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Description**Field of the Disclosure**

[0001] WO2015184177, WO2014081864, US2015290334 and WO2012158965 disclose peptide products and their use in the treatment of insulin resistance, cardiovascular disorders, Syndrome X, pain, bone loss and the like; however, none of these documents discloses the use of these peptide products for treating a liver disorder.

[0002] The disclosure provides improved peptide pharmaceuticals for treatment of a liver disorder, such as non-alcoholic steatohepatitis (NASH).

Summary of the Disclosure

[0003] The invention is set out in the appended set of claims.

Brief Description of the Drawings

[0004] Figures 1 to 11 are not according to the present invention and are present for illustration purposes only.

FIG. 1 shows specific peptide products, all of which are incorporated in the disclosure.

FIG. 2 shows specific peptide products, all of which are incorporated in the disclosure.

FIG. 3 shows specific peptide products, all of which are incorporated in the disclosure.

FIG. 4 shows specific peptide products, all of which are incorporated in the disclosure.

FIG. 5 illustrates the x-ray crystal structure of the binding site of the N-terminal region/ extracellular domain of the GLP-1 receptor and shows a critical hydrophobic ligand-binding region (Val^{19*}, Phe^{22*}, Trp^{25*} and Leu^{26*} of the ligand exendin-4, and the sequence of exendin-4 beyond Glu₁₅ interacts as an amphiphilic helix with this region).

FIG. 6 illustrates the structure of three representative peptide products, EU-A992, EU-A1022 and EU-A1169, in which the epsilon (side-chain) amino group of the lysine residue at position 24 of the peptide forms an amide bond with 1-O-octyl beta-D-glucuronic acid, 1-O-octyl beta-D-melibiouronic acid or 1-O-octyl alpha-D-melibiouronic acid, respectively.

FIG. 7 is a more detailed illustration of the structure of EU-A992.

FIG. 8 shows the concentrations of the peptide products EU-A993 and EU-A1023 and the native hormone GLP-1(7-36) over time during incubation in human plasma at 37 °C.

FIG. 9 shows the blood glucose response of db/db mice after subcutaneous injections of EU-A992, EU-A1167 and EU-A1168 (each at 250 nmol/kg) at t = 0 and 7 hr.

FIG. 10 shows the weight loss in diet-induced obese (DIO) mice after subcutaneous injection of the peptide product EU-A1024 at two different doses on days 1 (at T = 0 and 7 hr), 3, 6, 9, 12, 15, 18, 21 and 24.

FIG. 11 shows the change in whole-body fat tissue mass and lean tissue mass in the DIO mice treated so as measured by NMR on days 1 (pre-dose) and 26.

FIGS. 12A-12B show the effects of test compounds on body weight in a diet-induced obese (DIO) mouse model of NASH.

FIGS. 13A-13B show the effects of test compounds on whole-body fat tissue mass in DIO-NASH mice.

FIGS. 14A-14B show the effects of test compounds on plasma triglycerides (TG) and total cholesterol (TC) levels in DIO-NASH mice.

FIGS. 15A-15B show the effects of test compounds on plasma alanine transaminase (ALT) and aspartate transaminase (AST) levels in DIO-NASH mice.

inase (AST) levels in DIO-NASH mice.

FIG. 16 shows the effects of test compounds on liver weight in DIO-NASH mice.

FIGS. 17A-17E show the effects of test compounds on liver steatosis using hematoxylin and eosin stain in DIO-NASH mice (the large elliptical structure in FIG. 17C is a vein).

FIGS. 18A-18B show the effects of test compounds on post-biopsy liver steatosis in terms of % area affected and total liver lipid content as determined by histological quantitative measurement in DIO-NASH mice.

FIGS. 19A-19B show the effects of test compounds on liver triglycerides (TG) and total cholesterol (TC) levels in DIO-NASH mice.

FIG. 20 shows the effects of test compounds on total liver collagen type 1 alpha 1 (col1a1) content as measured immunohistochemically in DIO-NASH mice.

FIG. 21 shows the effects of test compounds on total liver galectin-3 content as measured immunohistochemically in DIO-NASH mice.

FIGS. 22A-22E show the effects of test compounds on liver steatosis score in DIO-NASH mice.

FIGS. 23A-23E show the effects of test compounds on liver inflammation score in DIO-NASH mice.

FIGS. 24A-24E show the effects of test compounds on hepatocyte ballooning score in DIO-NASH mice.

FIGS. 25A-25E show the effects of test compounds on NAS (non-alcoholic fatty liver disease activity score) score in DIO-NASH mice.

