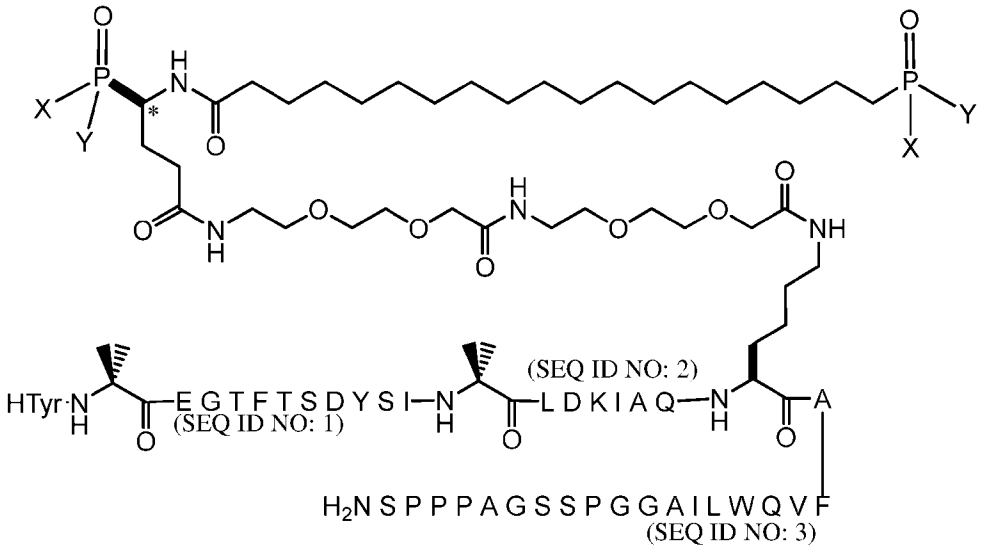
12. The pharmaceutical composition of claim 10 or 11, wherein Z^2 is selected from the group consisting of hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

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 alkoxy.

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 compound is a compound having the structure of Formula (I-c):



(I-c)

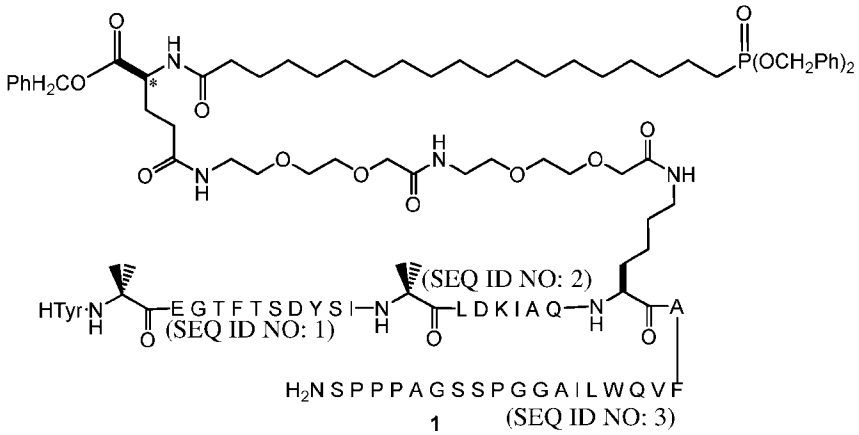
or a pharmaceutically acceptable salt thereof.

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

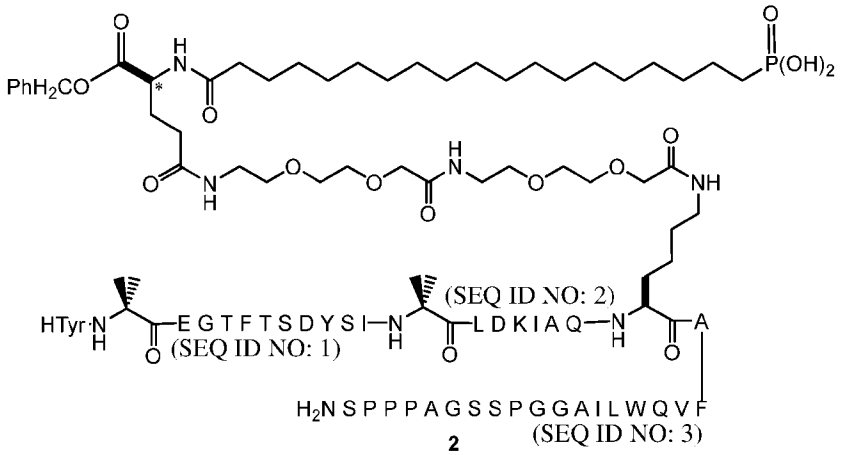
18. The pharmaceutical composition of claim 16 or 17, wherein each R^4 is independently selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

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

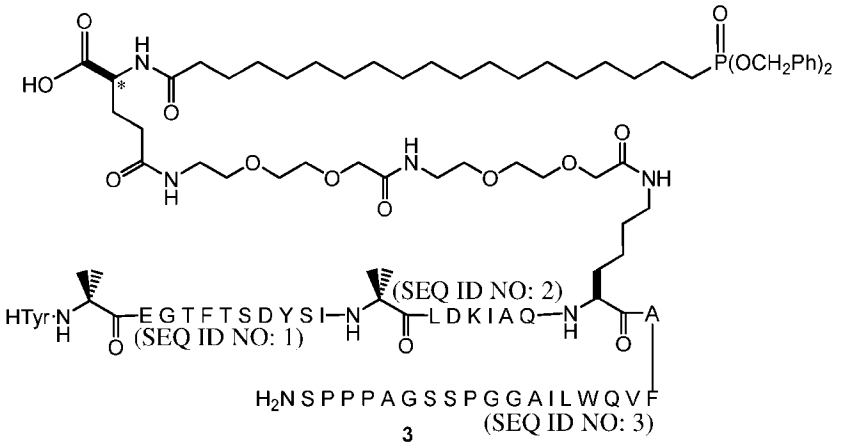
20. The pharmaceutical composition of claim 2 or 3, wherein the compound is a compound having the structure selected from the group consisting of:


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)

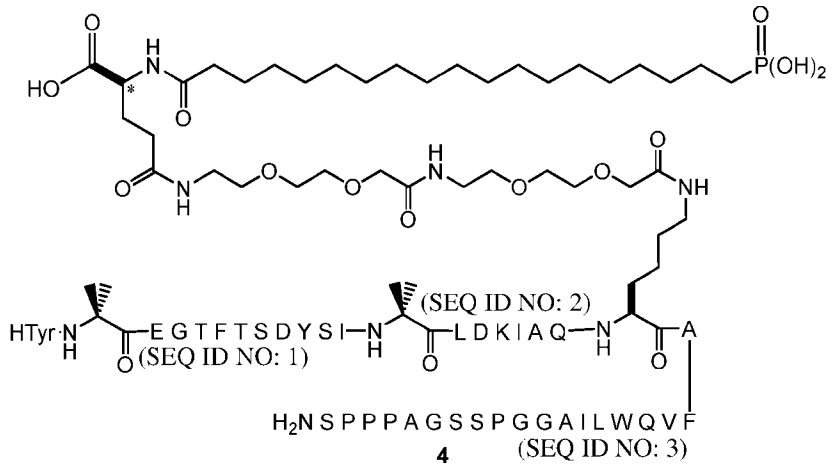
1


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)

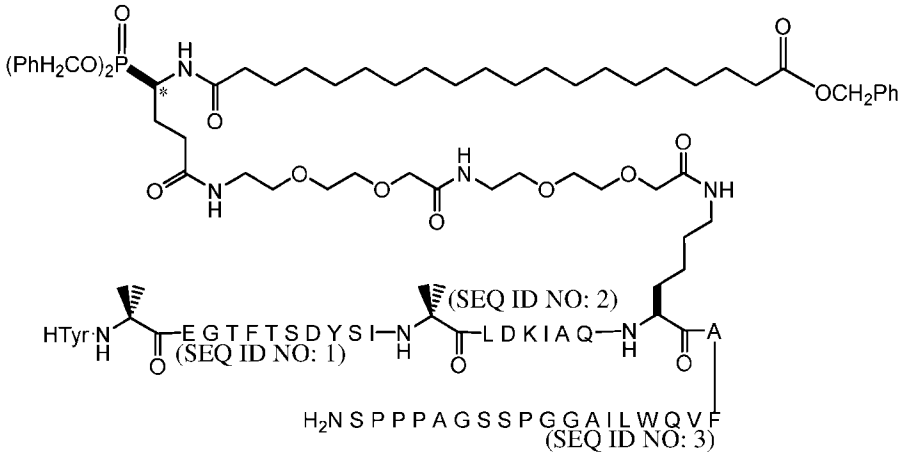
2


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)

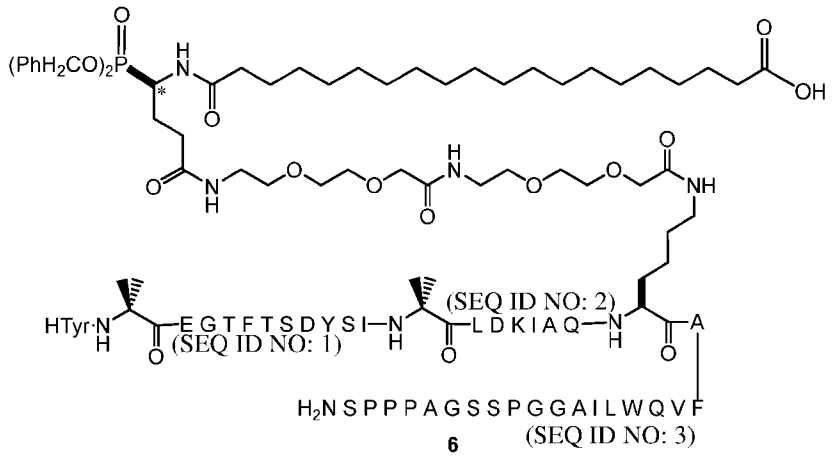
3


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)

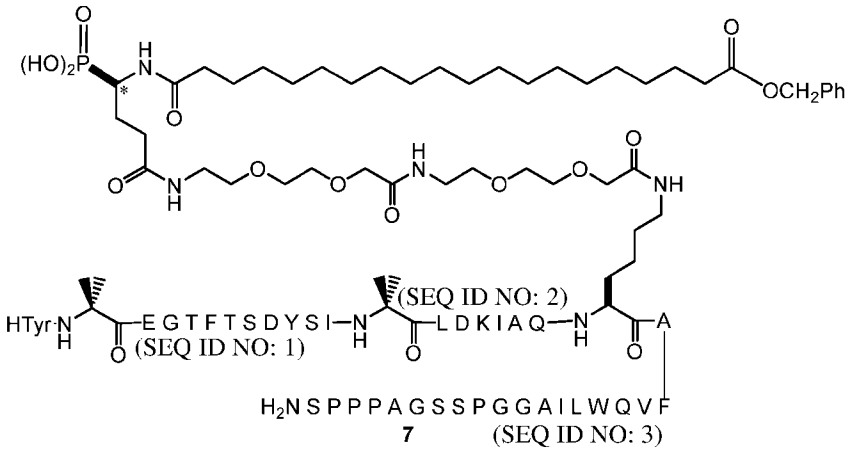
4


(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)

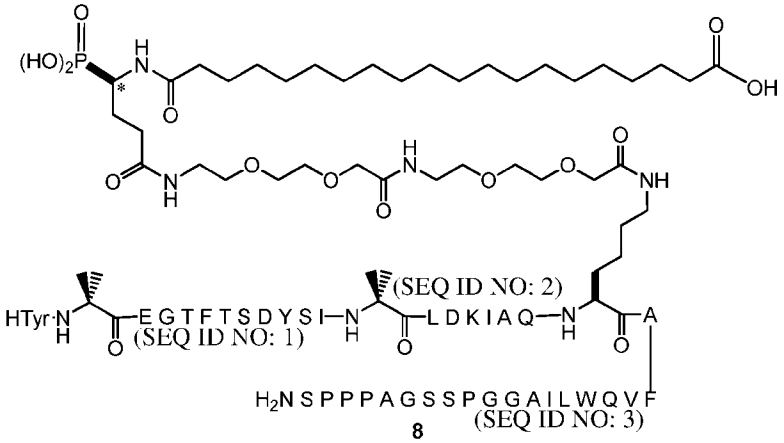
5


(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)

