

AMYLIN ANALOGS

INCOPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6, including U.S. Provisional Application No. 63/624,205, filed January 23, 2024.

REFERENCE TO 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 VIKNG029WO SEQ LIST.xml created on January 10, 2025, which is approximately 28,775 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 invention relates generally to the fields of chemistry and medicine. More specifically, the present disclosure relates to pharmaceutical formulations for the treatment of metabolic disorders and fatty liver diseases.

Description of the Related Art

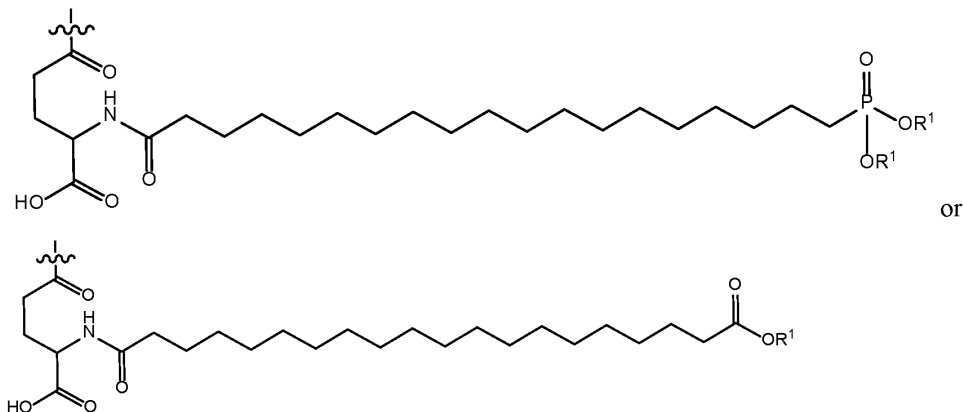
[0004] Amylin receptor agonism has produced significant interest as a potential candidate for promoting weight reduction and improved glucose control. Human amylin, (islet amyloid polypeptide (IAPP)), promotes glycemic regulation by slowing gastric emptying, and controlling food intake, facilitating control of blood glucose levels following meals. However, endogenous amylin is prone to fibril formation and has a half-life of only about 13 minutes, making it unsuitable for use as a therapeutic agent. Pramlintide (Symlin[®]) was developed as a synthetic analogue of human amylin, introducing proline substitutions at residues 25, 28, and

29. Pramlintide is approved for the treatment of diabetes, but with a half-life of approximately 48 minutes, pramlintide requires frequent subcutaneous injections up to four times a day and has been reported to cause nausea, vomiting, and/or diarrhea. Clinical trials 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. Pramlintide also precipitates above pH 5.5 and is therefore unsuitable for coformulation with insulin. Additionally, pramlintide only has a modest effect on body weight loss compared to GLP-1 receptor agonists. Therefore, a need exists for novel amylin analogues that can be used as agonist compounds to treat obesity, diabetes and other metabolic disorders without dose limiting side effects.

SUMMARY

[0005] Disclosed herein are polypeptides, and pharmaceutically acceptable salts thereof, that are effective as amylin analogs. Such polypeptides can have the general formula of Formula (I):

Ac-K-C-N-T-A-T-C-A-T-Q-R-L-A-X¹-F-L-X²-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂ (I) (SEQ ID NO: 1), or a pharmaceutically acceptable salt thereof, wherein: Ac is a lipidated isoglutamic acid residue having the structure:



X¹ can be a naturally occurring amino acid or an unnatural amino acid selected from aspartate (D), glutamate (E), glutamine (Q), arginine (R), phosphoaspartate (Dp) and phosphoglutamate (Ep);

X² can be a naturally occurring amino acid or an unnatural amino acid selected from lysine (K), glutamine (Q), tyrosine (Y), homohistidine (hH), aspartate (D) and glutamate (E); and each R¹ can independently be hydrogen, C₆₋₁₀ aryl or C₇₋₁₁ arylalkyl.

[0006] Some embodiments include a pharmaceutical composition comprising a polypeptide of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0007] Some embodiments include a method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes comprising administering a therapeutically effective amount of a polypeptide of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0008] Other embodiments include a method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes in a subject, comprising administering a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to a subject in need thereof, wherein the metabolic disorder or metabolic syndrome can be atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, prader-willi syndrome, or any combination thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 illustrates the effect of the compounds of the present disclosure on mean body weight change.

[0010] FIG. 2 illustrates the effects of the compounds of the present disclosure on percent body weight change after 14 days.

[0011] FIG. 3 illustrates the effects of the compounds of the present disclosure on blood glucose levels.

[0012] FIG. 4 illustrates the body weight ratio in monkeys at day 5 compared to day 0 following a single subcutaneous administration of Compound 10.

[0013] FIG. 5 illustrates the accumulated food intake in monkeys following the single subcutaneous administration of Compound 10.

[0014] FIG. 6 illustrates the body weight ratio in monkeys at day 5 compared to day 0 following a single subcutaneous administration of Compound 4.

[0015] FIG. 7 illustrates the accumulated food intake in monkeys following the single subcutaneous administration of Compound 4.

[0016] FIG. 8 illustrates the body weight ratio in monkeys at day 5 compared to day 0 following a single subcutaneous administration of Compound 6.

[0017] FIG. 9 illustrates the accumulated food intake in monkeys following the single subcutaneous administration of Compound 6.

DETAILED DESCRIPTION

Definitions

[0018] 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.

[0019] “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.

[0020] 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).

[0021] 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 “C₁ to C₄ alkyl” or “C₁₋₄ alkyl” group refers to all alkyl groups having from 1 to 4 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)- and (CH₃)₃C-.

[0022] 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 “C₁₋₄ alkyl” or similar designations. By way of example only, “C₁₋₄ 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, isopropyl, 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.

[0023] 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.

[0024] 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 “C₆₋₁₀ aryl,” “C₆ or C₁₀ aryl,” or similar designations. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, azulenyl, and anthracenyl.

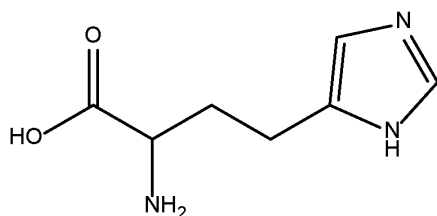
[0025] An “aralkyl” or “arylalkyl” is an aryl group connected, as a substituent, via an alkylene group, such as “C₇₋₁₄ aralkyl” and the like, including but not limited to benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group (i.e., a C₁₋₄ alkylene group).

[0026] An “amino” group refers to a “-NR_AR_B” group in which R_A and R_B are each independently selected from hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ carbocyclyl, C₆₋₁₀ aryl, 5-10 membered heteroaryl, and 5-10 membered heterocyclyl, as defined herein.