FIGS. 26A-26E show the effects of test compounds on liver fibrosis score in DIO-NASH mice, where liver fibrosis was assessed by picrosirius red staining.

FIGS. 27A-27F show the effects of test compounds in DIO-NASH mice on hepatic expression of mRNAs involved in fibrosis, inflammation, and monocyte recruitment and differentiation.

FIGS. 28A-28F show the effects of test compounds in DIO-NASH mice on hepatic expression of mRNAs involved in monocyte recruitment and differentiation.

FIGS. 29A-29I show the effects of test compounds in DIO-NASH mice on hepatic expression of mRNAs involved in fibrotic fiber formation.

FIGS. 30A-30F show the effects of test compounds in DIO-NASH mice on hepatic expression of mRNAs involved in hepatic stellate cell activation and myofibroblast proliferation.

FIGS. 31A-31F show the effects of test compounds in DIO-NASH mice on hepatic expression of mRNAs involved in pyroptosis.

Detailed Description of the Disclosure

Definitions

[0005] A peptide product for use in accordance with the invention is peptide product or a pharmaceutically acceptable salt thereof for use in the treatment of a liver disorder, wherein the peptide product is: His1-Aib2-Gln3-Gly4-Thr5-Phe6-Thr7-Ser8-Asp9-Tyr10-Ser11-Lys12-Tyr13 -Leu14-Asp15-Glu*16-Ly s(N-omega[1-(17-carboxyl-heptadecyloxy)beta-D-glucuronyl]) 17-Ala18-Ala19-Ly s*20-Glu21 -Phe22-Ile23 -Gln24-Trp25-Leu26-Leu27-Gln28-Thr29-NH2 (SEQ. ID. NO. 1119), wherein Glu16* and Lys20* denote residues that are cyclized through their side chains to form a lactam; other peptide products and uses described are not according to the present invention and are present for illustration purposes only.

[0006] Unless defined otherwise or clearly indicated otherwise by their use herein, all technical and scientific terms

used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this application belongs.

[0007] As used in the specification and the appended claims, the word "a" or "an" means one or more. As used herein, the word "another" means a second or more.

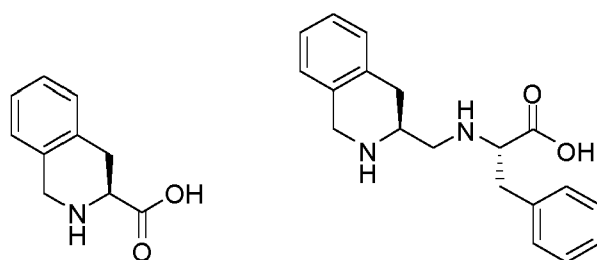
[0008] The acronym "aka" means also known as.

[0009] The term "exemplary" as used herein means "serving as an example, instance or illustration". Any embodiment or feature characterized herein as "exemplary" is not necessarily to be construed as preferred or advantageous over other embodiments or features.

[0010] The term "about" or "approximately" means within $\pm 10\%$ or 5% of the specified value. Whenever the term "about" or "approximately" precedes the first numerical value in a series of two or more numerical values or in a series of two or more ranges of numerical values, the term "about" or "approximately" applies to each one of the numerical values in that series of numerical values or in that series of ranges of numerical values.

[0011] A "peptide" comprises two or more natural or/and unnatural amino acid residues linked typically via peptide bonds. Such amino acids can include naturally occurring structural variants, naturally occurring non-proteinogenic amino acids, or/and synthetic non-naturally occurring analogs of natural amino acids. The terms "peptide" and "polypeptide" are used interchangeably herein. Peptides include short peptides (about 2-20 amino acids), medium-length peptides (about 21-50 amino acids) and long peptides (> about 50 amino acids, which can also be called "proteins"). A peptide product may comprise a surfactant moiety covalently attached to a peptide of no more than about 50, 40 or 30 amino acids. Synthetic peptides can be synthesized using an automated peptide synthesizer, for example. Peptides can also be produced recombinantly in cells expressing nucleic acid sequences that encode the peptides. Conventional notation is used herein to portray peptide sequences: the left-hand end of a peptide sequence is the amino (N)-terminus, and the right-hand end of a peptide sequence is the carboxyl (C)-terminus.