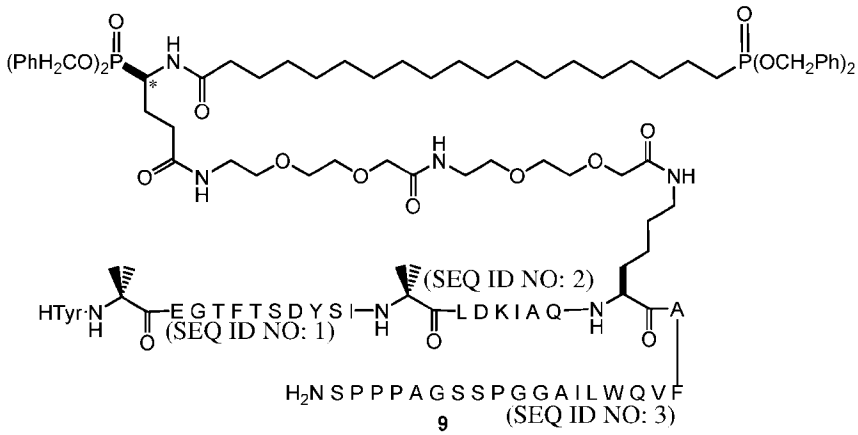
6


(HO)2P
OCH2Ph
HTyr-N
E G T F T S D Y S I
(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)

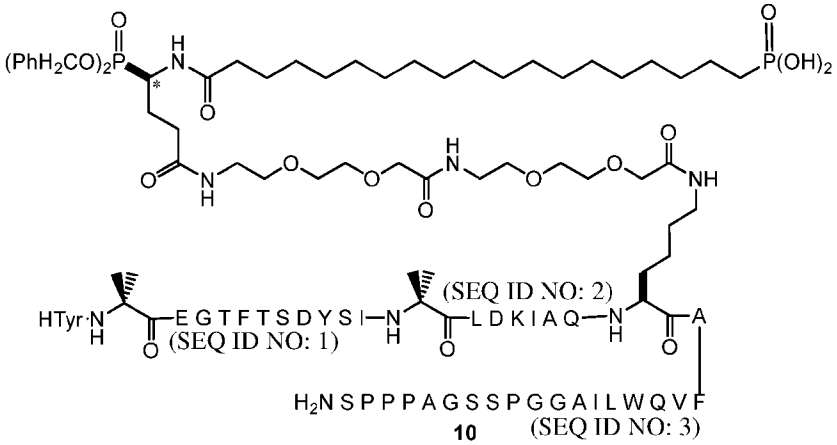
7


(HO)2P
OH
HTyr-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)

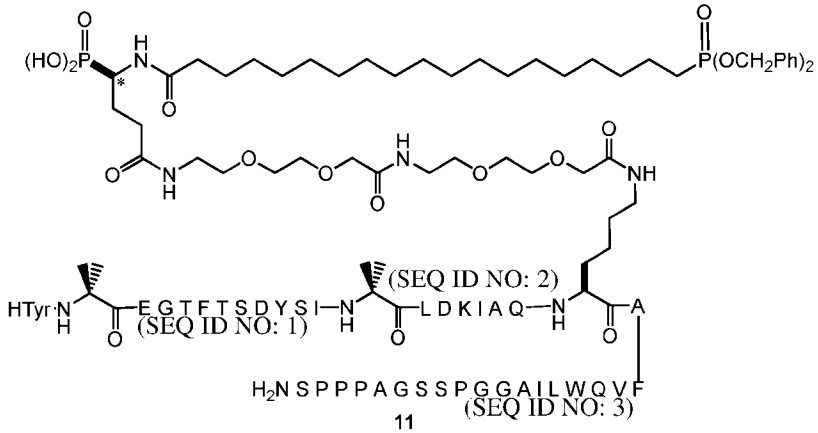
8


(PhH2CO)2P
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)

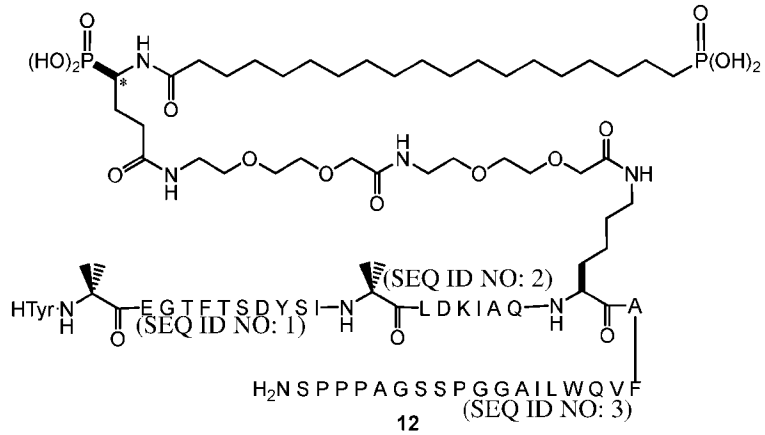
9



10



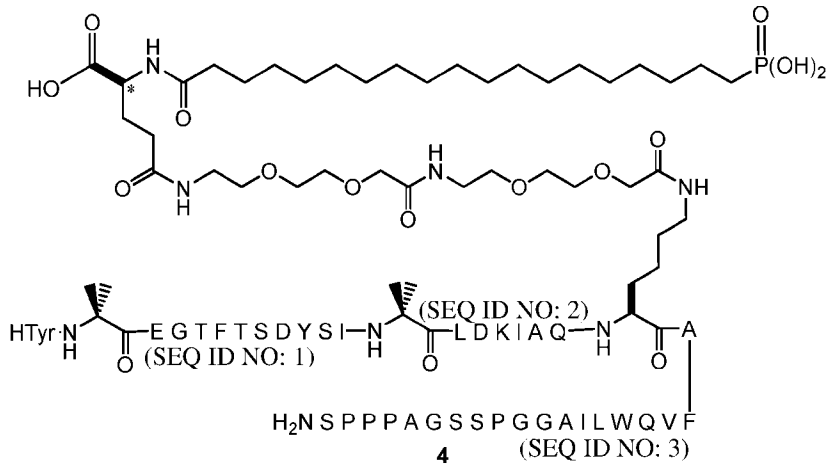
11



12

and pharmaceutically acceptable salts thereof.

21. The pharmaceutical composition of claim 20, wherein the compound is a compound having the structure:



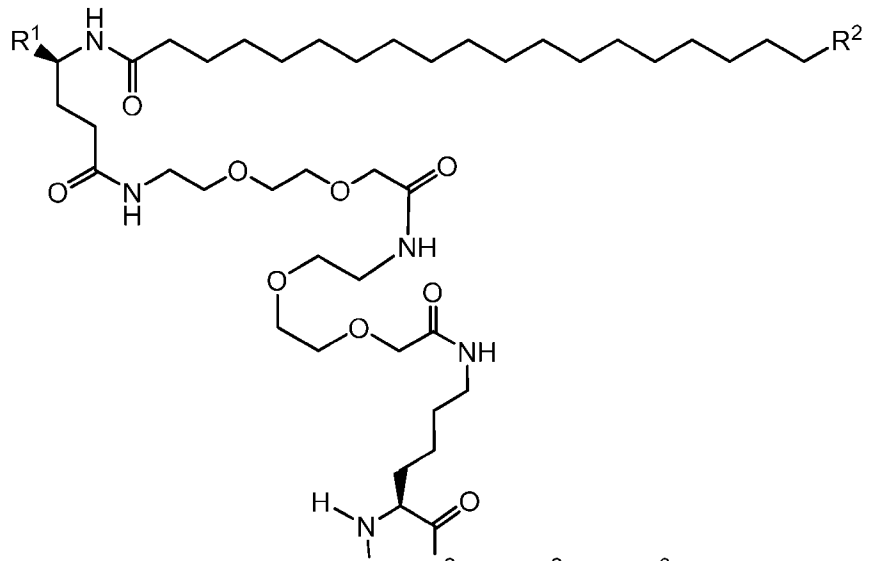
4

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 compound 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;

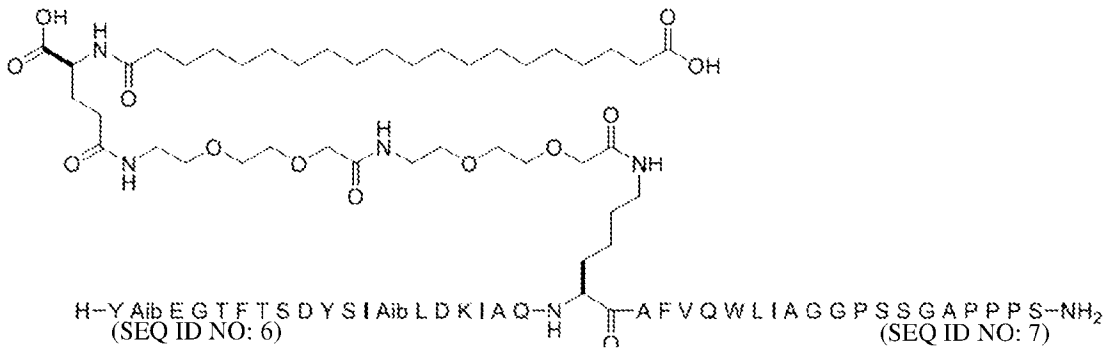
each R^4 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, C_{6-10} aryl and C_{7-11} arylalkyl;

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.

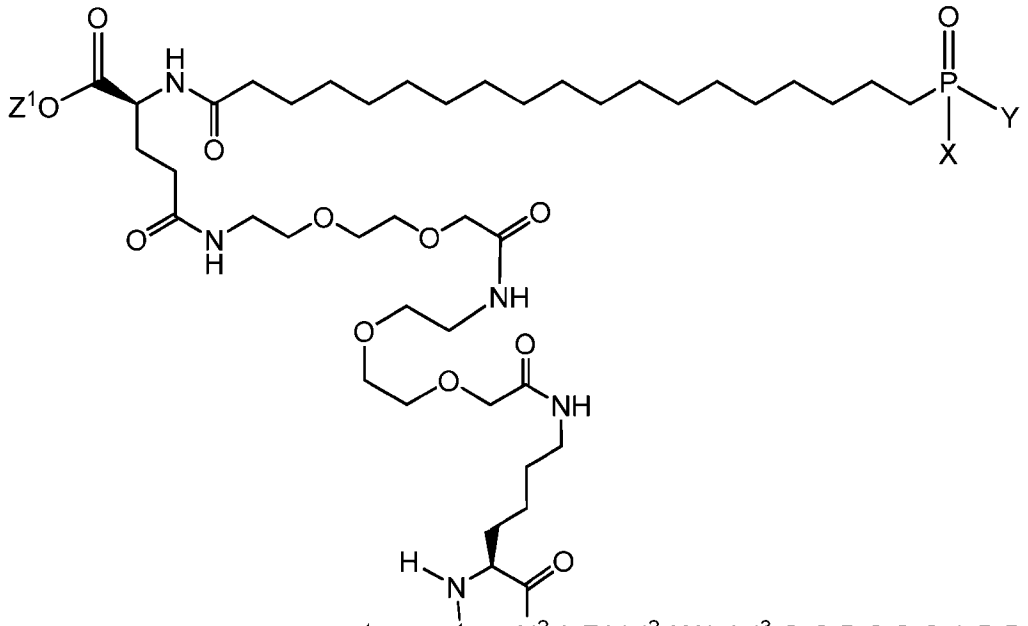
48. The pharmaceutical composition of any one of claims 24 to 47, wherein each instance of n1, n2, n3, and n4 is zero.

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.