[0027] An “aminoalkyl” group refers to an amino group connected via an alkylene group.

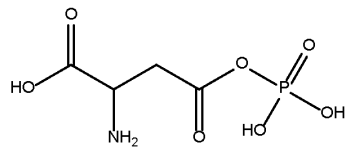
[0028] As used herein, a “natural amino acid side chain” refers to the side-chain substituent of a naturally occurring amino acid. Naturally occurring amino acids have a substituent attached to the α -carbon. Naturally occurring amino acids include Arginine, Lysine, Aspartic acid, Glutamic acid, Glutamine, Asparagine, Histidine, Serine, Threonine, Tyrosine, Cysteine, Methionine, Tryptophan, Alanine, Isoleucine, Leucine, Phenylalanine, Valine, Proline, and Glycine.

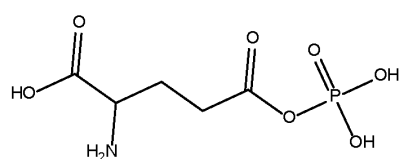
[0029] As used herein, a “non-natural amino acid side chain” refers to the side-chain substituent of a non-naturally occurring amino acid. Non-natural amino acids include β -amino acids (β^3 and β^2), Homo-amino acids, such as homohistidine (hH),



, Proline and Pyruvic acid derivatives, 3-substituted

Alanine derivatives, Glycine derivatives, Ring-substituted Phenylalanine and Tyrosine Derivatives, Linear core amino acids and N-methyl amino acids. Exemplary non-natural amino acids are available from Sigma-Aldrich, listed under “unnatural amino acids & derivatives.” Non-natural amino acids may also include, but are not limited to, phosphorylated derivatives,

such as phosphoaspartate (Dp), , and phosphoglutamate (Ep),



. See also, Travis S. Young and Peter G. Schultz, “Beyond the Canonical 20 Amino Acids: Expanding the Genetic Lexicon,” J. Biol. Chem. 2010 285: 11039-11044, which is incorporated by reference in its entirety.

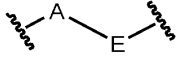
[0030] As used herein, a substituted group is derived from the unsubstituted parent group in which there has been an exchange of one or more hydrogen atoms for another atom or group. Unless otherwise indicated, when a group is deemed to be “substituted,” it is meant that the group is substituted with one or more substituents independently selected from C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, C₁-C₆ heteroalkyl, C₃-C₇ carbocyclyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), C₃-C₇-carbocyclyl-C₁-C₆-alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heterocyclyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heterocyclyl-C₁-C₆-alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), aryl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), aryl(C₁-C₆)alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heteroaryl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), 5-10 membered heteroaryl(C₁-C₆)alkyl (optionally substituted with halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkoxy), halo, cyano, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkoxy(C₁-C₆)alkyl (i.e., ether), aryloxy, sulfhydryl (mercapto), halo(C₁-C₆)alkyl (e.g., -CF₃), halo(C₁-C₆)alkoxy (e.g., -OCF₃), C₁-C₆ alkylthio, arylthio, amino,

amino(C₁-C₆)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.

[0031] In some embodiments, substituted group(s) is (are) substituted with one or more substituent(s) individually and independently selected from C₁-C₄ alkyl, amino, hydroxy, and halogen.

[0032] 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 $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, and the like. Other radical naming conventions clearly indicate that the radical is a di-radical such as “alkylene” or “alkenylene.”

[0033] 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 $-\text{AE}-$ 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.

[0034] 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.

[0035] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use

in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0036] "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.

[0037] 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).

[0038] "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.

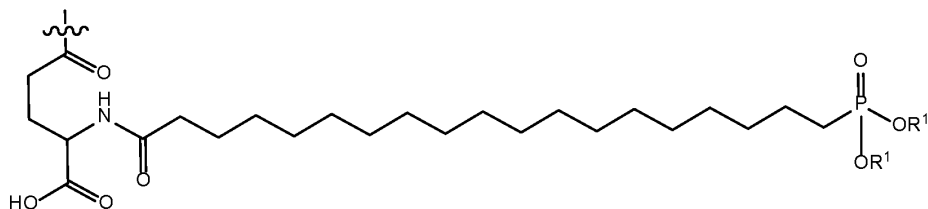
Compounds

[0039] Various embodiments of these compounds include compounds having the structure of Formula (I) as described herein or pharmaceutically acceptable salts thereof. The structure of Formula (I) encompasses all stereoisomers and racemic mixtures, including the following structure and mixtures thereof:

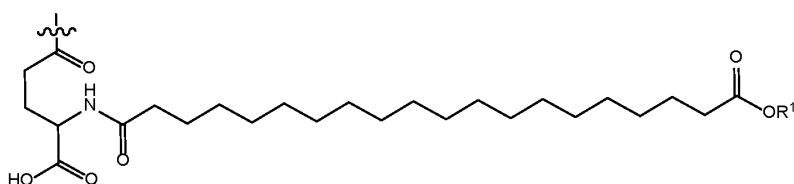
Ac-K-C-N-T-A-T-C-A-T-Q-R-L-A-X¹-F-L-X²-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂ (SEQ ID NO: 1)

(I)

or a pharmaceutically acceptable salt thereof. In Formula (I) and the compounds described herein, “Ac” represents a lipidated isoglutamic acid residue at the N-terminus having the structure:



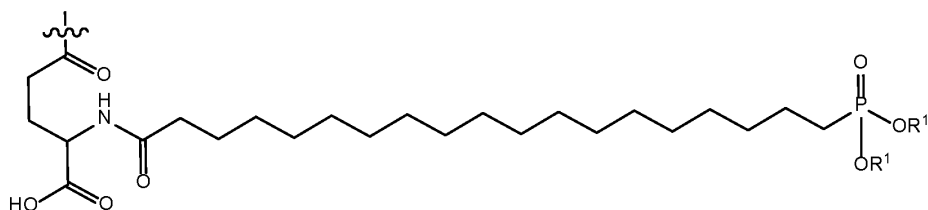
or



, wherein each R^1 can independently be hydrogen, C_{6-10} aryl or C_{7-11} arylalkyl. In some embodiments, R^1 can be H. In other embodiments, R^1 can be a C_{6-10} aryl, such as benzyl. In still other embodiments, R^1 can be a C_{7-11} arylalkyl. In Formula (I) and the compounds described herein “-NH₂” represents an amino group forming a C-terminal amide.