[0012] Standard one-letter and three-letter abbreviations for the common amino acids are used herein. Although the abbreviations used in the amino acid sequences disclosed herein represent L-amino acids unless otherwise designated as D- or DL- or the amino acid is achiral, the counterpart D-isomer generally can be used at any position (e.g., to resist proteolytic degradation). Abbreviations for other amino acids used herein include: Ac3c = 1-aminocyclopropane-1-carboxylic acid; Ac4c = 1-aminocyclobutane-1-carboxylic acid; Ac5c = 1-aminocyclopentane-1-carboxylic acid; Ac6c = 1-aminocyclohexane-1-carboxylic acid; Aib = α -aminoisobutyric acid (or 2-methylalanine or $C\alpha$ -methylalanine); Bip = 3-(biphenyl-4-yl)alanine; Bip2Et = 3-(2'-ethylbiphenyl-4-yl)alanine; Bip2EtMeO = 3-(2'-ethyl-4'-methoxybiphenyl-4-yl)alanine; Cit = citrulline; Deg = 2,2-diethylglycine; Dmt = (2,6-dimethyl)tyrosine; 2FPhe = (2-fluorophenyl)alanine; 2FMePhe or 2F α MePhe = $C\alpha$ -methyl-(2-fluorophenyl)alanine; hArg = homoarginine; MeLys or α MeLys = $C\alpha$ -methyllysine; MePhe or α MePhe = $C\alpha$ -methylphenylalanine; MePro or α MePro = $C\alpha$ -methylproline; Nal1 or Nal(1) = 3-(1-naphthyl)alanine; Nal2 or Nal(2) = 3-(2-naphthyl)alanine; Nle = norleucine; Orn = ornithine; and Tmp = (2,4,6-trimethylphenyl)alanine. 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) and a Tic-Phe dipeptide moiety with a reduced amide bond between the residues (designated as Tic- Ψ [CH₂-NH]- Ψ -Phe) have the following structures:



Tic

Tic- Ψ [CH₂-NH]- Ψ -Phe

[0013] Unless specifically stated otherwise or the context clearly indicates otherwise, the disclosure encompasses any and all forms of a peptide that may be produced, whether the peptide is produced synthetically (e.g., using a peptide synthesizer) or by a cell (e.g., by recombinant production). Such forms of a peptide can include one or more modifications that may be made during the course of synthetic or cellular production of the peptide, such as one or more post-translational modifications, whether or not the one or more modifications are deliberate. A peptide can have the same type of modification at two or more different places, or/and can have two or more different types of modifications. Modifications that may be made during the course of synthetic or cellular production of a peptide, including chemical and post-translational modifications, include without limitation glycosylation (e.g., N-linked glycosylation and O-linked glycosylation), lipidation, phosphorylation, sulfation, acetylation (e.g., acetylation of the N-terminus), amidation (e.g., amidation of the C-terminus), hydroxylation, methylation, formation of an intramolecular or intermolecular disulfide bond,

formation of a lactam between two side chains, formation of pyroglutamate, and ubiquitination. A peptide can have one or more modifications anywhere, such as the N-terminus, the C-terminus, one or more amino acid side chains, or the peptide backbone, or any combination thereof. A peptide may be acetylated at the N-terminus or/and has a carboxamide (-CONH₂) group at the C-terminus, which can increase the stability of the peptide.

[0014] Potential modifications of a peptide also include deletion of one or more amino acids, addition/insertion of one or more natural or/and unnatural amino acids, or substitution with one or more natural or/and unnatural amino acids, or any combination or all thereof. A substitution can be conservative or non-conservative. Such modifications may be deliberate, such as via site-directed mutagenesis or in the chemical synthesis of a peptide, or may be accidental, such as via mutations arising in the host cell that produces the peptide or via errors due to PCR amplification. An unnatural amino acid can have the same chemical structure as the counterpart natural amino acid but have the D stereochemistry, or it can have a different chemical structure and the D or L stereochemistry. Unnatural amino acids can be utilized, e.g., to promote α -helix formation or/and to increase the stability of the peptide (e.g., to resist proteolytic degradation).

[0015] A peptide having one or more modifications relative to a reference peptide may be called an "analog" or "variant" of the reference peptide as appropriate. An "analog" typically retains one or more essential properties (e.g., receptor binding, activation of a receptor or enzyme, inhibition of a receptor or enzyme, or other biological activity) of the reference peptide. A "variant" may or may not retain the biological activity of the reference peptide, or/and may have a different biological activity. An analog or variant of a reference peptide may have a different amino acid sequence than the reference peptide.