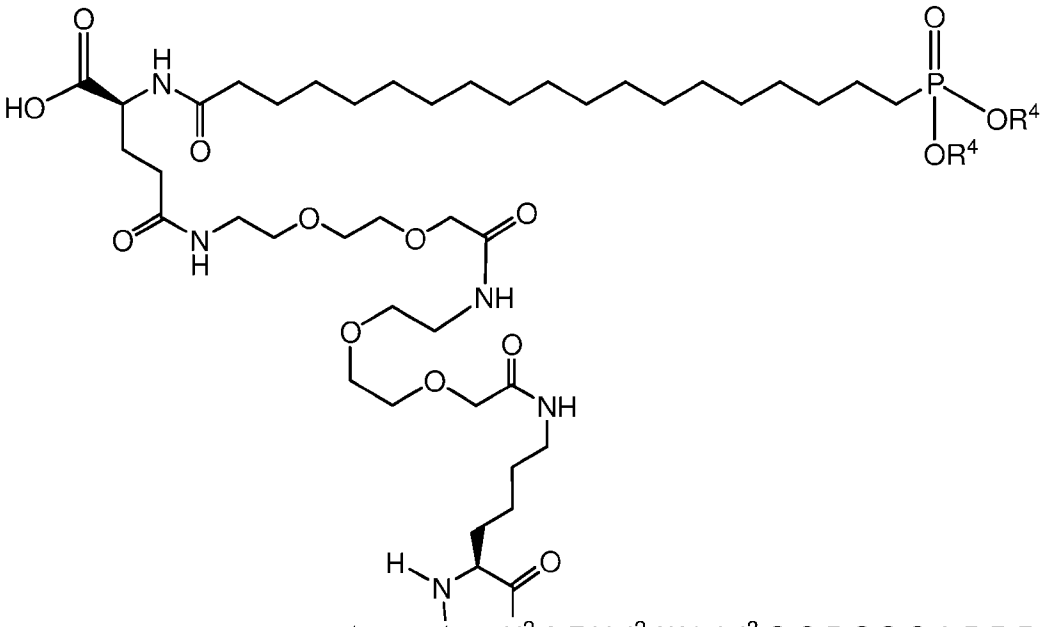
53. The pharmaceutical composition of claim 52, wherein Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

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 compound is a compound having the structure of Formula (II-b):



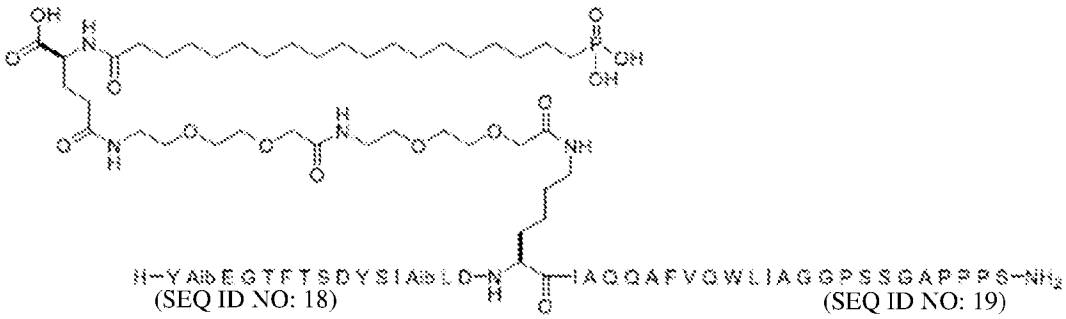
(II-b)

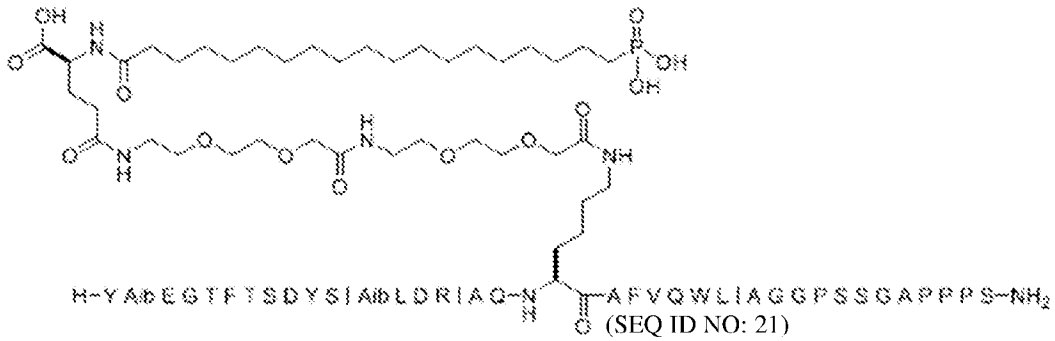
or a pharmaceutically acceptable salt thereof.

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.

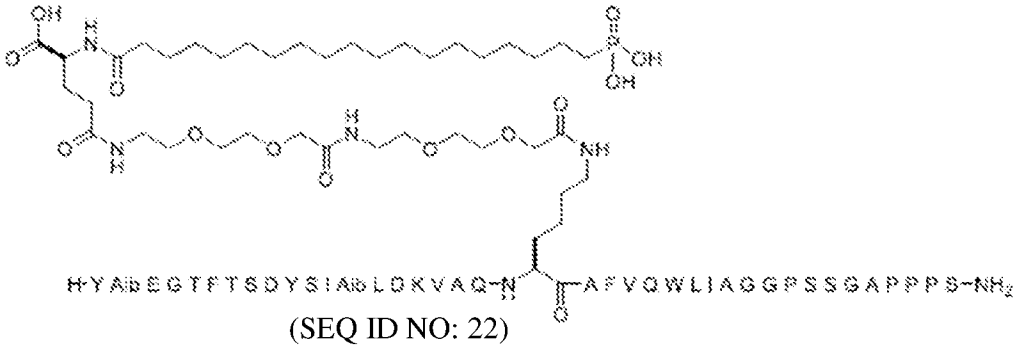
59. The pharmaceutical composition of claim 58, wherein each R^4 is hydrogen.

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

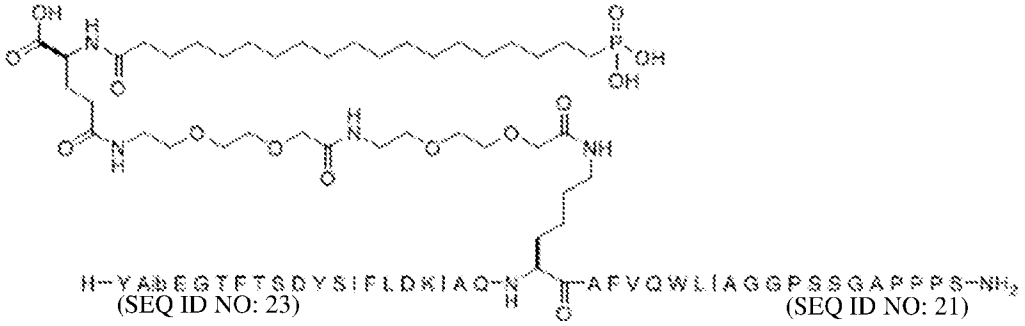




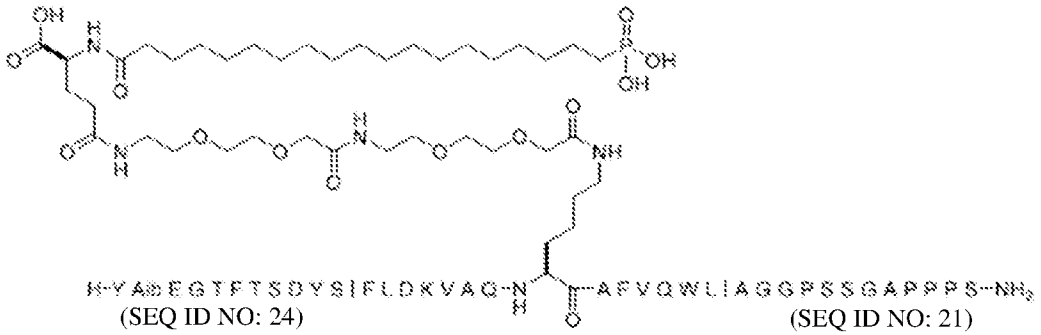
(SEQ ID NO: 21)



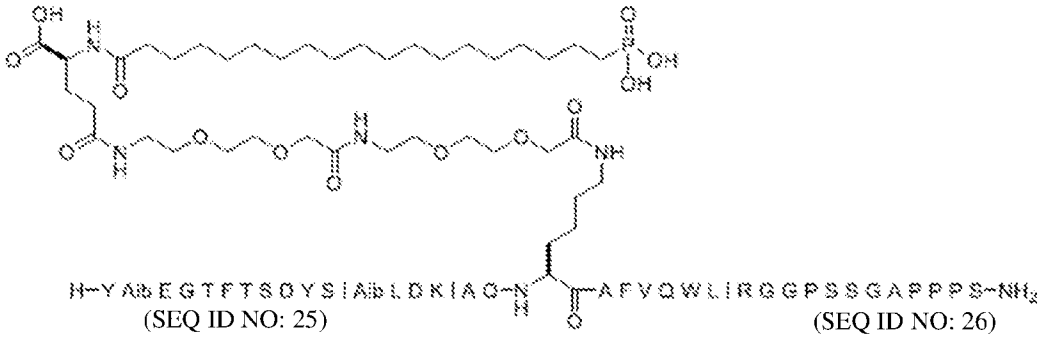
(SEQ ID NO: 22)



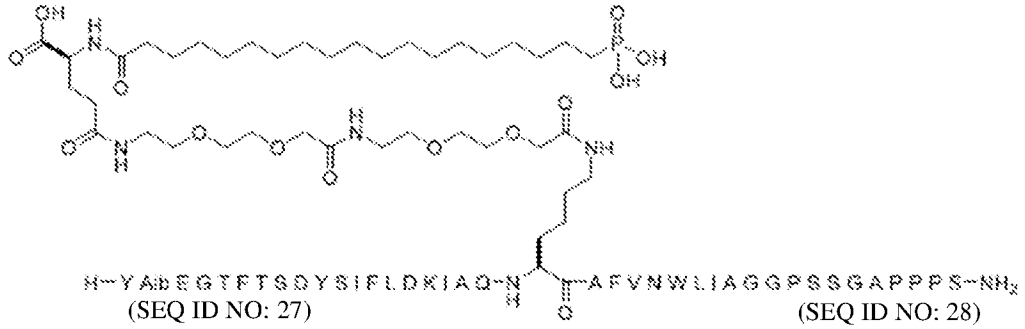
(SEQ ID NO: 23) (SEQ ID NO: 21)



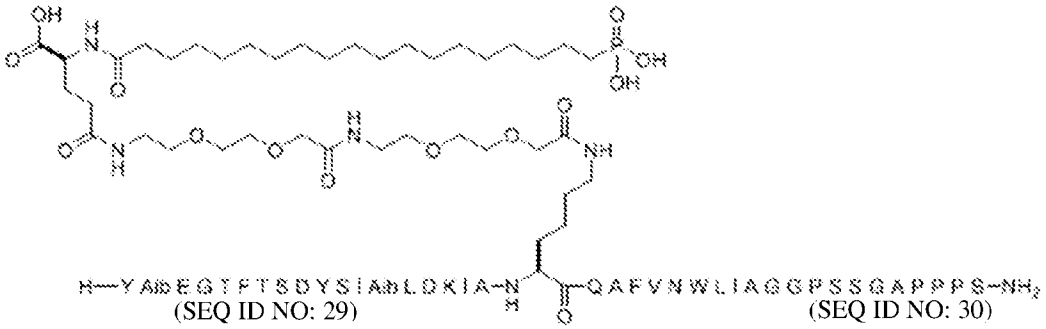
(SEQ ID NO: 24) (SEQ ID NO: 21)



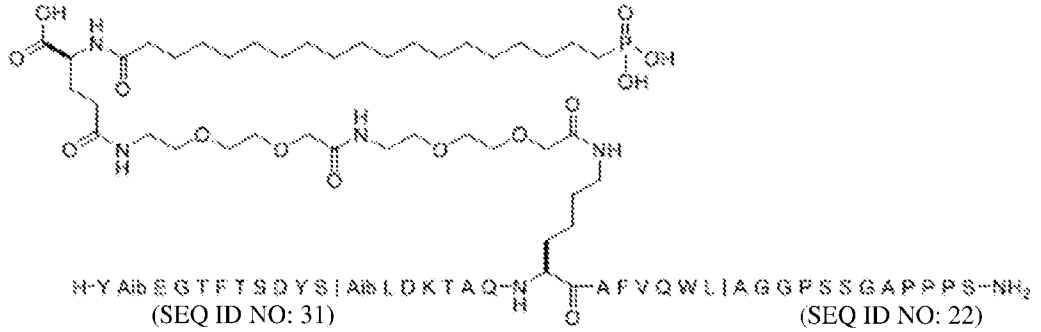
(SEQ ID NO: 25) (SEQ ID NO: 26)



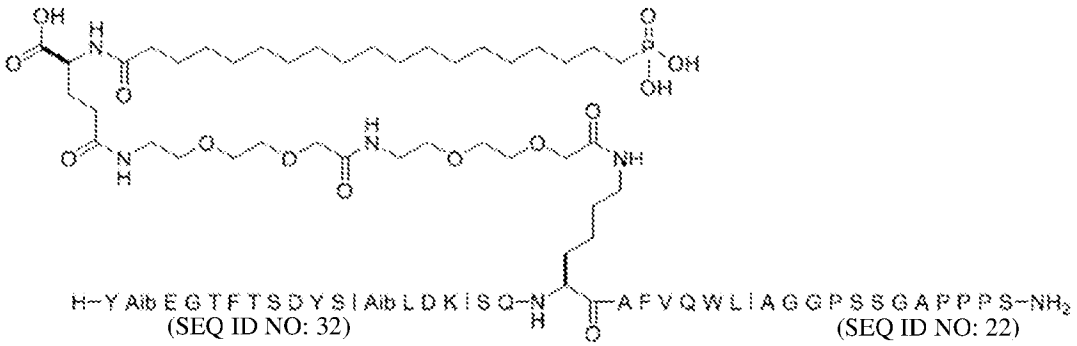
(SEQ ID NO: 27) (SEQ ID NO: 28)



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



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

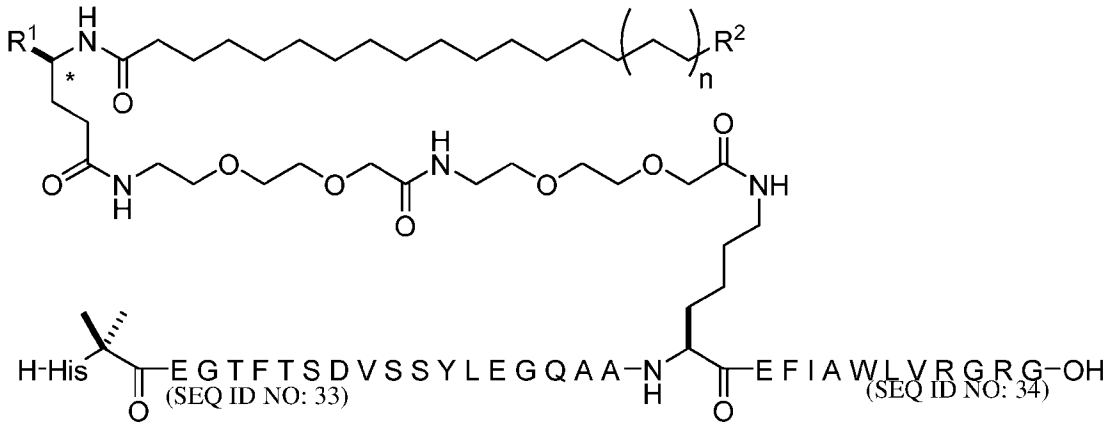


(SEQ ID NO: 32) (SEQ ID NO: 22)

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

and pharmaceutically acceptable salts thereof.