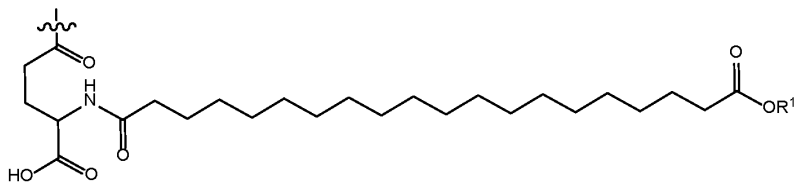
[0040] In some embodiments of compounds of Formula (I), X^1 can be a naturally occurring amino acid or an unnatural amino acid. In some embodiments, X^1 can be selected from aspartate (D), glutamate (E), glutamine (Q), arginine (R), phosphoaspartate (Dp) or phosphoglutamate (Ep). In some embodiments of compounds of Formula (I), X^2 can be a naturally occurring amino acid or an unnatural amino acid. In some embodiments, X^2 can be selected from lysine (K), glutamine (Q), tyrosine (Y), homohistidine (hH), aspartate (D), and glutamate (E).

[0041] In some embodiments, Ac can be



and each

R¹ can be benzyl. In other embodiments, R¹ can be H. In still other embodiments, Ac can be



and R¹ can be H.

[0042] In some embodiments of compounds of Formula (I), at least one of X¹ and X² can be glutamine, tyrosine, or homohistidine.

[0043] In some embodiments of compounds of Formula (I), X¹ can be selected from aspartate (D), phosphoaspartate (Dp), glutamine (Q), arginine (R), and phosphoglutamate (Ep).

[0044] In some embodiments of compounds of Formula (I), X¹ can be selected from aspartate (D), phosphoaspartate (Dp), glutamine (Q), and arginine (R).

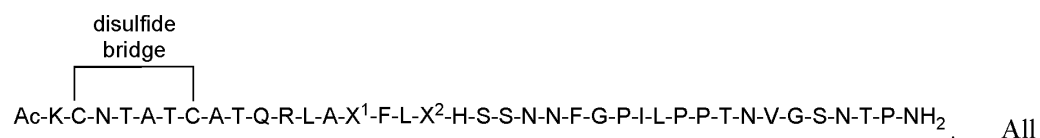
[0045] In some embodiments of compounds of Formula (I), X¹ can be phosphoaspartate (Dp) or phosphoglutamate. (Ep). In some embodiments, X¹ can be phosphoaspartate (Dp). In other embodiments, X¹ can be phosphoglutamate (Ep).

[0046] In some embodiments of compounds of Formula (I), X¹ can be aspartate (D). In other embodiments, X¹ can be glutamine (Q). and X² can be homohistidine (hH).

[0047] In some embodiments of compounds of Formula (I), X² can be tyrosine (Y). In other embodiments, X² can be glutamine (Q). In still other embodiments, X² can be homohistidine (hH).

[0048] In some embodiments of compounds of Formula (I), X¹ can be glutamine (Q) and X² can be tyrosine (Y). In other embodiments of Formula (I), X¹ can be aspartate (D) and X² can be tyrosine (Y). In other embodiments of Formula (I), X¹ can be aspartate (D) and X² can be homohistidine (hH).

[0049] In some embodiments of compounds of Formula (I), a disulfide bridge is formed between two cysteine residues so as to have the following structure:

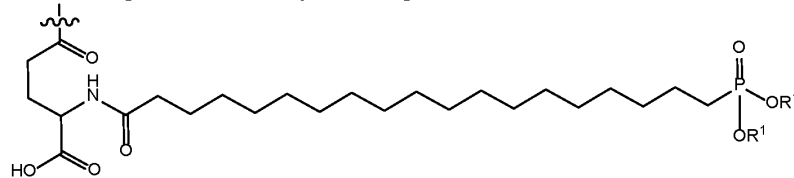


sequences depicted herein are to be understood as encompassing disulfide bridges between cysteine residues as shown above.

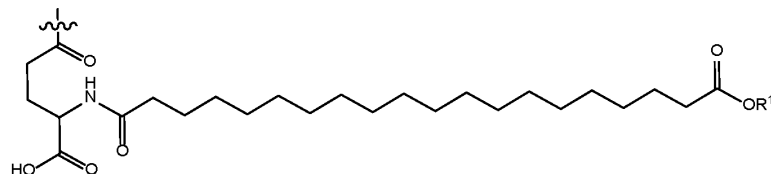
[0050] In some embodiments of compounds of Formula (I), the compound can be selected from the group consisting of:

Compound No.	SEQ ID No.	Sequence
Compound 1	SEQ ID NO. 2	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 2	SEQ ID NO. 3	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 3	SEQ ID NO. 4	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 4	SEQ ID NO. 5	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 5	SEQ ID NO. 6	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 6	SEQ ID NO. 7	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 7	SEQ ID NO. 8	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 8	SEQ ID NO. 9	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-E-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 9	SEQ ID NO. 10	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 10	SEQ ID NO. 11	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 11	SEQ ID NO. 12	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 12	SEQ ID NO. 13	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 13	SEQ ID NO. 14	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-D-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 14	SEQ ID NO. 15	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-R-F-L-E-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 15	SEQ ID NO. 16	Ac ² -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂

or a pharmaceutically acceptable salt thereof, wherein Ac^1 can be



and Ac^2 can be



and each R^1 can be H.

[0051] 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.

[0052] 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.

Methods of Preparation

[0053] The compounds 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.

[0054] In the following schemes, 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)).

[0055] 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.

[0056] 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).

[0057] The methods for making compounds described herein may include constructing a peptide backbone using solid-phase peptide synthesis techniques to provide a resin-bound peptide. 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.

Administration and Pharmaceutical Compositions

[0058] Some embodiments provide a pharmaceutical composition comprising a therapeutically effective amount of at least one of the compounds as described elsewhere in and a pharmaceutically acceptable excipient.

[0059] The compounds are administered at a therapeutically effective dosage. While human dosage levels have yet to be optimized for the compounds described herein, generally, a daily dose may be 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. The amount of active compound administered will, of course, be 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.

[0060] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarily, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0061] The compounds useful as described above can be formulated into pharmaceutical compositions for use in treatment of these conditions. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated by reference in its entirety. Accordingly, some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound described herein (including enantiomers, diastereoisomers, tautomers, polymorphs, and solvates thereof), or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0062] In addition to the selected compound useful as described above, some embodiments include compositions containing a pharmaceutically-acceptable carrier. The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0063] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose;

starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0064] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

[0065] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to an animal, preferably mammal subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. Such dosage forms are contemplated to be administered once, twice, thrice or more per day and may be administered as infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours), or administered as a continuous infusion, and may be given more than once during a course of therapy, though a single administration is not specifically excluded. The skilled artisan will recognize that the formulation does not specifically contemplate the entire course of therapy and such decisions are left for those skilled in the art of treatment rather than formulation.

[0066] The compositions useful as described above may be in any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, subcutaneous, or other parental routes of administration. In some embodiments, the compositions may be in a form suitable for subcutaneous administration. The skilled artisan will appreciate that oral and nasal compositions comprise compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers

well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the inhibitory activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman *et al.*, Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0067] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0068] The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmellose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical, and can be readily made by a person skilled in the art.