[0016] The term "conservative substitution" refers to substitution of an amino acid in a peptide with a functionally, structurally or chemically similar natural or unnatural amino acid. The following groups each contain natural amino acids that are conservative substitutions for one another:

- 1) Glycine (Gly/G), Alanine (Ala/A);
- 2) Isoleucine (Ile/I), Leucine (Leu/L), Methionine (Met/M), Valine (Val/V);
- 3) Phenylalanine (Phe/F), Tyrosine (Tyr/Y), Tryptophan (Trp/W);
- 4) Serine (Ser/S), Threonine (Thr/T), Cysteine (Cys/C);
- 5) Asparagine (Asn/N), Glutamine (Gln/Q);
- 6) Aspartic acid (Asp/D), Glutamic acid (Glu/E); and
- 7) Arginine (Arg/R), Lysine (Lys/K), Histidine (His/H).

[0017] The following groups each contain natural amino acids that are conservative substitutions for one another:

- 1) non-polar: Ala, Val, Leu, Ile, Met, Pro (proline/P), Phe, Trp;
- 2) hydrophobic: Val, Leu, Ile, Phe, Trp;
- 3) aliphatic: Ala, Val, Leu, Ile;
- 4) aromatic: Phe, Tyr, Trp, His;
- 5) uncharged polar or hydrophilic: Gly, Ala, Pro, Ser, Thr, Cys, Asn, Gln, Tyr;
- 6) aliphatic hydroxyl- or sulfhydryl-containing: Ser, Thr, Cys;
- 7) amide-containing: Asn, Gln;
- 8) acidic: Asp, Glu;
- 9) basic: Lys, Arg, His; and
- 10) small: Gly, Ala, Ser, Cys.

[0018] Amino acids may be grouped as set out below:

- 1) hydrophobic: Val, Leu, Ile, Met, Phe, Trp;
- 2) aromatic: Phe, Tyr, Trp, His;
- 3) neutral hydrophilic: Gly, Ala, Pro, Ser, Thr, Cys, Asn, Gln;
- 4) acidic: Asp, Glu;
- 5) basic: Lys, Arg, His; and
- 6) residues that influence backbone orientation: Pro.

[0019] Examples of unnatural or non-proteinogenic amino acids include without limitation alanine analogs (e.g., α -ethylGly [α -aminobutyric acid or Abu], α -n-propylGly [norvaline or Nva], α -tert-butylGly [Tbg], α -vinylGly [Vg or Vlg], α -allylGly [Alg], α -propargylGly [Prg], 3-cyclopropylAla [Cpa] and Aib), leucine analogs (e.g., Nle), proline analogs (e.g., α -MePro), phenylalanine analogs {e.g., Phe(2-F), Phe(2-Me), Tmp, Bip, Bip(2'-Et-4'-OMe), Nal1, Nal2, Tic, α -MePhe, α -MePhe(2-F) and α -MePhe(2-Me)}, tyrosine analogs (e.g., Dmt and α -MeTyr), serine analogs (e.g., homoserine [isothreonine or hSer]), glutamine analogs (e.g., Cit), arginine analogs (e.g., hArg), lysine analogs (e.g., homolysine [hLys]),

Orn and α -MeLys), α,α -disubstituted amino acids (e.g., Aib, α,α -diethylGly [Deg], α -cyclohexylAla [2-Cha], Ac3c, Ac4c, Ac5c and Ac6c), and other unnatural amino acids disclosed in A. Santoprete et al., J. Pept. Sci., 17:270-280 (2011). α,α -Disubstituted amino acids can provide conformational restraint or/and α -helix stabilization. A reduced amide bond between two residues (as in, e.g., Tic- Ψ [CH₂-NH]- Ψ -Phe) increases protease resistance and may also, e.g., alter receptor binding.

[0020] The disclosure encompasses all pharmaceutically acceptable salts of peptides, including those with a positive net charge, those with a negative net charge, and those with no net charge.

[0021] Saccharides include monosaccharides, disaccharides and oligosaccharides (e.g., trisaccharides, tetrasaccharides and so on). A reducing saccharide exists in a ring form and an open-chain form in equilibrium, which generally favors the ring form. A functionalized saccharide of a surfactant moiety has a functional group suitable for forming a covalent bond with an amino acid of a peptide.

[0022] An "alkyl" group refers to an aliphatic hydrocarbon group. An alkyl group can be saturated or unsaturated, and can be straight-chain (linear), branched or cyclic. In some instances, an alkyl group is not cyclic. In some instances, an alkyl group contains 1-30, 6-30, 6-20 or 8-20 carbon atoms. A "substituted" alkyl group is substituted with one or more substituents. The one or more substituents may be independently selected from halogens, nitro, cyano, oxo, hydroxy, alkoxy, haloalkoxy, aryloxy, thiol, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, arylsulfone, amino, alkylamino, dialkylamino, arylamino, alkoyl, carboxyl, carboxylate, esters, amides, carbonates, carbamates, ureas, alkyl, haloalkyl, fluoroalkyl, aralkyl, alkyl chains containing an acyl group, heteroalkyl, heteroalicyclic, aryl, alkoxyaryl, heteroaryl, hydrophobic natural compounds (e.g., steroids), and the like.