61. The pharmaceutical composition of claim 1, wherein the compound is a compound having the structure of Formula (III), or a pharmaceutically acceptable salt thereof



(III),

or a pharmaceutically acceptable salt thereof, 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 1-4 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 $-C(=O)(OZ^2)$, $-(CH_2CH_2)_nP(=O)(X)(Y)$ and a 5-10 membered heteroaryl containing 1-4 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 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} aryloxy and C_{6-10} aryl alkoxy;

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

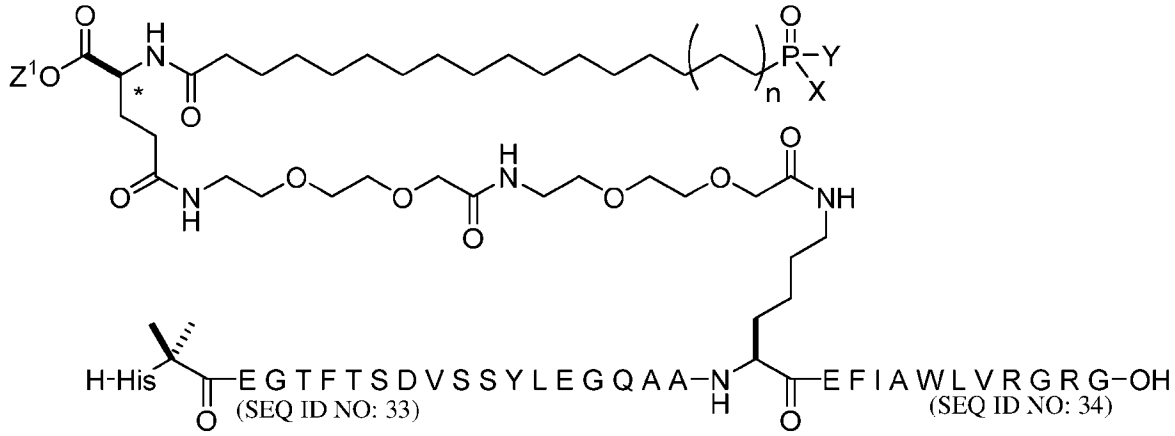
each R^6 is independently hydrogen or C_{1-6} alkyl;

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; and

n is 0, 1, 2, 3 or 4.

62. The pharmaceutical composition of claim 61, wherein at least one of Z^1 and Z^2 is not hydrogen.

63. The pharmaceutical composition of claim 61 or 62, wherein the compound is a compound having the structure of Formula (III-a):



(III-a),

or a pharmaceutically acceptable salt thereof.

64. The pharmaceutical composition of claim 63, 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 $-OR^4$.

65. The pharmaceutical composition of claims 63 or 64, wherein Z^1 is selected from the group consisting of hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

66. The pharmaceutical composition of any one of claims 63 to 65, wherein Z^1 is hydrogen and each R^4 independently is hydrogen or C_{6-10} aryl alkoxy.

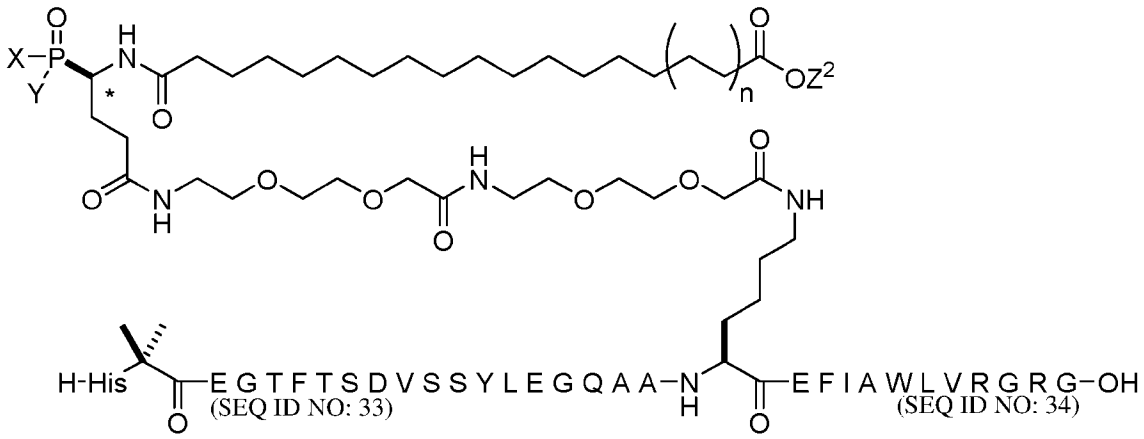
67. The pharmaceutical composition of any one of claims 63 to 66, wherein each R^4 is hydrogen.

68. The pharmaceutical composition of any one of claims 63 to 67, wherein Z^1 is hydrogen and each R^4 is hydrogen.

69. The pharmaceutical composition of any one of claims 63 to 68, wherein n is 1.

70. The pharmaceutical composition of any one of claims 63 to 68, wherein n is 2.

71. The pharmaceutical composition of claim 59, wherein the compound is a having the structure of Formula (III-b):



(III-b)

or a pharmaceutically acceptable salt thereof.

72. The pharmaceutical composition of claim 71, wherein Z^2 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 $-OR^4$.

73. The pharmaceutical composition of claim 71 or 72, wherein Z^2 is selected from the group consisting of hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

74. The pharmaceutical composition of any one of claims 71 to 73, wherein Z^2 is hydrogen and each R^4 is hydrogen or C_{6-10} aryl alkoxy.

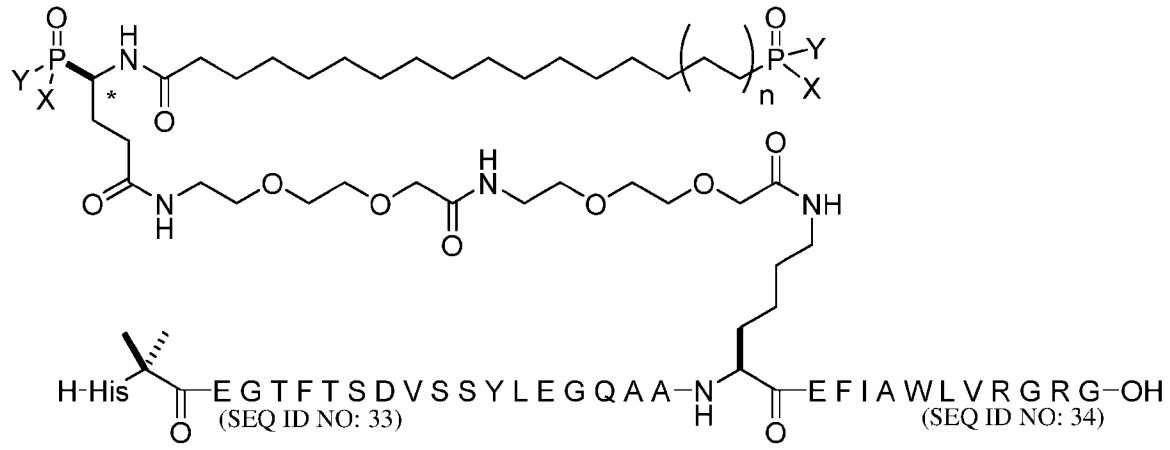
75. The pharmaceutical composition of any one of claims 71 to 74, wherein each R^4 is hydrogen.

76. The pharmaceutical composition of any one of claims 71 to 75, wherein Z^2 is hydrogen and each R^4 is hydrogen.

77. The pharmaceutical composition of any one of claims 71 to 76, wherein n is 1.

78. The pharmaceutical composition of any one of claims 71 to 76, wherein n is 2.

79. The pharmaceutical composition of claim 61 or 62, wherein the compound is a compound having the structure of Formula (III-c):



(III-c),

or a pharmaceutically acceptable salt thereof.

80. The pharmaceutical composition of claim 79, wherein X and Y each are $–OR^4$.

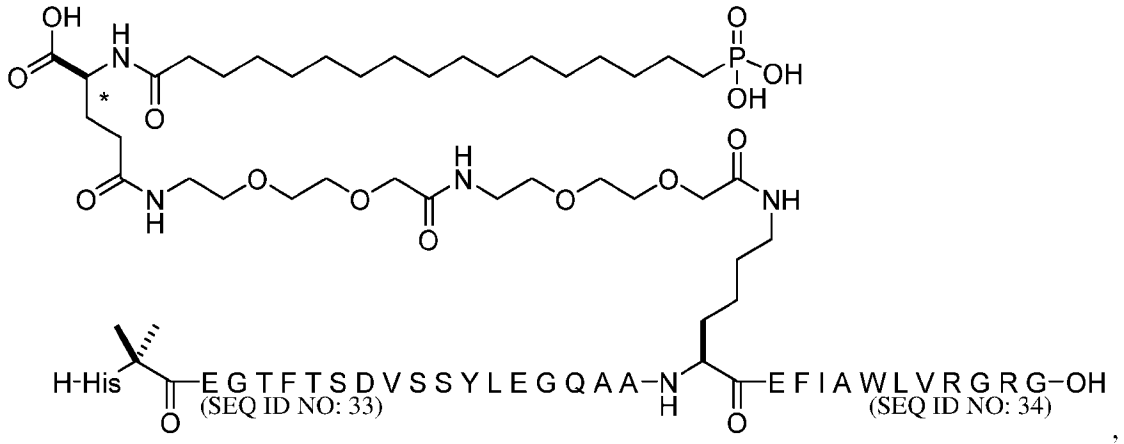
81. The pharmaceutical composition of claim 80, wherein each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryloxy and C_{6-10} aryl alkoxy.

82. The pharmaceutical composition of claim 80 or 81, wherein each R^4 is hydrogen.

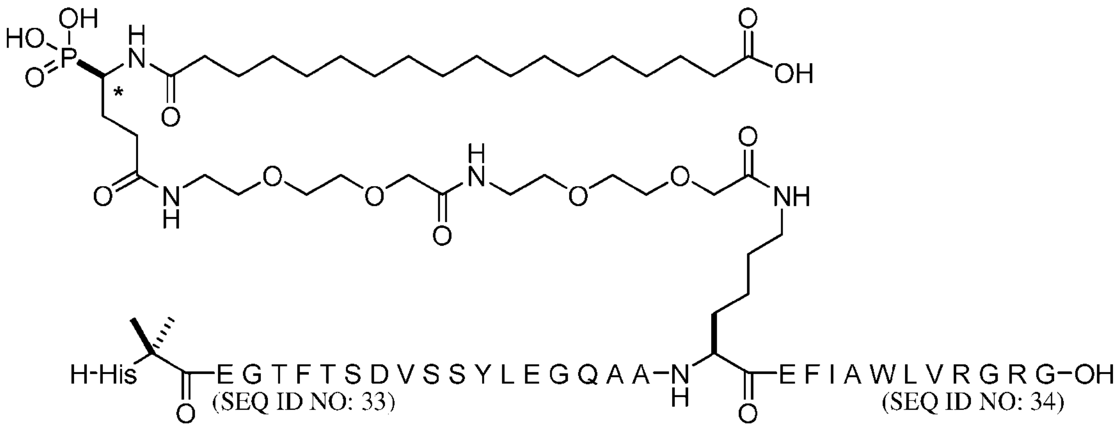
83. The pharmaceutical composition of any one of claims 79 to 82, wherein n is 1.