[0069] Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0070] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0071] Compositions described herein may optionally include other drug actives.

[0072] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0073] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort should be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid should be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid should either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0074] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions should

preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0075] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0076] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0077] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0078] In a similar vein, an ophthalmically acceptable antioxidant includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0079] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0080] For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0081] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including

but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., *Compendium of Excipients for Parenteral Formulations, 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, both of which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0082] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0083] The actual dose of the active compounds described herein depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

[0084] The compounds and compositions described herein, if desired, may be presented in a pack or dispenser device containing one or more unit dosage forms containing the active ingredient. Such a pack or device may, for example, comprise metal or plastic foil, such as a blister pack, or glass, and rubber stoppers such as in vials. The pack or dispenser device may be accompanied by instructions for administration. Compounds and compositions

described herein are formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0085] The amount of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt %) basis, from about 0.01-99.99 wt % of a compound of the present technology based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. Preferably, the compound is present at a level of about 1-80 wt %. Representative pharmaceutical formulations are described below.

Methods of Treatment

[0086] Some embodiments provide pharmaceutical compositions comprising one or more compounds disclosed herein and a pharmaceutically acceptable excipient.

[0087] Some embodiments provide a method of preventing, treating, or ameliorating one or more metabolic disorders or metabolic syndromes in a subject. In some embodiments, the method includes administering one or more of the compounds disclosed herein to a subject in need thereof. In some embodiments, the method includes administering a pharmaceutically acceptable salt thereof of one or more of the compounds disclosed herein to a subject in need thereof.

[0088] In some embodiments, the one or more metabolic disorders or syndromes can be atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, or prader-willi syndrome. In some embodiments, the method includes administering one or more of the compounds disclosed herein to a subject in need thereof. In some embodiments, the method includes administering a pharmaceutically acceptable salt thereof of one or more of the compounds disclosed herein to a subject in need thereof.

[0089] Some embodiments provide a method of preventing, treating, or ameliorating type 2 diabetes mellitus that includes administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the method includes co-administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, with an additional medicament selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase

4 inhibitors, and sodium glucose co-transporters for use in the treatment of type 2 diabetes mellitus.

[0090] Some embodiments provide a method for glycemic control in subjects with type 2 diabetes mellitus, optionally as an adjunct to diet and exercise, that includes administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0091] Some embodiments provide a method for acute weight management (for example, in subjects with type 2 diabetes mellitus), optionally as an adjunct to a reduced-calorie diet and increased physical activity, that includes administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0092] Some embodiments provide a method for chronic weight management (for example, in subjects with type 2 diabetes mellitus), optionally as an adjunct to a reduced-calorie diet and increased physical activity, that includes administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0093] Some embodiments provide a method for chronic weight management in subjects with type 2 diabetes mellitus and an initial body mass index >27, optionally as an adjunct to a reduced-calorie diet and increased physical activity, that includes administering one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0094] Some embodiments provide a method for the manufacture of a medicament for the treatment of type 2 diabetes mellitus from one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof. Some embodiments provide a method for the manufacture of a medicament for the treatment of type 2 diabetes mellitus from one or more of the compounds disclosed herein, or a pharmaceutically acceptable salt thereof with an additional medicament selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters for use in the treatment of type 2 diabetes mellitus.

[0095] Some embodiments include co-administering a compound, composition, and/or pharmaceutical composition 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.

[0096] To further illustrate this invention, the following examples are included. The examples should not, of course, be construed as specifically limiting the invention. 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 invention 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 invention without exhaustive examples. The following examples will further describe the present invention, and are used for the purposes of illustration only, and should not be considered as limiting.

EXAMPLES

General Procedures

[0097] 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.

[0098] 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 invention were used without further purification unless otherwise specified.

[0099] 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.

[0100] 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.

[0101] Trademarks used herein are examples only and reflect illustrative materials used at the time of the invention. 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 invention.

[0102] The following abbreviations have the indicated meanings:

Bn = benzyl

Boc = *tert*-butoxycarbonyl

DBAD = di-*tert*-butyl azodicarboxylate

DMAP = (4-dimethylamino)pyridine

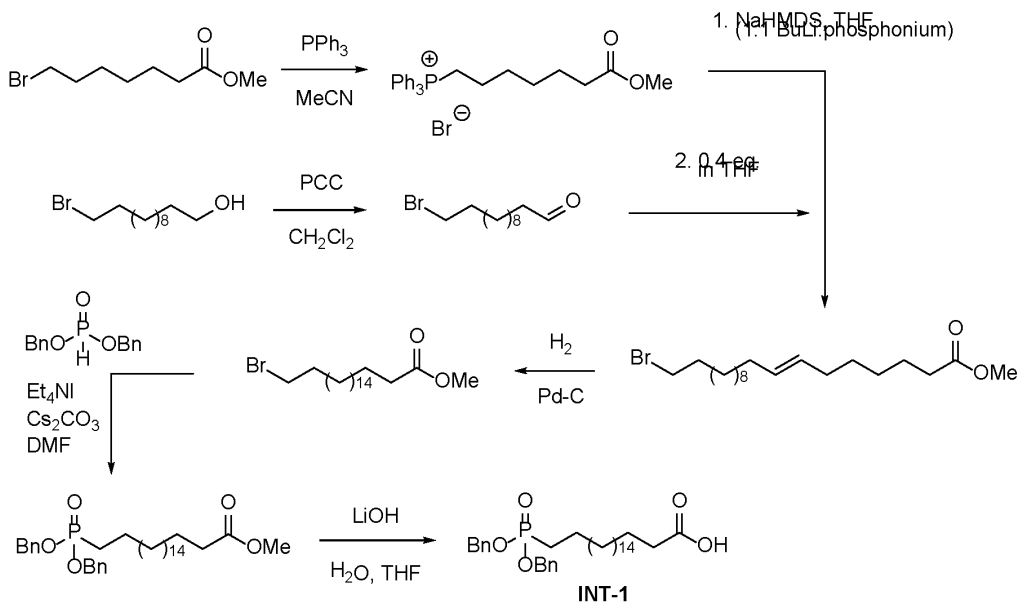
DMF = dimethylformamide
EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et = ethyl
Fmoc = fluorenylmethoxycarbonyl
Fmoc-Osu = N-(9-fluorenylmethoxycarbonyloxy)succinimide
HATU = hexafluorophosphate azabenzotriazole tetramethyl uranium
HBTU = hexafluorophosphate benzotriazole tetramethyl uranium
Me = methyl
NaHMDS = sodium hexamethyldisilazide
NBS = *N*-bromosuccinimide
NMR = nuclear magnetic resonance
PCC = pyridinium chlorochromate
Ph = phenyl
PTSA = *p*-Toluenesulfonic acid
RT = room temperature
TBAI = triisobutyl aluminum
TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)-oxyl
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TMS = trimethylsilyl

[0103] The following example schemes are provided for the guidance of the reader, and collectively represent an example method for making the compounds provided 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.