[0023] An alkyl group as a substituent may be a linear or branched C₁-C₆ alkyl, which can be called "lower alkyl". Non-limiting examples of lower alkyl groups include methyl, ethyl, propyl (including n-propyl and isopropyl), butyl (including all isomeric forms, such as n-butyl, isobutyl, sec-butyl and tert-butyl), pentyl (including all isomeric forms, such as n-pentyl), and hexyl (including all isomeric forms, such as n-hexyl).

[0024] An alkyl group may be attached to the N α -atom of a residue (e.g., Tyr or Dmt) of a peptide. An N-alkyl group may be straight or branched C₁-C₁₀ alkyl, or aryl-substituted alkyl such as benzyl, phenylethyl or the like. One or two alkyl groups can be attached to the N α -atom of the N-terminal residue.

[0025] An alkyl group may be a 1-alkyl group that is attached to the C-1 position of a saccharide (e.g., glucose) via a glycosidic bond (e.g., an O-, S-, N- or C-glycosidic bond). A 1-alkyl group may be an unsubstituted or substituted C₁-C₃₀, C₆-C₃₀, C₆-C₂₀ or C₈-C₂₀ alkyl group.

[0026] An alkyl group (e.g., a 1-alkyl group) may be substituted with one or more (e.g., 2 or 3) groups independently selected from aryl, -OH, -OR¹, -SH, -SR¹, -NH₂, -NHR¹, -N(R¹)₂, oxo (=O), -C(=O)R², carboxyl (-CO₂H), carboxylate (-CO₂⁻), -C(=O)OR¹, -OC(=O)R³, -C(=O)N(R¹)₂, -NR⁴C(=O)R³, -OC(=O)OR⁵, -OC(=O)N(R¹)₂, -NR⁴C(=O)OR⁵, and -NR⁴C(=O)N(R¹)₂, wherein:

R¹ at each occurrence independently is hydrogen, alkyl or aryl, or both occurrences of R¹ and the nitrogen atom to which they are connected form a heterocyclyl or heteroaryl ring;

R² at each occurrence independently is alkyl, heterocyclyl, aryl or heteroaryl;

R³ at each occurrence independently is hydrogen, alkyl, heterocyclyl, aryl or heteroaryl;

R⁴ at each occurrence independently is hydrogen or alkyl; and

R⁵ at each occurrence independently is alkyl or aryl.

[0027] An alkyl group (e.g., a 1-alkyl group) may be internally or/and terminally substituted with a carboxyl/carboxylate group, an aryl group or an -O-aryl group. An alkyl group (e.g., a 1-alkyl group) may be substituted with a carboxyl or carboxylate group at the distal end of the alkyl group. An alkyl group (e.g., a 1-alkyl group) may be substituted with an aryl group at the distal end of the alkyl group. An alkyl group (e.g., a 1-alkyl group) may be substituted with an -O-aryl group at the distal end of the alkyl group.

[0028] The terms "halogen", "halide" and "halo" refer to fluoride, chloride, bromide and iodide.

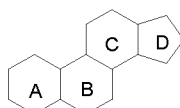
[0029] The term "acyl" refers to -C(=O)R, where R is an aliphatic group that can be saturated or unsaturated, and can be linear, branched or cyclic. R may contain 1-20, 1-10 or 1-6 carbon atoms. An acyl group can optionally be substituted with one or more groups, such as halogens, oxo, hydroxyl, alkoxy, thiol, alkylthio, amino, alkylamino, dialkylamino, cycloalkyl, aryl, acyl, carboxyl, esters, amides, hydrophobic natural compounds (e.g., steroids), and the like.

[0030] The terms "heterocyclyl" and "heterocyclic" refer to a monocyclic non-aromatic group or a multicyclic group that contains at least one non-aromatic ring, wherein at least one non-aromatic ring contains one or more heteroatoms independently selected from O, N and S. The non-aromatic ring containing one or more heteroatoms may be attached or fused to one or more saturated, partially unsaturated or aromatic rings. A heterocyclyl or heterocyclic group may have from 3 to 15, or 3 to 12, or 3 to 10, or 3 to 8, or 3 to 6 ring atoms. Heterocyclyl or heterocyclic groups include without limitation aziridinyl, azetidyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, azepanyl, azocanyl, oxiranyl, oxetanyl, tetrahydrofuranyl (oxolanyl), tetrahydropyranyl, oxepanyl and oxocanyl.