84. The pharmaceutical composition of any one of claims 79 to 82, wherein n is 2.

85. The pharmaceutical composition of claim 61 or 62, wherein the compound is a compound having the structure selected from the group consisting of:



,



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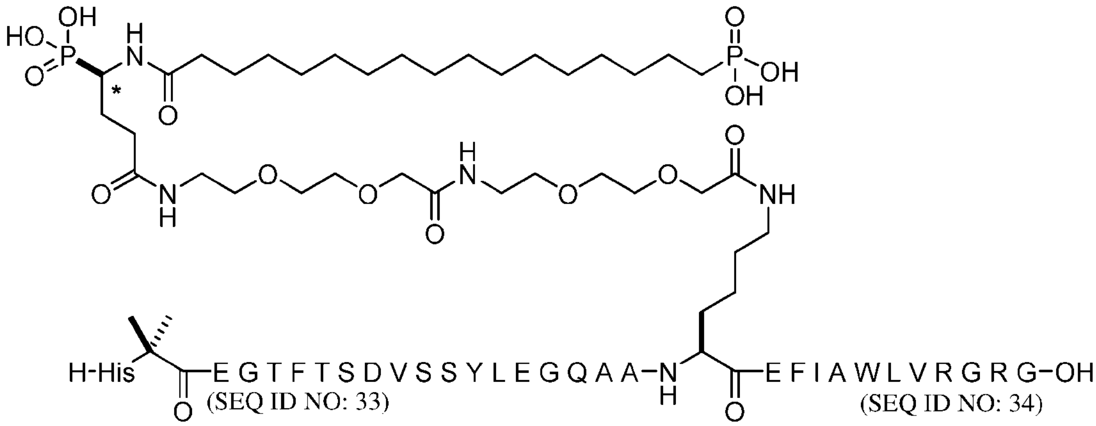
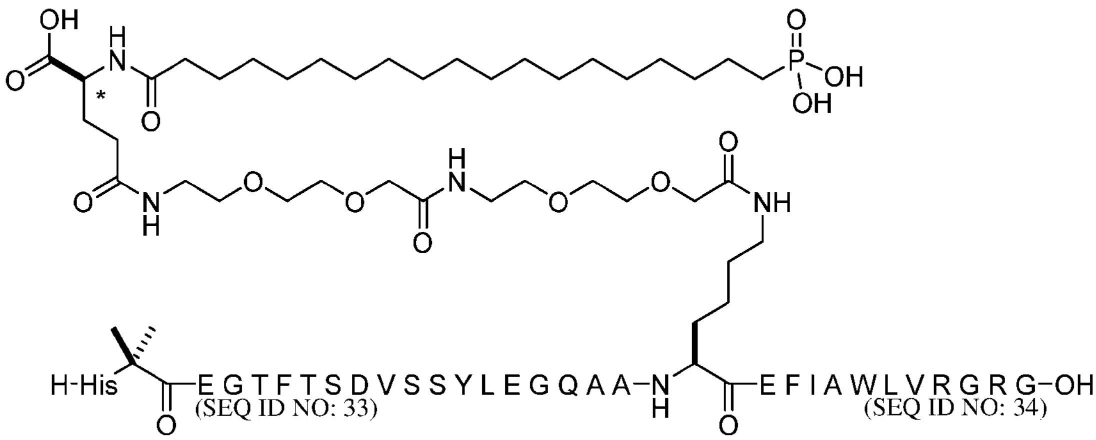


,



,

and pharmaceutically acceptable salts thereof.

86. The pharmaceutical composition of any one of claims 61 to 85, wherein "*" indicates a chiral carbon with "S" configuration.

87. The pharmaceutical composition of any one of claims 61 to 85, wherein "*" indicates a chiral carbon with "R" configuration.

88. The pharmaceutical composition of any one of Claims 1 to 87, wherein the mass of the permeability enhancer is from about 350 mg to about 1000 mg.

89. The pharmaceutical composition of any one of Claims 1 to 87, wherein the mass of the permeability enhancer is from about 400 mg to about 800 mg.

90. The pharmaceutical composition of any one of Claims 1 to 87, wherein the mass of the permeability enhancer is from about 500 mg to about 750 mg.

91. The pharmaceutical composition of any one of Claims 1 to 87, wherein the mass of the permeability enhancer is about 500 mg; or wherein the mass of the permeability enhancer is 450 mg.

92. The pharmaceutical composition of any one of Claims 1 to 91, wherein the permeability enhancer comprises from about 40% to about 90% by weight of the composition.

93. The pharmaceutical composition of any one of Claims 1 to 91, wherein the permeability enhancer comprises from about 50% to about 80% by weight of the composition.

94. The pharmaceutical composition of any one of Claims 1 to 91, wherein the one or more permeability enhancer comprises from about 70% to about 80% by weight of the composition.

95. The pharmaceutical composition of any one of Claims 1 to 91, wherein the permeability enhancer comprises about 73% of the composition.

96. The pharmaceutical composition of any one of Claims 1 to 95, wherein the permeability enhancer is salcaprozate sodium (SNAC), sodium caprate (C10), or a combination thereof.

97. The pharmaceutical composition of any one of Claims 1 to 95, wherein the permeability enhancer is salcaprozate sodium.

98. The pharmaceutical composition of any one of Claims 1 to 95, wherein the permeability enhancer is sodium caprate.

99. The pharmaceutical composition of any one of Claims 1 to 95, wherein the one or more permeability enhancer is a combination of salcaprozate sodium and sodium caprate.

100. The pharmaceutical composition of any one of Claims 1 to 99, comprising from about 1 mg to about 50 mg of the compound.

101. The pharmaceutical composition of any one of Claims 1 to 99, comprising from about 5 mg to about 40 mg of the compound.

102. The pharmaceutical composition of any one of Claims 1 to 99, comprising from about 10 mg to about 30 mg of the compound.

103. The pharmaceutical composition of any one of Claims 1 to 99, comprising from about 20 mg to about 30 mg of the compound.

104. The pharmaceutical composition of any one of Claims 1 to 99, comprising from about 25 mg of the compound.

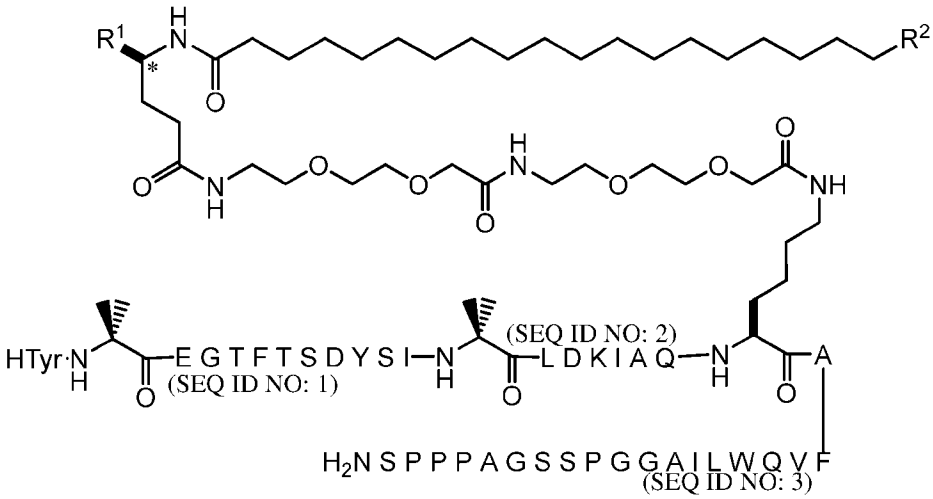
105. The pharmaceutical composition of any one of Claims 1 to 104, further comprising a disintegrant.

106. The pharmaceutical composition of Claim 105, wherein the disintegrant is croscarmellose sodium.

107. A pharmaceutical composition, comprising:

salcaprozate sodium; and

a therapeutically effective amount of a compound having the structure of Formula I, or a pharmaceutically acceptable salt thereof:



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 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_{6-10} 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; and

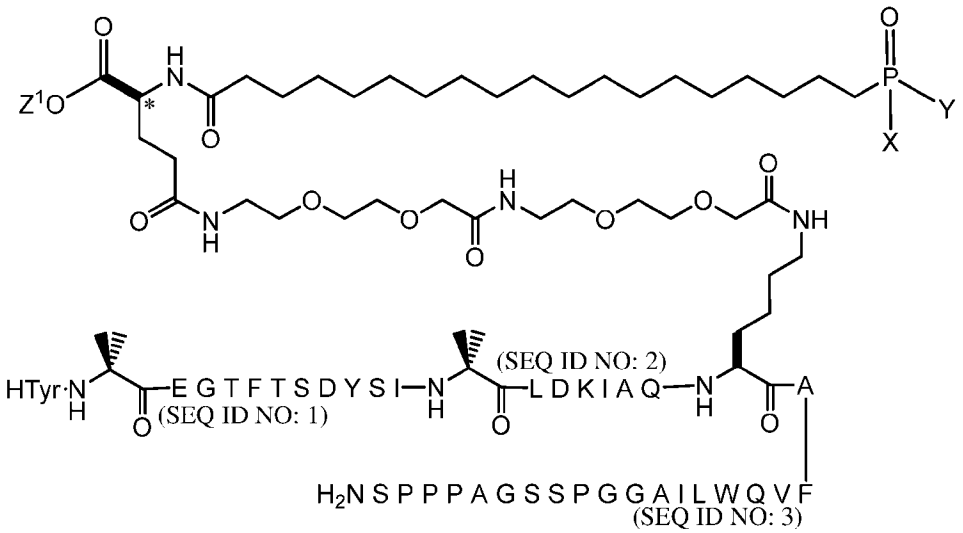
wherein the mass of salcaprozate is greater than about 300 mg.

108. The pharmaceutical composition of any one of Claims 1 to 107, wherein at least one of Z^1 and Z^2 is not hydrogen.

109. The pharmaceutical composition of any one of Claims 1 to 107, wherein the composition further comprises one or more excipient.

110. The pharmaceutical composition of Claim 109, wherein the one or more excipient is selected from the group consisting of microcrystalline cellulose, magnesium stearate, and polyvinylpyrrolidone.

111. The pharmaceutical composition of any one of Claims 1 to 110, wherein the compound has the structure of Formula I-a:



IA

or a pharmaceutically acceptable salt thereof.

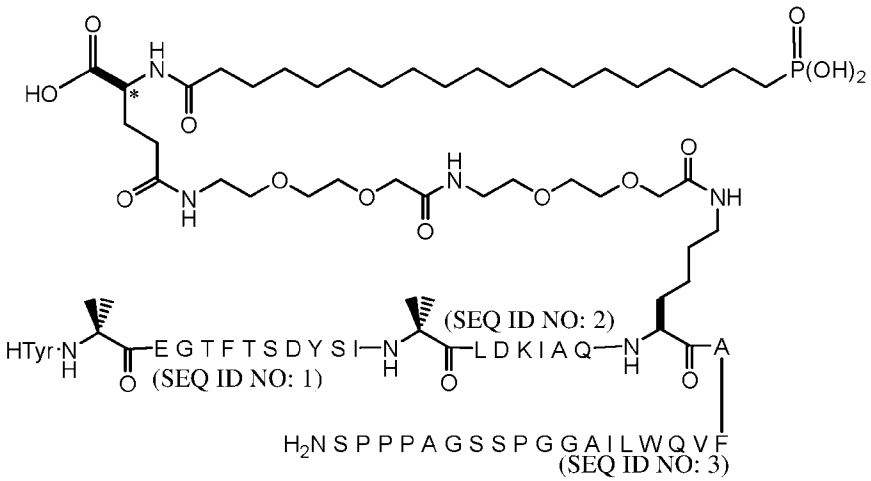
112. The pharmaceutical composition of any one of Claims 1 to 111, wherein Z^1 is selected from the group consisting of hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkoxy, C_{3-10} cycloalkyl and C_{6-10} aryl; and X and Y each are $-OR^4$.

113. The pharmaceutical composition of any one of Claims 1 to 112, wherein Z^1 is selected from the group consisting of hydrogen, haloC_{1-6} alkoxy and C_{1-6} alkoxy; and each R^4 independently is selected from the group consisting of hydrogen, C_{6-10} aryl and C_{6-10} arylalkyl.

114. The pharmaceutical composition of any one of Claims 1 to 113, wherein Z^1 is hydrogen and each R^4 independently is hydrogen or C_{6-10} arylalkyl.

115. The pharmaceutical composition of any one of Claims 1 to 114, wherein each R^4 is hydrogen.

116. The pharmaceutical composition of any one of Claims 1 to 115, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

117. The pharmaceutical composition of any one of Claims 1 to 116, wherein the composition is formulated for oral administration.

118. The pharmaceutical composition of any one of Claims 1 to 117, wherein the pharmaceutical composition comprises:

from about 1.0 to about 5.0% by weight of the compound;

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 3.0% by weight polyvinylpyrrolidinone; and

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

119. The pharmaceutical composition of any one of Claims 1 to 118, wherein the pharmaceutical composition comprises:

about 3.6% by weight of the compound;

about 72.7% by weight salcaprozate sodium;

about 19.4% by weight microcrystalline cellulose;

about 1.9% by weight polyvinylpyrrolidinone; and

about 2.3% by weight magnesium stearate.

120. The pharmaceutical composition of any one of Claims 1 to 119, wherein the pharmaceutical composition is enterically coated.