Example 1: Synthesis of Phosphonate Lipid Ester Intermediate

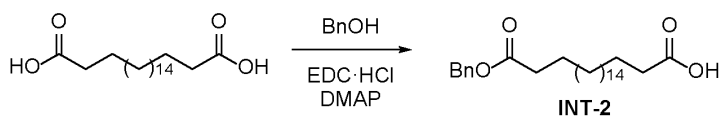
[0104] Methyl 7-bromoheptanoate was reacted with triphenylphosphine to form the corresponding phosphonium bromide salt. The thoroughly dried salt was treated with one equivalent of NaHMDS to make an ylide, which was reacted immediately in a Wittig reaction with the aldehyde from PCC oxidation of 12-bromo-1-dodecanol. The resulting alkene was purified by silica gel chromatography to give a pale yellow oil. The alkene was hydrogenated, and the bromoester could be triturated 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 $\text{DMSO}-d_6$.



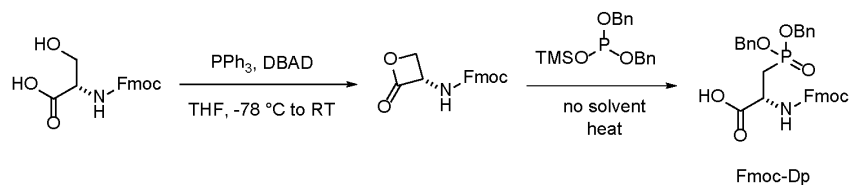
Example 2: Synthesis of Carboxylate Lipid Ester Intermediate

[0105] Docosanedioic acid was coupled to benzyl alcohol with EDC HCl and DMAP in THF to give **INT-2** as the desired monobenzyl carboxylate ester.



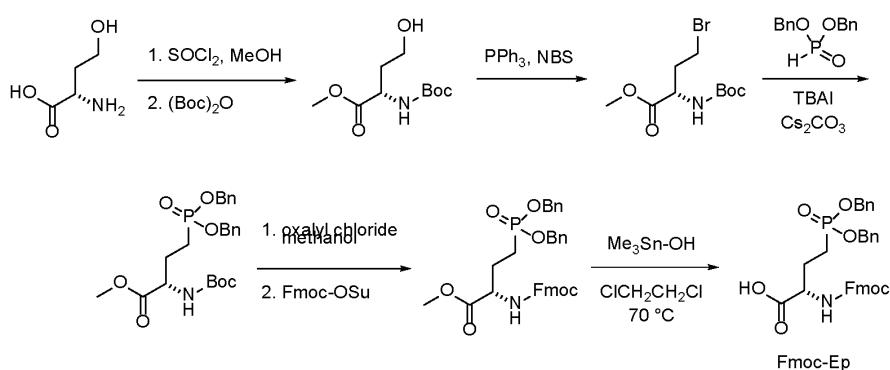
Example 3: Synthesis of Protected Phosphonic Acid Analogue of L-aspartic Acid (**Fmoc-Dp**)

[0106] An intramolecular Mitsunobu reaction of Fmoc-L-Ser-OH, with triphenylphosphine and DBAD afforded β -lactone. The β -lactone was opened by heating neat with dibenzyl trimethylsilyl phosphite to yield the desired dibenzyl phosphonate ester of **Fmoc-Dp**.

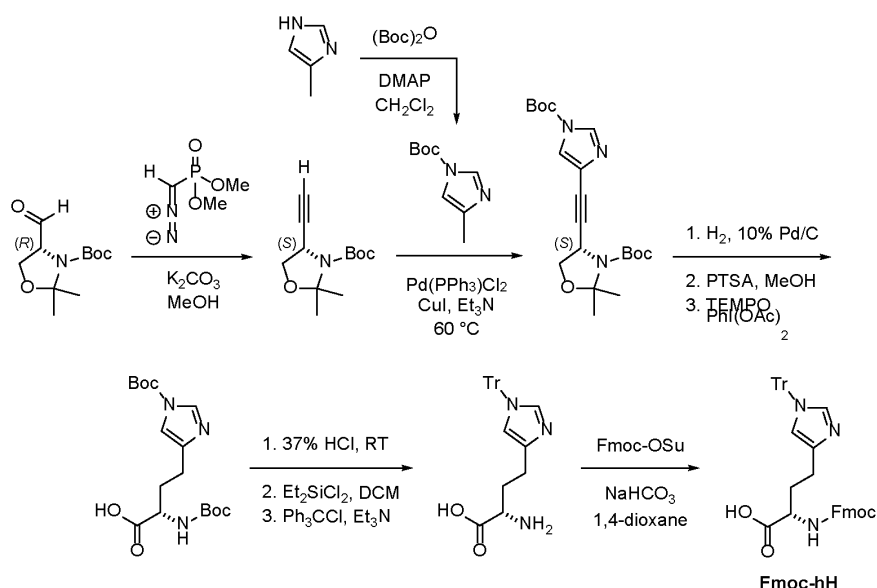


Example 4: Synthesis of Protected Phosphonic Acid Analogue of L-glutamic Acid (**Fmoc-Ep**)

[0107] L-Homoserine was treated with a solution of SOCl_2 in methanol to give the corresponding methyl ester. The nitrogen was protected with $(\text{Boc})_2\text{O}$. An Appel-type reaction with triphenylphosphine and NBS converted the homoserine alcohol to a bromide. The required phosphonate was installed through an Arbuzov reaction with dibenzylphosphite. The Boc group was removed with oxalyl chloride in methanol, and the nitrogen was immediately re-protected with Fmoc by reaction with Fmoc-OSu. Heating with Me_3SnOH cleaved the methyl ester to afford the desired dibenzyl phosphonate ester of **Fmoc-Ep**.

Example 5: Synthesis of Protected L-homohistidine (**Fmoc-hH**)

[0108] The starting aldehyde, (*R*)-Garner aldehyde, was reacted with dimethyl (diazomethyl)phosphonate to form a terminal alkyne. The alkyne was coupled with 1-Boc-4-iodoimidazole, prepared through Boc-protection of 4-iodoimidazole. Subsequent alkyne reduction, acetonide cleavage with PTSA in methanol, and TEMPO-catalyzed oxidation provided L-homoserine. Both Boc groups were removed with concentrated HCl . The imidazole ring was protected through initial treatment with dichlorodimethylsilane followed by trityl chloride. Protection of the amino group with Fmoc-OSu afforded the desired N-trityl protected **Fmoc-hH**.