[0031] The term "aryl" refers to a monocyclic aromatic hydrocarbon group or a polycyclic group that contains at least one aromatic hydrocarbon ring. An aryl group may have from 6 to 15, or 6 to 12, or 6 to 10 ring atoms. Aryl groups include without limitation phenyl, naphthalenyl (naphthyl), fluorenyl, azulenyl, anthryl, phenanthryl, biphenyl and terphenyl. The aromatic hydrocarbon ring of an aryl group may be attached or fused to one or more saturated, partially unsaturated or aromatic rings - e.g., dihydronaphthyl, indenyl, indanyl and tetrahydronaphthyl (tetralinyl). An aryl group can optionally be substituted with one or more (e.g., 2 or 3) substituents independently selected from halogens (including -F and -Cl), cyano, nitro, hydroxyl, alkoxy, thiol, alkylthio, alkylsulfoxide, alkylsulfone, amino, alkylamino, dialkylamino, alkyl, haloalkyl (including fluoroalkyl such as trifluoromethyl), acyl, carboxyl, esters, amides, and the like.

[0032] The term "heteroaryl" refers to a monocyclic aromatic group or a polycyclic group that contains at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, N and S. The heteroaromatic ring may be attached or fused to one or more saturated, partially unsaturated or aromatic rings that may contain only carbon atoms or that may contain one or more heteroatoms. A heteroaryl group may have from 5 to 15, or 5 to 12, or 5 to 10 ring atoms. Monocyclic heteroaryl groups include without limitation pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl (thiophenyl), oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridonyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridazinonyl and triazinyl. Non-limiting examples of bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzothiadiazolyl, benzoxazolyl, benzisoxazolyl, benzothienyl (benzothiophenyl), quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzotriazolyl, indoliziny, benzofuranyl, isobenzofuranyl, chromonyl, coumarinyl, cinnolinyl, quinazolinyl, quinoxalinyl, indazolyl, naphthyridinyl, phthalazinyl, quinazolinyl, purinyl, pyrrolopyridinyl, furopyridinyl, thienopyridinyl, dihydroisoindolyl and tetrahydroquinolyl.

[0033] The term "steroid nucleus" refers to the core of steroids comprising an arrangement of four fused rings designated A, B, C and D as shown below:



A steroid nucleus can bear one or more groups, such as halogens, hydroxyl, oxo, alkyl, acyl, carboxyl, esters, amides, and the like. Steroid nucleus-containing moieties include, but are not limited to, cholesterol and the like.

[0034] The term "pharmaceutically acceptable" refers to a substance (e.g., an active ingredient or an excipient) that is suitable for use in contact with the tissues and organs of a subject without excessive irritation, allergic response, immunogenicity and toxicity, is commensurate with a reasonable benefit/risk ratio, and is effective for its intended use. A "pharmaceutically acceptable" excipient or carrier of a pharmaceutical composition is also compatible with the other ingredients of the composition.

[0035] The term "therapeutically effective amount" refers to an amount of a compound that, when administered to a subject, is sufficient to prevent, reduce the risk of developing, delay the onset of, slow the progression of or cause regression of the medical condition being treated, or to alleviate to some extent the medical condition or one or more symptoms or complications of that condition, at least in some fraction of the subjects taking that compound. The term "therapeutically effective amount" also refers to an amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, organ or human which is sought by a medical doctor or clinician.

[0036] The terms "treat," "treating" and "treatment" include alleviating, ameliorating, inhibiting the progress of, reversing or abrogating a medical condition or one or more symptoms or complications associated with the condition, and alleviating, ameliorating or eradicating one or more causes of the condition. Reference to "treatment" of a medical condition includes prevention of the condition. The terms "prevent", "preventing" and "prevention" include precluding, reducing the risk of developing and delaying the onset of a medical condition or one or more symptoms or complications associated with the condition.

[0037] The term "medical conditions" (or "conditions" for brevity) includes diseases and disorders. The terms "diseases" and "disorders" are used interchangeably herein.