121. A method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes in a subject, comprising administering a pharmaceutical composition of any one of Claims 1 to 120, to a subject in need thereof.

122. The method of Claim 119, 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.

123. The method of Claim 119 or 120, wherein the metabolic disorder or metabolic syndrome is obesity or hypothalamic obesity.

124. A method of preventing, treating, or ameliorating one or more fatty liver diseases in a subject, comprising administering a pharmaceutical composition of any one of Claims 1 to 120, to a subject in need thereof.

125. The method of Claim 122, wherein said wherein said fatty liver disease is selected from the group consisting of steatosis, non-alcoholic steatohepatitis and non-alcoholic fatty liver disease.

126. The method of Claim 122 or 125, wherein said administration of said pharmaceutical composition results in the prevention, treatment, or amelioration, of a fibrosis, fibrotic condition, or fibrotic symptoms.

127. The method of any one of Claims 122 to 126, 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.

128. The method of any of Claims 122 to 127, 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.

129. The method of Claim 128, 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.

130. A method of preventing, treating, or ameliorating one or disease or disorders in a subject, comprising administering a pharmaceutical composition of any one of Claims 1 to 118 to a subject in need thereof, 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.

131. The method of Claim 130, 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.

132. The method of any one of Claims 121 to 131, wherein the route of administration is oral.

133. A method of preparing a pharmaceutical composition, the method comprising the steps of:

(i) combining salcaprozate sodium and magnesium stearate to form first granules;

(ii) combining microcrystalline cellulose, Compound 4, and polyvinylpyrrolidinone to form second granules

(iii) combining the first granules and the second granules to form a mixture;

(iv) adding magnesium stearate to the mixture to form third granules;

(v) pressing the third granules into tablets.

134. A method of preparing a pharmaceutical composition, the method comprising the steps of:

(i) combining microcrystalline cellulose and compound disclosed therein in a first vessel;

(ii) combining polyvinylpyrrolidinone and water in a second vessel;

(iii) adding the contents of the first vessel to the second vessel to form wet granules;

(iv) drying the wet granules to form dry granules;

(v) combining the dry granules with magnesium stearate; and

(vi) pressing the resulting mixture of step (v) into granules.

135. The pharmaceutical composition prepared by the method of Claim 133 or 134.

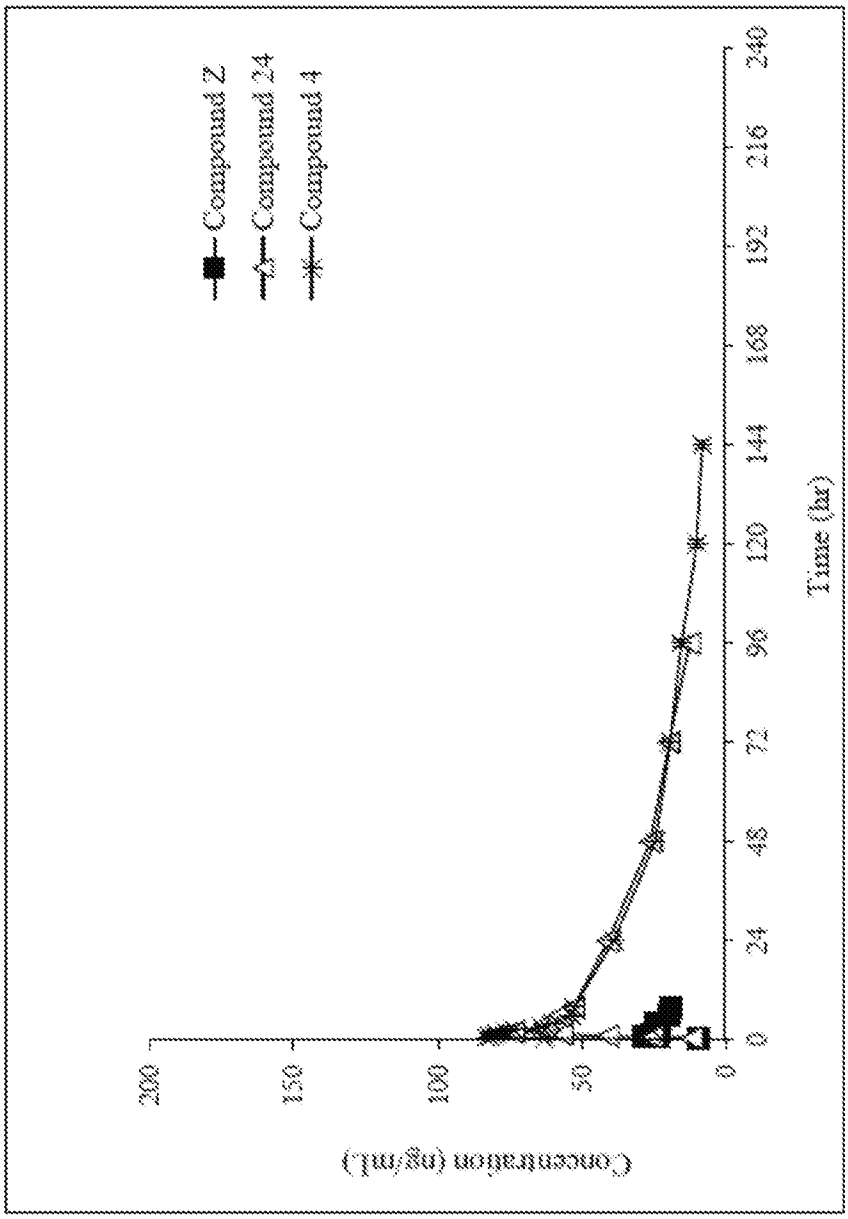

Compound 2
Compound 24
Compound 4
Concentration (ng/mL)
200
150
100
50
0
0
24
48
72
96
120
144
168
192
216
240
Time (hr)

FIG. 1

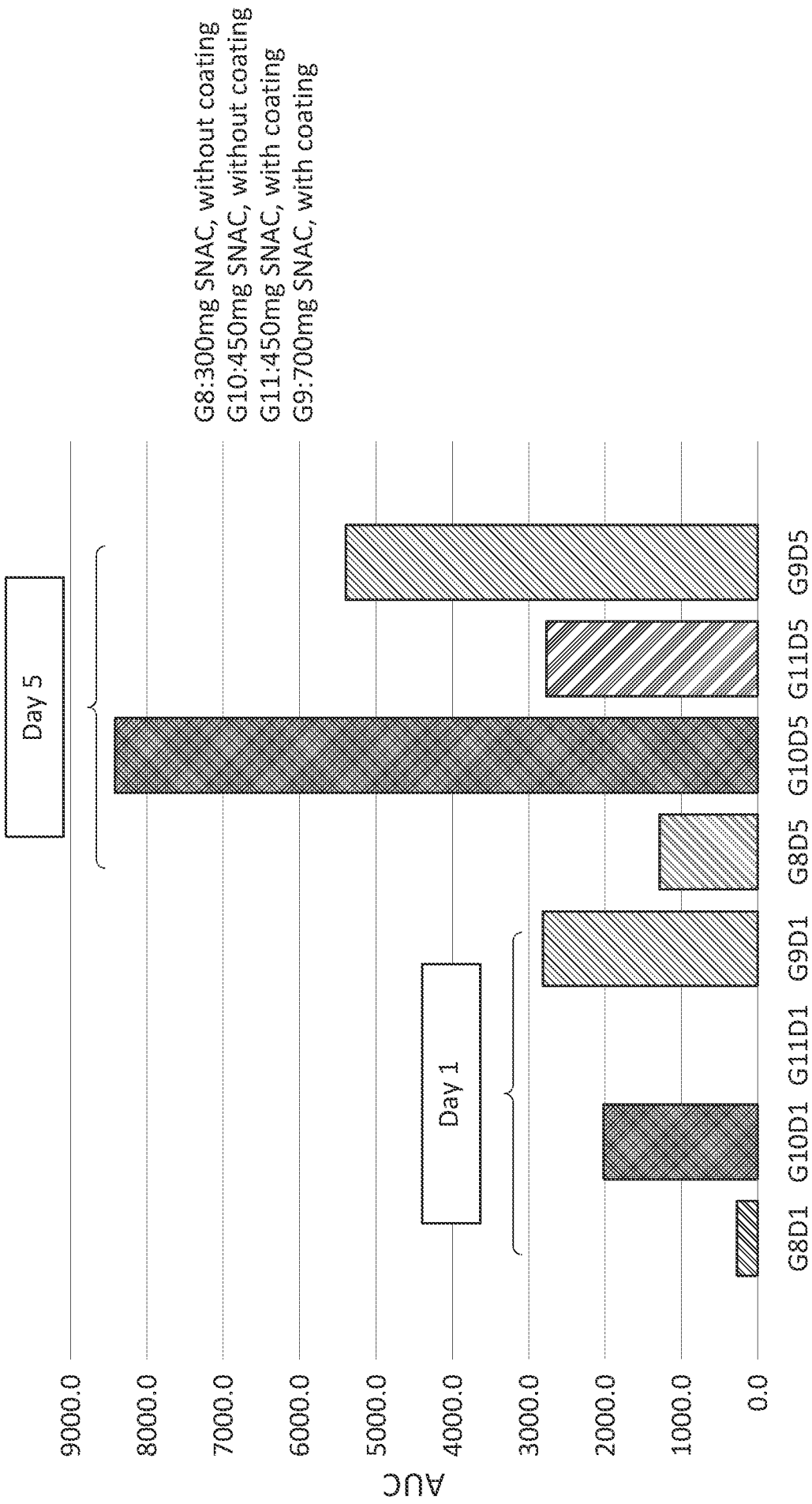

G8:300mg SNAC, without coating
G10:450mg SNAC, without coating
G11:450mg SNAC, with coating
G9:700mg SNAC, with coating
Day 5
Day 1
AUC
9000.0
8000.0
7000.0
6000.0
5000.0
4000.0
3000.0
2000.0
1000.0
0.0
G8D1
G10D1
G11D1
G9D1
G8D5
G10D5
G11D5
G9D5

FIG. 2

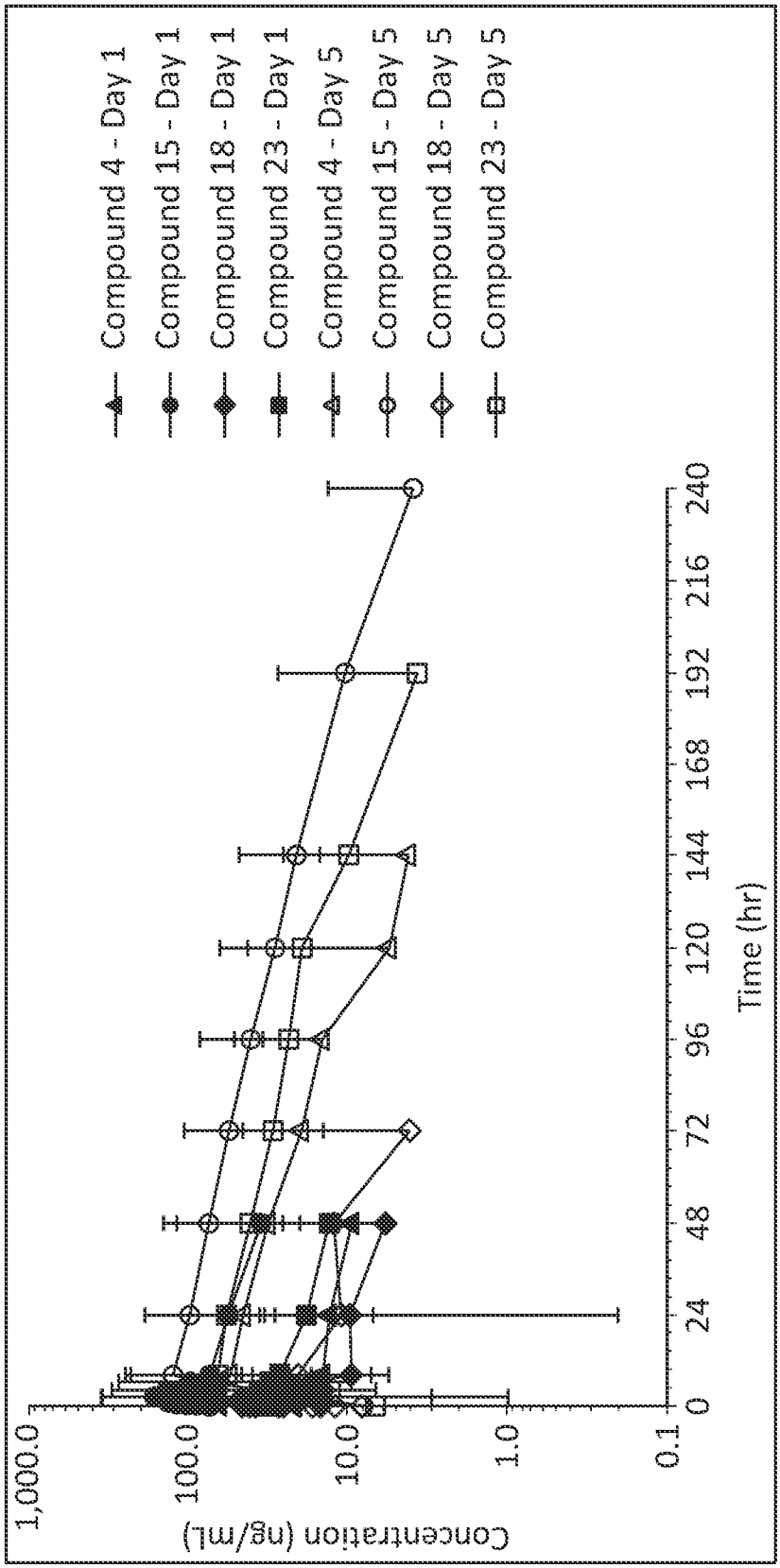

Compound 4 - Day 1
Compound 15 - Day 1
Compound 18 - Day 1
Compound 23 - Day 1
Compound 4 - Day 5
Compound 15 - Day 5
Compound 18 - Day 5
Compound 23 - Day 5
Concentration (ng/mL)
1,000.0
100.0
10.0
1.0
0.1
Time (hr)
0
24
48
72
96
120
144
168
192
216
240