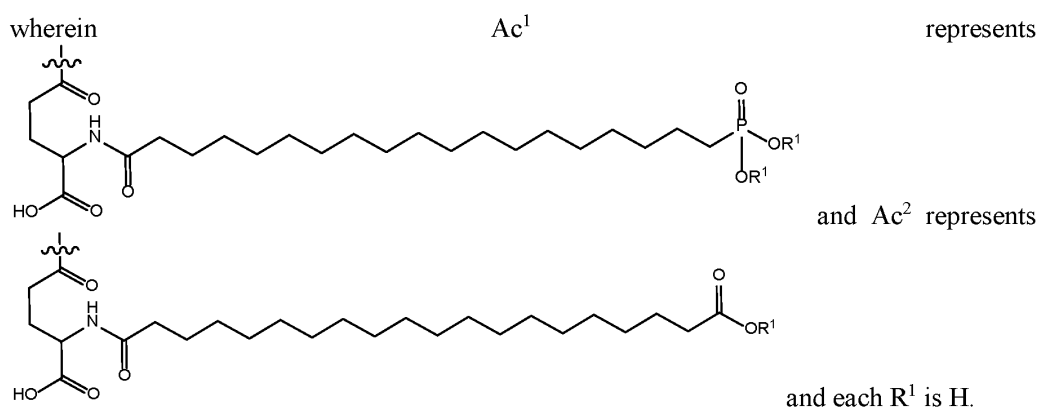


Example 6: Solid-Phase Synthesis of Lipidated Peptides

[0109] Each 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. In some cases, dipeptides were used to assemble the peptide backbone. The final amide linkage between the lipid chain and the N-terminus was achieved via an amide coupling. Upon completion of the synthesis, cleavage of the Rink resin, removal of the protecting groups on the peptide backbone, and cleavage of esters on the lipid chain were accomplished using TFA. Formation of the disulfide bridge near the N-terminus was accomplished using solution-phase oxidative conditions with I_2 and acetic acid. The final peptides were purified through RP-HPLC. Using these methods, the following compounds (with disulfide bridges between the cysteine residues) were synthesized:

Compound No.	SEQ ID No.	Sequence
Compound 1	SEQ ID NO. 2	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 2	SEQ ID NO. 3	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 3	SEQ ID NO. 4	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 4	SEQ ID NO. 5	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂

Compound 5	SEQ ID NO. 6	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 6	SEQ ID NO. 7	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 7	SEQ ID NO. 8	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 8	SEQ ID NO. 9	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-E-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 9	SEQ ID NO. 10	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 10	SEQ ID NO. 11	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 11	SEQ ID NO. 12	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 12	SEQ ID NO. 13	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 13	SEQ ID NO. 14	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-D-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 14	SEQ ID NO. 15	Ac ¹ -K-C-N-T-A-T-C-A-T-Q-R-L-A-R-F-L-E-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂
Compound 15	SEQ ID NO. 16	Ac ² -K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH ₂



Example 7: Functional Assays

[0110] Increases in cellular cyclic adenosine monophosphate (cAMP) and β -arrestin result from activation of the human calcitonin receptor (hCTR) or human amylin 3 receptor (hAMY₃R). Accumulating cAMP and β -arrestin can be measured in vitro using common detection techniques. Thus, it is possible to estimate in vitro potency (EC₅₀) for

peptides activating each of the hCTR and hAMY₃R receptors using dose-response curves for cAMP and β -arrestin accumulation.

[0111] cAMP HunterTM cells were seeded in a total volume of 20 μ L into white 384-well microplates and incubated at 37°C. cAMP modulation was determined using HitHunter cAMP XS+ assay (DiscoverX). Cells were incubated with sample compounds to induce response. Media was aspirated from cells and replaced with 15 μ L of 2:1 HBSS/10mM Hepes : cAMP XS + Ab reagent. Sample stocks were diluted to generate 4X sample in assay buffer. To the cells, 5 μ L of 4X sample was added and the cells were incubated at 37°C or room temperature for 30 or 60 minutes. Assay signal was generated through incubation with 20 μ L cAMP XS+ ED/CL lysis cocktail for one hour followed by incubation with 20 μ L cAMP XS+ EA reagent for three hours at room temperature. Microplates were read following signal generation with a PerkinElmer EnvisionTM instrument for chemiluminescent signal detection. Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). The percentage is calculated using formula: % Activity= 100% x (mean RLU of test sample – mean RLU of vehicle)/ (mean RLU of MAX control – mean RLU of vehicle control). The EC₅₀ results are summarized in Table 1.

[0112] Compounds 10 and 11 demonstrated higher affinity to both hAMY₃R and hCTR compared to pramlintide suggesting that the compounds are potent dual amylin and calcitonin receptor agonists (DACRAs).

Table 1. Functional Assay: cAMP

Compound	cAMP [pM]		
	hAMY ₃ R	hCTR	hCTR/hAMY ₃ R
Calcitonin		18.69	N/A
Pramlintide	43.26	186.75	4.32
Compound 1	31.58	17.89	0.57
Compound 3	393.24	162.25	0.41
Compound 4	39.86	9.13	0.23
Compound 6	192.55	27.97	0.15
Compound 9	75.87	26.83	0.35
Compound 10	13.86	5.91	0.43

Compound 11	20.71	5.71	0.28
Compound 13	177.77	37.19	0.21
Compound 14	61.24	25.45	0.42

[0113] β -arrestin activity can serve as an index of GPCR desensitization for agonist detection. PathHunter® cells were seeded in a total volume of 20 μ L into white 384-well microplates and incubated at 37°C. Cells were incubated with the sample compounds to induce response. Immediate dilution of the sample stocks was performed to generate 5X sample in assay buffer. To the cells, 5 μ L of 5X sample was added and incubated at 37°C for 90 to 180 minutes. Assay signal was generated through a single addition of 12.5 or 15 μ L (50% v/v) of PathHunter Detection reagent cocktail, followed by a one-hour incubation at room temperature. Microplates were read following signal generation with a PerkinElmer Envision™ instrument for chemiluminescent signal detection. Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA). The percentage is calculated using formula: % Activity = 100% x (mean RLU of test sample – mean RLU of vehicle) / (mean RLU of MAX control – mean RLU of vehicle control). The EC50 results are summarized in Table 2.