Obesity and Insulin Resistance

[0038] Obesity leads to insulin resistance, which is a decreased ability of the cells in the body to respond to insulin stimulation through a decreased number of insulin receptors and a decreased coupling of insulin receptors to critical intracellular signaling systems. The obese state also leads to metabolic syndrome, which is a constellation of disorders including insulin resistance, hypertension, atherosclerosis, etc. Insulin resistance often results in type 2 diabetes. Prolonged hyperglycemia increases the risk of micro- and macrovascular complications, sensory neuropathy, myocardial infarction, stroke, macrovascular mortality, and all-cause mortality. Type 2 diabetes, metabolic syndrome, and other

obesity- and insulin resistance-associated diseases are huge financial and healthcare burdens worldwide.

Metabolic Hormones

[0039] Incretins are metabolic hormones that induce a decrease in blood glucose levels. Incretins are released after eating and stimulate insulin production and secretion from pancreatic beta cells of the islets of Langerhans by a blood glucose-dependent mechanism. Incretins also slow the rate of absorption of nutrients into the bloodstream by slowing gastric emptying, which induces satiety and thus suppresses appetite. Furthermore, incretins inhibit glucagon release from the alpha cells of the islets of Langerhans. The two main incretins are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP, also known as glucose-dependent insulintropic polypeptide), which are secreted by intestinal L-cells and are members of the glucagon peptide superfamily. GLP-1 and GIP are rapidly degraded by dipeptidyl peptidase 4 (DPP-4). People with type 2 diabetes have impaired insulin secretion from pancreatic beta cells in response to GLP-1.

[0040] GLP-1 has other beneficial effects. For example, GLP-1 stimulates pancreatic beta-cell proliferation, increases peripheral insulin sensitivity and liver glucose uptake and glycogen production, and improves cardiac function (e.g., left ventricular function).

[0041] Like GLP-1, oxyntomodulin (OXM) is derived from preproglucagon and is secreted from L-cells in the gut in response to eating. OXM is essentially glucagon with a C-terminal extension of 8 amino acid residues. OXM activates both the glucagon receptor (GCGR) and the GLP-1 receptor (GLP1R), but with a 10- to 100-fold lower potency than glucagon and GLP-1. OXM induces satiety and reduces body fat (e.g., white adipose tissue). OXM causes weight loss by reducing food intake and body fat.

[0042] Glucagon is produced from preproglucagon in pancreatic alpha cells of the islets of Langerhans. Glucagon induces satiety, induces lipolysis in adipose tissues, and increases energy expenditure. Glucagon reduces body weight by reducing food intake and stimulating fat burning.

[0043] The amino acid sequences of the biologically active forms of human GLP-1, glucagon and oxyntomodulin are shown below:

GLP-1 (using glucagon numbering):

His₁-Ala₂-Glu₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Val₁₀-Ser₁₁-Ser₁₂-Tyr₁₃-Leu₁₄-Glu₁₅-Gly₁₆-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Ala₂₄-Trp₂₅-Leu₂₆-Val₂₇-Lys₂₈-Gly₂₉-Arg₃₀
(SEQ. ID. NO. 1)

Glucagon:

His₁-Ser₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Ser₁₆-
Arg₁₇-Arg₁₈-Ala₁₉-Gln₂₀-Asp₂₁-Phe₂₂-Val₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Met₂₇-Asn₂₈-Thr₂₉
(SEQ. ID. NO. 2)

Oxyntomodulin:

His₁-Ser₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Ser₁₆-
Arg₁₇-Arg₁₈-Ala₁₉-Gln₂₀-Asp₂₁-Phe₂₂-Val₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Met₂₇-Asn₂₈-Thr₂₉-Lys₃₀-
Arg₃₁-Asn₃₂-Arg₃₃-Asn₃₄-Asn₃₅-Ile₃₆-Ala₃₇ (SEQ. ID. NO. 3)

[0044] Amino acid residues throughout the sequences of GLP-1 and glucagon can be replaced while retaining biological activity. For example, replacement by Ala is well accepted in the N-terminal region of GLP-1, especially at positions 2, 3, 5, 8, 11 and 12 (Adelhorst et al., J. Biol. Chem., 269:6275-6278 [1994]). Furthermore, short N-terminal analogs of GLP-1 can potently bind and activate GLP1R (Mapelli et al., J. Med. Chem., 52:7788-7799 [2009]; and Haque et al., Peptides, 31:950-955 and 1353-1360 [2010]). Chimeric analogs able to bind to both GLP1R and GCGR can be created by grafting C-terminal residues from GLP-1 onto N-terminal residues of glucagon (Hjorth et al., J. Biol. Chem., 269:30121-30124 [1994]).