FIG. 3

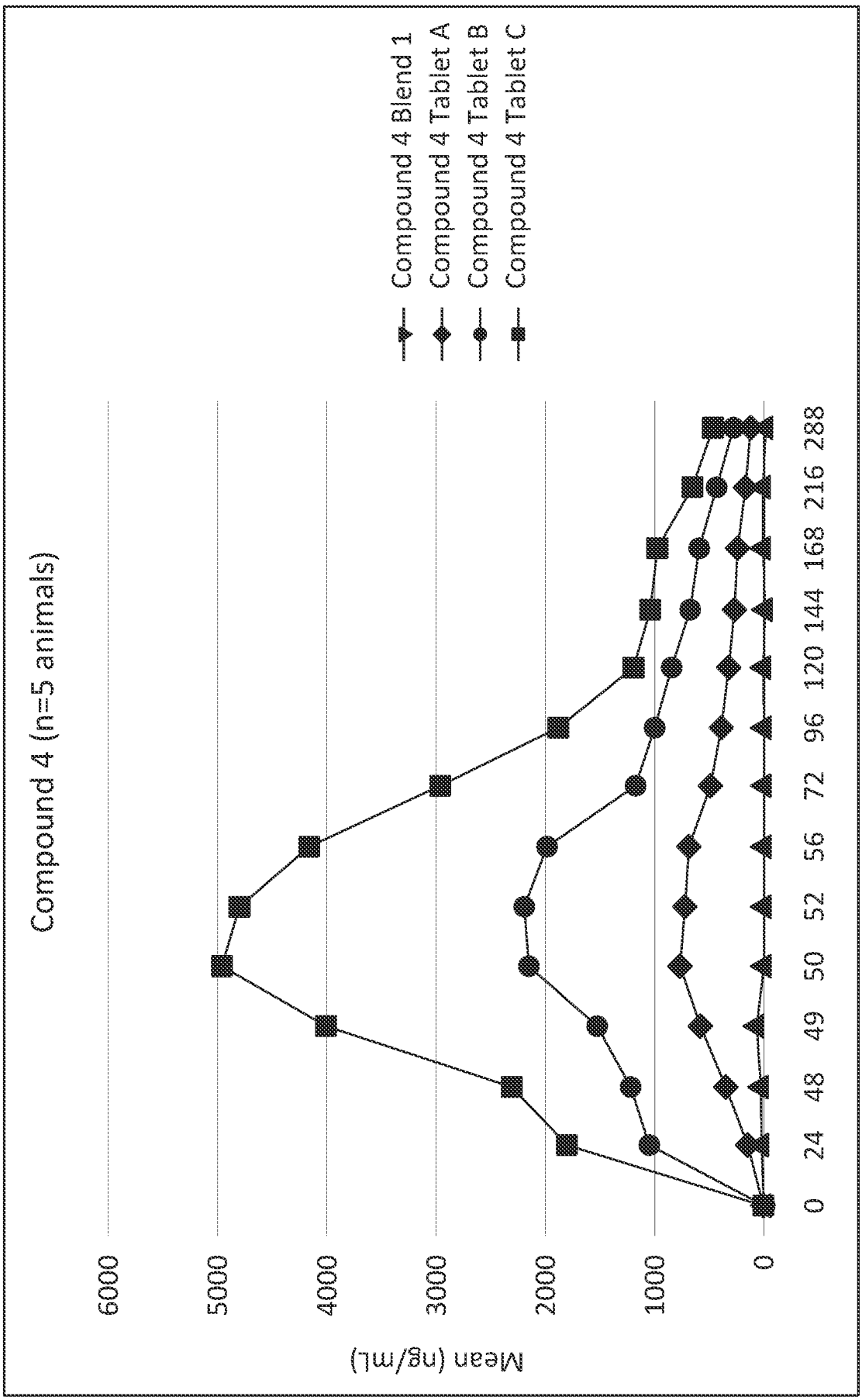

Compound 4 (n=5 animals)
Mean (ng/mL)
6000
5000
4000
3000
2000
1000
0
0 24 48 49 50 52 56 72 96 120 144 168 216 288
Compound 4 Blend 1
Compound 4 Tablet A
Compound 4 Tablet B
Compound 4 Tablet C

FIG. 4

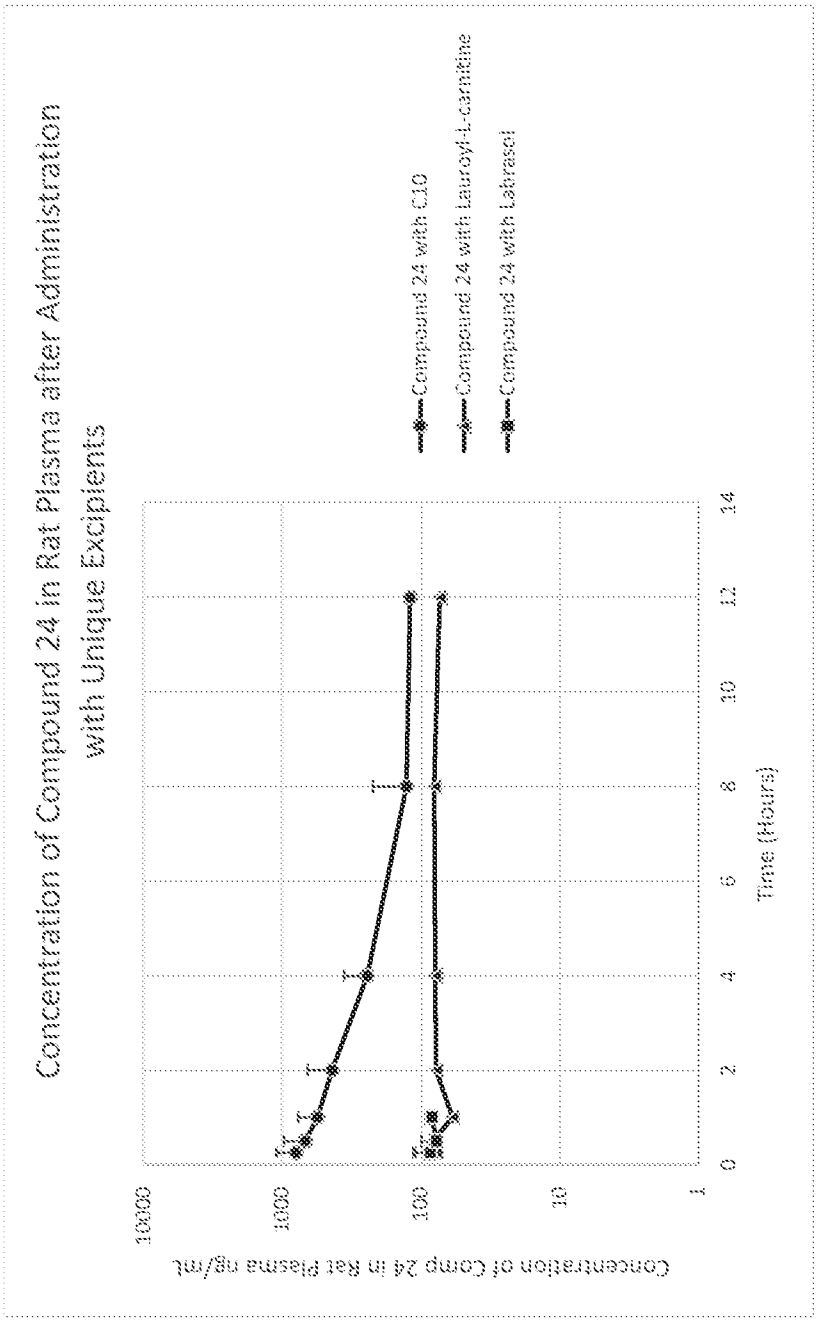

Concentration of Compound 24 in Rat Plasma after Administration with Unique Excipients
Compound 24 with C10
Compound 24 with Lauroyl-L-carnitine
Compound 24 with Labrasol
Concentration of Comp 24 in Rat Plasma ng/mL
10000
1000
100
10
1
0
2
4
6
8
10
12
14
Time (Hours)

FIG. 5A

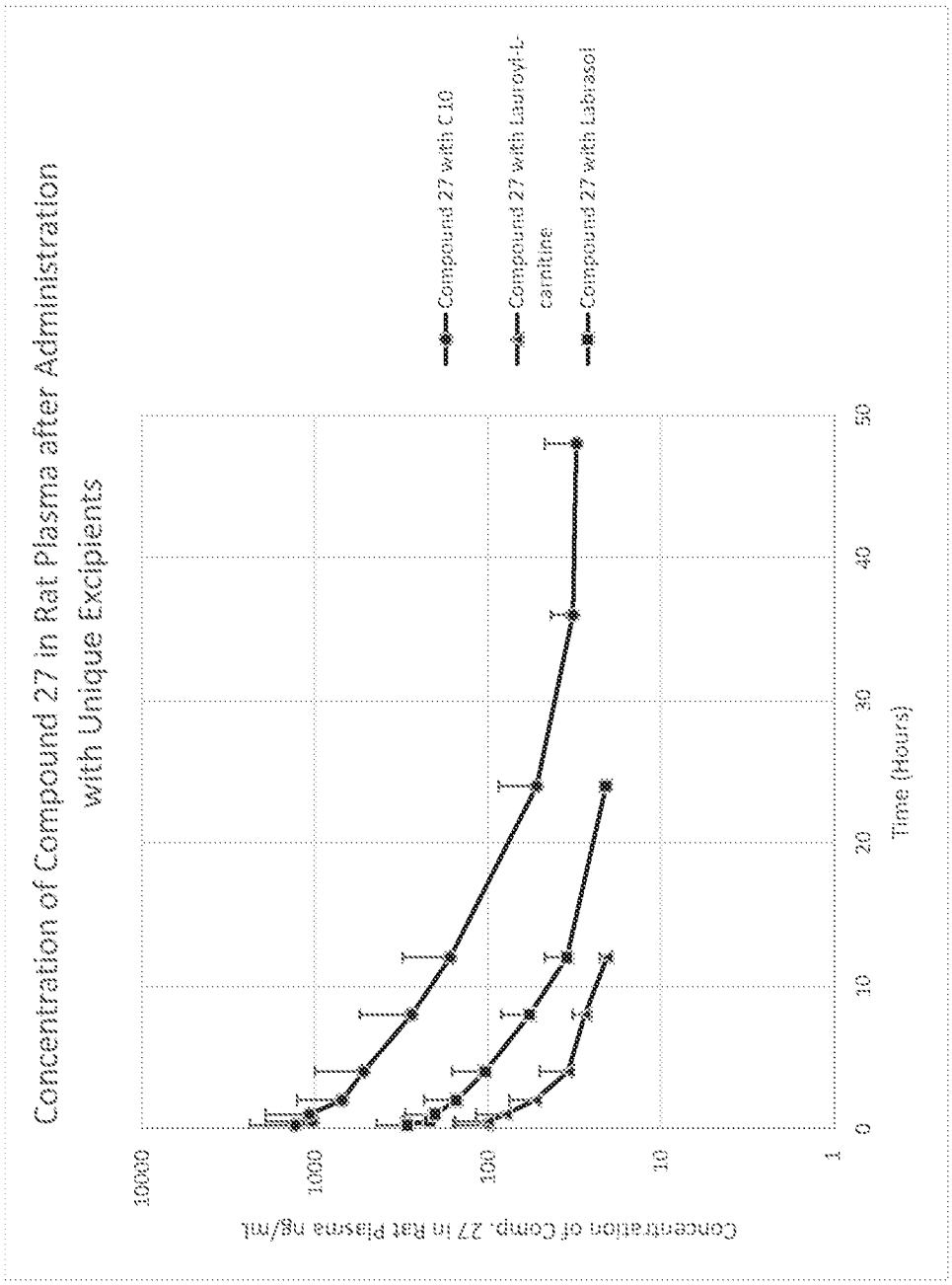

Concentration of Compound 27 in Rat Plasma after Administration with Unique Excipients
Compound 27 with C10
Compound 27 with Lauroyl-L-carnitine
Compound 27 with Labrasol
Concentration of Comp. 27 in Rat Plasma ng/mL
10000
1000
100
10
1
0
10
20
30
40
50
Time (Hours)