Table 2. Functional Assay: β -arrestin

β -arrestin [μ M]			
Compound	hAMY ₃ R	hCTR	hCTR/hAMY ₃ R
Calcitonin	0.42	0.02	0.05
Pramlintide	0.01	0.25	39.22
Compound 1	0.10	0.65	6.66
Compound 3	>10	0.60	N/A
Compound 4	0.07	0.45	6.01
Compound 5	0.65	2.10	3.24
Compound 6	0.46	2.39	5.21
Compound 7	0.16	0.14	0.84
Compound 8	0.17	0.42	2.56

Compound 9	0.12	1.23	10.22
Compound 10	0.04	0.06	1.53
Compound 11	0.05	0.05	1.02
Compound 12	0.13	0.18	1.40
Compound 13	0.53	4.20	7.99
Compound 14	0.09	>10	N/A
Compound 15	0.04	0.06	1.57

Example 8: Thioflavin T Assay (Amyloid Fibril Formation)

[0114] Amyloid fibril formation was assessed for selected polypeptides using a thioflavin T fluorescence assay. Samples were prepared by dissolving each compound in 10 mM HEPES buffer (pH 5.0-7.0) at 1-100 μ M, followed by the addition of a ThT (Sigma-Aldrich, Steinheim, Germany) stock solution (0.1 mM) to a final ThT concentration of 1 μ M. Each solution is aliquoted (200 μ L/well; n = 4) to a microtiter plate (OptiPlate-96, White Opaque 96-well Microplate, PerkinElmer, US) sealed with a transparent foil. Mechanical stress was applied at 37 °C incubation, 960 rpm, 1 mm amplitude, with 20 min fluorescence reading intervals for 72 h (filters: excitation 444 nm; emission 485 nm). The plates were shaken 180 seconds before every read. The polypeptides were monitored for amyloid fibril formation at 7.0, 6.5, 6.0, 5.5, and 5.0 pH values over 72 h. If no fibril formation was detected, the lag-time was set equal to the length of the test (72 h). Compounds 6 and 10 generally demonstrated the longest lag times, particularly at higher pH values.

Table 3. Amylin Fibril Formation (pH 7.0)

pH = 7.0 – Lag Time (h)						
Compound	Concentration [μ M]					
	100	50	25	10	3	1
Compound 4	23	21	21	34	72	72
Compound 6	44	47	37	72	72	72
Compound 10	20	37	53	72	72	72
Compound 11	5	5	9	11	72	72

Table 4. Amylin Fibril Formation (pH 6.5)

pH = 6.5 – Lag Time (h)						
Compound	Concentration [μ M]					
	100	50	25	10	3	1
Compound 4	14	13	20	32	72	72
Compound 6	24	22	23	33	72	72
Compound 10	22	29	35	28	72	72
Compound 11	4	5	5	7	72	72

Table 5. Amylin Fibril Formation (pH 6.0)

pH = 6.0 – Lag Time (h)						
Compound	Concentration [μ M]					
	100	50	25	10	3	1
Compound 4	10	8	9	21	72	72
Compound 6	21	19	20	20	72	72
Compound 10	12	18	15	29	72	72
Compound 11	4	4	5	7	72	72

Table 6. Amylin Fibril Formation (pH 5.5)

pH = 5.5 – Lag Time (h)						
Compound	Concentration [μ M]					
	100	50	25	10	3	1
Compound 4	8	8	7	10	72	72
Compound 6	17	15	20	29	72	72
Compound 10	13	10	9	11	72	72
Compound 11	6	6	5	72	72	72

Table 7. Amylin Fibril Formation (pH 5.0)

pH = 5.0 – Lag Time (h)						
Compound	Concentration [μ M]					
	100	50	25	10	3	1
Compound 4	8	8	8	72	72	72
Compound 6	13	14	72	31	72	72
Compound 10	18	9	11	72	72	72
Compound 11	6	6	5	72	72	72

Example 9: Diet-Induced Obesity Mouse Model

[0115] The mean body weight change of a diet-induced obesity mouse model was assessed. Mice were administered with a dosage of the compounds of 1 nmol/kg/day for days 1-7, 2 nmol/kg/day for days 8-9, 3 nmol/kg/day for days 10-15, 5 nmol/kg/day for days 16-19 and 10 nmol/kg/day for days 20-24. The results are shown in FIG. 1. On day 14, Compounds 10 and 11 demonstrated the largest decrease in mean BW % compared to the vehicle as seen in FIG. 2. Blood glucose levels were also measured on Day 1, Day 7 and Day 24. The results are shown in FIG. 3.

Example 10: Primate Body Weight and Food Intake Studies

[0116] FIG. 4 shows the ratio of body weight for monkeys five days after subcutaneous administration of Compound 10 compared to the body weight on the day of administration (Day 0). Five days after administration of a dose of 1 nmol/kg of Compound 10, the subject monkeys had a body weight that was 97.5% of the pre-dosing body weight. In comparison, monkeys dosed with 30 nmol/kg of Compound 10 had a body weight ratio of 90.8%. FIG. 5 shows the accumulated food intake over the course of 5 days following a single subcutaneous dose of Compound 10. A 30 nmol/kg dose of Compound 10 most significantly suppressed food intake.

[0117] FIG. 6 shows the body weight ratio for monkeys five days after subcutaneous administration of Compound 4 compared to the measured body weight on the day of administration (Day 0). Dosages of 10 nmol/kg and 30 nmol/kg resulted in a Day 5 to Day 0 ratio of 93.7% and 93.4%, respectively compared to 97.8 and 97.1% for 1 nmol/kg and

3 nmol/kg dosages. As seen in FIG. 7, the 10 nmol/kg and 30 nmol/kg dosages also suppressed appetite, resulting the significantly lower average accumulated food intake over the 5 days following administration of Compound 4.

[0118] Studies with Compound 6 showed less appetite reduction and smaller changes in body weight as seen in FIGs. 8 and 9 compared to Compounds 10 and 4.

[0119] 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.

[0120] 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.

[0121] 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.

[0122] 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.

[0123] 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.

[0124] Other embodiments are set forth in the following claims, along with the full scope of equivalents to which such claims are entitled.

[0125] While the invention 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 invention.

[0126] 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.

[0127] Although the invention 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 invention. Accordingly, the invention is limited only by the following claims.

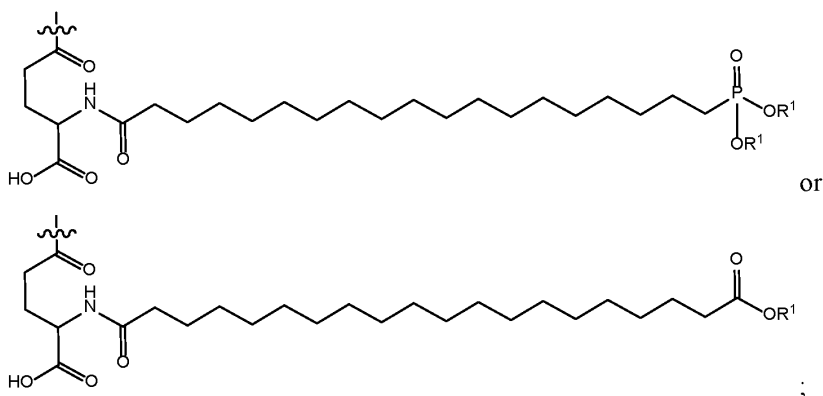
WHAT IS CLAIMED IS:

1. A polypeptide having the structure of Formula (I):

Ac-K-C-N-T-A-T-C-A-T-Q-R-L-A-X¹-F-L-X²-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂ (I) (SEQ ID NO: 1),

or a pharmaceutically acceptable salt thereof, wherein:

Ac is a lipidated isoglutamic acid residue having the structure:

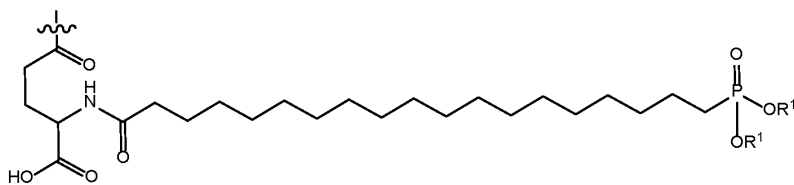


X¹ is a naturally occurring amino acid or an unnatural amino acid selected from the group consisting of aspartate (D), glutamate (E), glutamine (Q), arginine (R), phosphoaspartate (Dp) and phosphoglutamate (Ep);

X² is a naturally occurring amino acid or an unnatural amino acid selected from the group consisting of lysine (K), glutamine (Q), tyrosine (Y), homohistidine (hH), aspartate (D), and glutamate (E); and

each R¹ is independently hydrogen, C₆₋₁₀ aryl or C₇₋₁₁ arylalkyl.

2. The polypeptide of Claim 1, wherein Ac is



and each R¹ is H.

3. The polypeptide of Claim 1 or 2, wherein at least one of X¹ and X² is glutamine (Q), tyrosine (Y), or homohistidine (hH).

4. The polypeptide of any one of Claims 1-3, wherein X^1 is selected from the group consisting of: aspartate (D), phosphoaspartate (Dp), glutamine (Q), arginine (R), and phosphoglutamate (Ep).

5. The polypeptide of any one of Claims 1-4, wherein X^1 is selected from the group consisting of: aspartate (D), phosphoaspartate (Dp), glutamine (Q), and arginine (R).

6. The polypeptide of any one of Claims 1-4, wherein X^1 is phosphoaspartate (Dp) or phosphoglutamate (Ep).

7. The polypeptide of Claim 6, wherein X^1 is phosphoaspartate (Dp).

8. The polypeptide of Claim 6, wherein X^1 is phosphoglutamate (Ep).

9. The polypeptide of any one of Claims 1-5, wherein X^1 is aspartate (D).

10. The polypeptide of any one of Claims 1-5, wherein X^1 is glutamine (Q).

11. The polypeptide of Claim 9 or 10, wherein X^2 is tyrosine (Y).

12. The polypeptide of Claim 9 or 10, wherein X^2 is homohistidine (hH).

13. The polypeptide of Claim 1, wherein the polypeptide is selected from the group consisting of:

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Dp-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Ep-F-L-Q-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-E-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-K-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

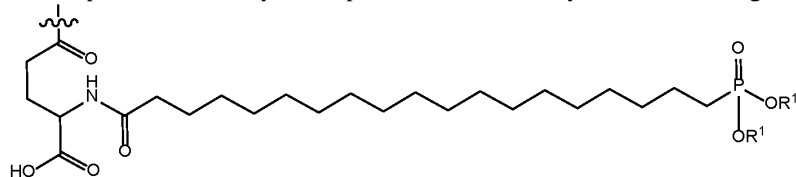
Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-hH-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-Q-F-L-D-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

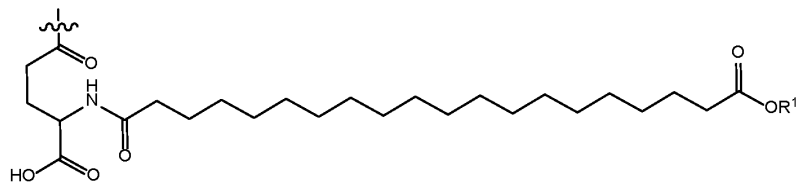
Ac¹-K-C-N-T-A-T-C-A-T-Q-R-L-A-R-F-L-E-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

Ac²-K-C-N-T-A-T-C-A-T-Q-R-L-A-D-F-L-Y-H-S-S-N-N-F-G-P-I-L-P-P-T-N-V-G-S-N-T-P-NH₂,

or a pharmaceutically acceptable salt of any of the foregoing, wherein Ac¹ is

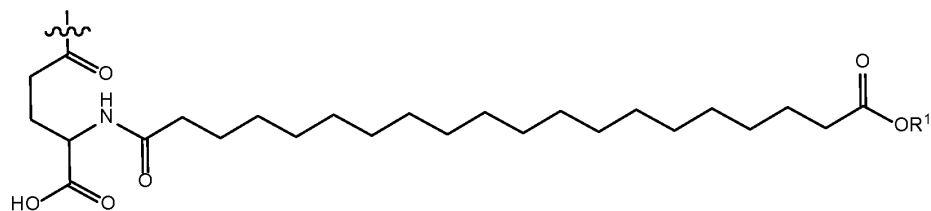


and Ac² is



and R¹ is H.

14. The polypeptide of Claim 11, wherein Ac² is



wherein R¹ is H.

15. A pharmaceutical composition comprising the polypeptide of any one of Claims 1-14 and a pharmaceutically acceptable excipient.
16. A method of treating a metabolic disorder or metabolic syndrome in a subject in need thereof comprising administration of a therapeutically effective amount of a polypeptide of any one of Claims 1-14.
17. The method of Claim 16, wherein the metabolic disorder or metabolic syndrome is selected from the group consisting of atherosclerosis, diabetes, hyperglycemic diabetes, type 2 diabetes mellitus, dyslipidemia, hypercholesterolemia, hyperlipidemia, hypertension, hypoglycemia, obesity, prader-willi syndrome, and any combination thereof.
18. The method of Claim 17, wherein the metabolic disorder or metabolic syndrome is diabetes, hyperglycemic diabetes, or type 2 diabetes mellitus.
19. The method of Claim 17, wherein the metabolic disorder or metabolic syndrome is obesity.
20. The method of any one of Claims 16-19, wherein the subject is a mammal.
21. The method of Claim 20, wherein the subject is a human.
22. The method of any one of Claims 16-21, wherein the route of administration is selected from the group consisting of enteral, intravenous, oral, intraarticular, intramuscular, subcutaneous, intraperitoneal, epidural, transdermal, and transmucosal.
23. The method of Claim 22, wherein the route of administration is subcutaneous.