FIG. 5B

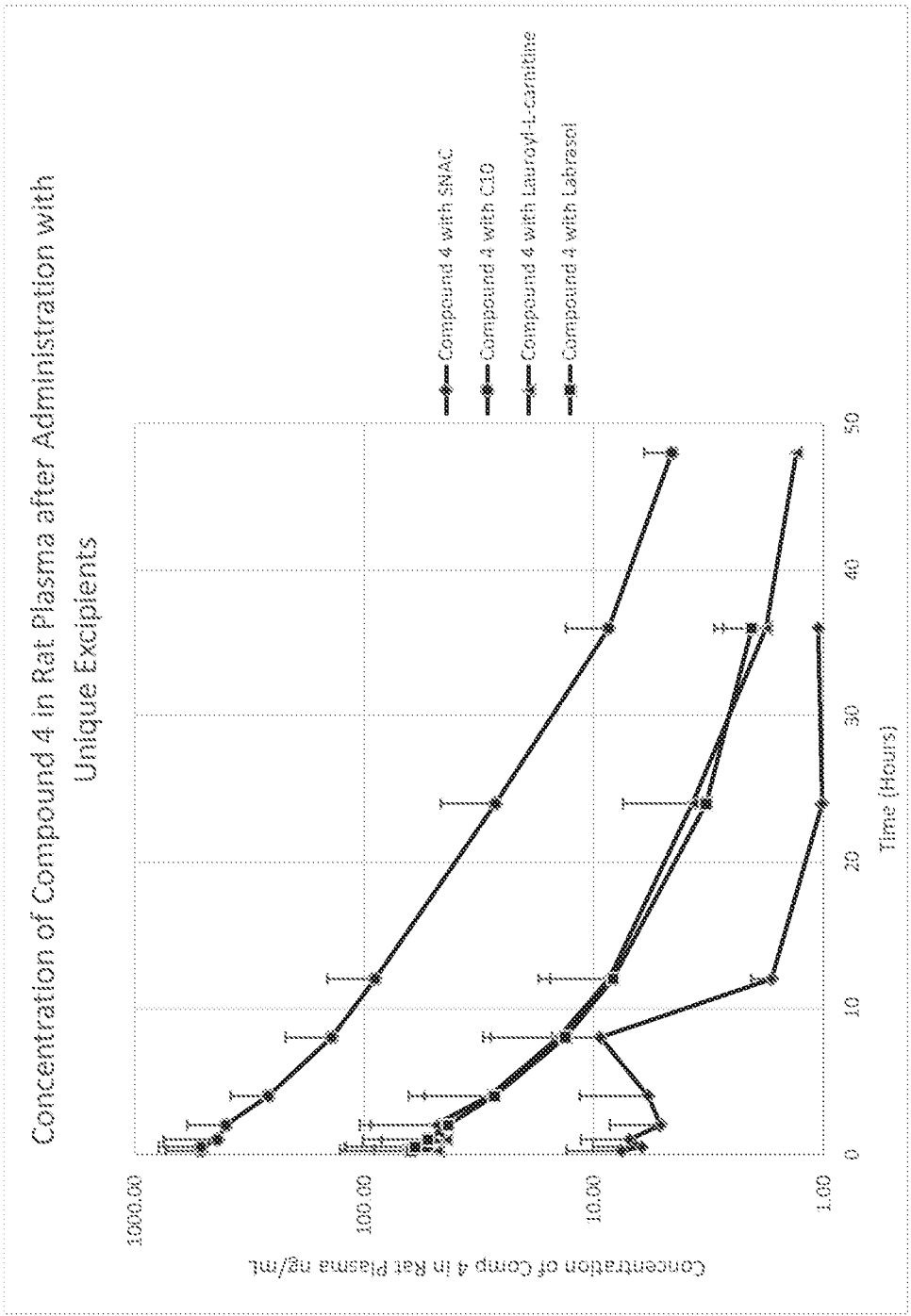

Concentration of Compound 4 in Rat Plasma after Administration with Unique Excipients
Compound 4 with SNAC
Compound 4 with C10
Compound 4 with Lauroyl-L-carnitine
Compound 4 with Labrasol
Concentration of Comp 4 in Rat Plasma ng/mL
1000.00
100.00
10.00
1.00
0
10
20
30
40
50
Time (Hours)

FIG. 5C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019883

A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/26 (2006.01) A61K 9/00 (2006.01) A61K 9/20 (2006.01) A61K 47/12 (2006.01) A61K 47/18 (2017.01) A61K 47/32 (2006.01) A61K 47/38 (2006.01) A61P 1/16 (2006.01) A61P 3/10 (2006.01) A61P 13/12 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

STN Registry Caplus Sub Structure Search based on formula (I), (I-a), (I-b), (I-c), (II), (II-a), (II-b), (III), (III-a), (III-b), or (III-c) and Google Scholar Keyword Search GLP-1 and permeability enhancer and like terms. Applicant and Inventors Search in external databases and internal databases provided by IP Australia: asn=(VIKING NEAR THERAPEUTICS NEAR INC.) AND inn=((LIAN NEAR Brian) OR (BARKER NEAR Geoffrey NEAR E.) OR (BARNES NEAR Maureen) OR (YAGIZ NEAR Kader) OR (GONZALEZ NEAR Jake))

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2024	17 June 2024

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Ricky Fung AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6222 3648

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2024/019883**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pechenov, S., et al, 2021. Development of an orally delivered GLP-1 receptor agonist through peptide engineering and drug delivery to treat chronic disease. Scientific reports, 11(1), p.22521. See whole document especially third paragraph on page 6, table 3 on page 8 and 4th paragraph on page 12	1, 88-106, 109, 110, 117-132.
X	WO 2016/111971 A1 (ELI LILLY AND COMPANY) 14 July 2016 See whole document especially SEQ ID. NO. 3 (claim 12) see lines 3-12 on page 9, lines 4-11 on page 27 and lines 13-17 on page 8	1-3, 22-51, 88-110, 117, 120-132
A	WO 2019/245893 A3 (ELI LILLY AND COMPANY) 26 December 2019 See abstract, compound CAS RN 2023788-19-2 refer to on line 13-20	1-132
A	Knudsen, L.B. and Lau, J., 2019. The discovery and development of liraglutide and semaglutide. Frontiers in endocrinology, 10, p.440904. See whole document	1-132
A	Ismail, R., et al. 2019. Encapsulation in polymeric nanoparticles enhances the enzymatic stability and the permeability of the GLP-1 analog, liraglutide, across a culture model of intestinal permeability. Pharmaceutics, 11(11), p.599. See whole document especially abstract	1-132
A	Maher, S. and Brayden, D.J., 2012. Overcoming poor permeability: translating permeation enhancers for oral peptide delivery. Drug Discovery Today: Technologies, 9(2), pp.e113-e119. See whole document especially abstract	1-132
A	Aroda, V.R., Blonde, L. and Pratley, R.E., 2022. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. Reviews in Endocrine and Metabolic Disorders, 23(5), pp.979-994. See whole document especially section 5.2 last paragraph of the left had column on page 984	1-132

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/019883

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **133 -135**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See Supplemental Box

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of **Box II**

The claims do not comply with Rule 6.2(a) because they rely on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2024/019883**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2016/111971 A1	14 July 2016	WO 2016111971 A1	14 Jul 2016
		AR 103242 A1	26 Apr 2017
		AU 2016205435 A1	08 Jun 2017
		AU 2016205435 B2	29 Mar 2018
		BR 112017010596 A2	06 Mar 2018
		CA 2973352 A1	14 Jul 2016
		CL 2017001760 A1	16 Mar 2018
		CN 107207576 A	26 Sep 2017
		CN 107207576 B	24 Nov 2020
		CN 112608377 A	06 Apr 2021
		CN 112608377 B	13 Feb 2024
		CO 2017006737 A2	29 Sep 2017
		CR 20170310 A	17 Aug 2017
		DO P2017000153 A	15 Jul 2017
		EA 201791281 A1	30 Nov 2017
		EA 031591 B1	31 Jan 2019
		EA 201892057 A1	28 Feb 2019
		EA 035055 B1	22 Apr 2020
		EA 202090392 A2	31 May 2020
		EC SP17043648 A	30 Nov 2017
		EP 3242887 A1	15 Nov 2017
		EP 3242887 B1	14 Aug 2019
		EP 3597662 A1	22 Jan 2020
		IL 252499 B	31 Aug 2020
		IL 276492 A	30 Sep 2020
		IL 276492 B	29 Apr 2021
		IL 281545 A	31 May 2021
		JO 3575 B1	05 Jul 2020
		JO P20200119 A1	16 Jun 2017
		JP 2017507124 A	16 Mar 2017
		JP 6219534 B2	25 Oct 2017
		JP 2018052933 A	05 Apr 2018
		JP 6545766 B2	17 Jul 2019
		JP 2019203000 A	28 Nov 2019

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2024/019883**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		JP 6754867 B2	16 Sep 2020
		KR 20170092661 A	11 Aug 2017
		KR 101957620 B1	13 Mar 2019
		KR 20190026967 A	13 Mar 2019
		KR 102330764 B1	25 Nov 2021
		KR 20210145311 A	01 Dec 2021
		KR 20230023822 A	17 Feb 2023
		MA 41315 A	15 Nov 2017
		MA 41315 B1	29 Nov 2019
		MA 50422 A	26 Aug 2020
		ME 03494 B	20 Jan 2020
		MX 2017008927 A	11 Oct 2017
		MX 2021005835 A	15 Jul 2021
		MY 193616 A	20 Oct 2022
		NZ 732000 A	30 Nov 2018
		NZ 748274 A	25 Mar 2022
		PE 20170954 A1	13 Jul 2017
		PH 12017501252 A1	30 Oct 2017
		RS 59146 B1	30 Sep 2019
		SG 11201705603Y A	30 Aug 2017
		SV 2017005453 A	27 Aug 2018
		TN 2017000198 A1	19 Oct 2018
		TW 201636362 A	16 Oct 2016
		TW I582109 B	11 May 2017
		US 2016199438 A1	14 Jul 2016
		US 9474780 B2	25 Oct 2016
		ZA 201703930 B	26 Jun 2019
WO 2019/245893 A3	26 December 2019	WO 2019245893 A2	26 Dec 2019
		AR 115542 A1	27 Jan 2021
		AU 2019289110 A1	21 Jan 2021
		AU 2019289110 B2	06 Oct 2022
		AU 2022279524 A1	02 Feb 2023
		BR 112020023452 A2	23 Feb 2021
		CA 3103469 A1	26 Dec 2019
		CL 2020003359 A1	25 Jun 2021

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2024/019883**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		CN 112312926 A	02 Feb 2021
		CR 20200634 A	21 Jan 2021
		EA 202092713 A1	05 Apr 2021
		EC SP20082717 A	29 Jan 2021
		EP 3810201 A2	28 Apr 2021
		EP 3810201 B1	07 Jun 2023
		EP 4257185 A2	11 Oct 2023
		IL 279504 A	31 Jan 2021
		IL 279504 B	01 Sep 2022
		IL 295433 A	01 Oct 2022
		IL 295433 B1	01 Nov 2023
		IL 295433 B2	01 Mar 2024
		JO P20200335 A1	20 Dec 2020
		JP 2021167314 A	21 Oct 2021
		JP 7413315 B2	15 Jan 2024
		JP 2021506952 A	22 Feb 2021
		JP 6896945 B2	30 Jun 2021
		JP 2024041808 A	27 Mar 2024
		KR 20210010572 A	27 Jan 2021
		KR 102523489 B1	21 Apr 2023
		KR 20230058172 A	02 May 2023
		KR 20240060873 A	08 May 2024
		MA 52965 A	28 Apr 2021
		MA 52965 B1	31 Aug 2023
		MX 2020013727 A	02 Mar 2021
		PE 20210049 A1	08 Jan 2021
		PH 12020552215 A1	28 Jun 2021
		RS 64288 B1	31 Jul 2023
		SG 11202012744U A	28 Jan 2021
		TW 202015717 A	01 May 2020
		TW I705820 B	01 Oct 2020
		US 2019388502 A1	26 Dec 2019
		US 11357820 B2	14 Jun 2022
		US 2022273762 A1	01 Sep 2022
		US 11918623 B2	05 Mar 2024

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2024/019883**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.