[0045] The disclosure provides peptide products comprising a peptide gut hormone (e.g., GLP-1, GIP, glucagon,

oxyntomodulin or an exendin [e.g., exendin-4]), or an analog or variant thereof, that is covalently attached to a surfactant moiety. The peptide products are potent agonists of the receptor(s) of the underlying peptide, promote metabolic homeostasis, and have a long duration of action and enhanced bioavailability. In some embodiments, the peptide products are agonists of the GLP-1 receptor (GLP1R). GLP1R agonists stimulate blood glucose-dependent insulin secretion and increase insulin sensitivity with a reduced risk of hypoglycemia, and induce satiety that reduces food intake and hence reduces weight gain or causes weight loss. The peptide products for use in accordance with the invention are dual agonists of GLP1R and the glucagon receptor (GCGR), which adds the benefits of GCGR activation, including stimulation of fat burning, loss of body fat mass and prevention of hypoglycemia.

Peptide Products

[0046] Peptide and proteins often have deficiencies in their use as medicines, including instability in the formulation, aggregation, short duration of action and poor bioavailability. Disclosed herein are peptide products that have improved properties as pharmaceuticals, including increased stability, half-life, duration of action and bioavailability, and reduced immunogenicity. The peptide products comprise a peptide covalently attached to a surfactant moiety containing a hydrophilic saccharide group and a hydrophobic group. In some embodiments, the peptide is attached to the saccharide group, which is in turn attached to the hydrophobic group. In some embodiments, the peptide is a metabolic hormone, such as GLP-1, glucagon, oxyntomodulin or an exendin (e.g., exendin-4), or an analog or variant thereof. The peptide products are useful for treating, e.g., insulin resistance, diabetes, obesity, metabolic syndrome and cardiovascular diseases, and conditions linked thereto, such as NASH and PCOS.

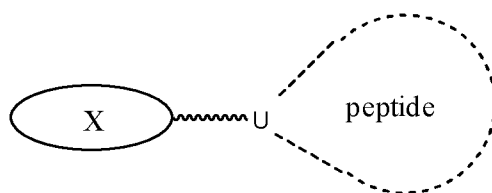
[0047] A peptide product may comprise GLP-1 or an analog or variant thereof covalently attached to a surfactant moiety (e.g., an alkyl glycoside such as a 1-alkyl glycoside). The GLP-1 peptide can have a native or non-native amino acid sequence or structure. The alkyl group can be unsubstituted or substituted (e.g., with a carboxyl/carboxylate, aryl or oxyaryl group). In certain embodiments, the alkyl glycoside is a 1-O-alkyl β -D-glucuronic acid.

[0048] A peptide product may comprise glucagon or an analog or variant thereof covalently attached to a surfactant moiety (e.g., an alkyl glycoside such as a 1-alkyl glycoside). The glucagon peptide can have a native or non-native amino acid sequence or structure. The alkyl group can be unsubstituted or substituted (e.g., with a carboxyl/carboxylate, aryl or oxyaryl group). In certain embodiments, the alkyl glycoside is a 1-O-alkyl β -D-glucuronic acid.

[0049] A peptide product may comprise oxyntomodulin or an analog or variant thereof covalently attached to a surfactant moiety (e.g., an alkyl glycoside such as a 1-alkyl glycoside). The oxyntomodulin peptide can have a native or non-native amino acid sequence or structure. The alkyl group can be unsubstituted or substituted (e.g., with a carboxyl/carboxylate, aryl or oxyaryl group). The alkyl glycoside may be a 1-O-alkyl β -D-glucuronic acid.

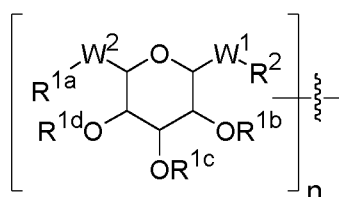
[0050] A peptide product may comprise an exendin (e.g., exendin-4) or an analog or variant thereof covalently attached to a surfactant moiety (e.g., an alkyl glycoside such as a 1-alkyl glycoside). The exendin peptide can have a native or non-native amino acid sequence or structure. The alkyl group can be unsubstituted or substituted (e.g., with a carboxyl/carboxylate, aryl or oxyaryl group). In certain embodiments, the alkyl glycoside is a 1-O-alkyl β -D-glucuronic acid.

[0051] Some embodiments relate to peptide products of Formula I-A comprising a surfactant X covalently attached to a peptide, the peptide comprising a linker amino acid U and at least one other amino acid:



Formula I-A

wherein the surfactant X is a moiety of Formula I:



Formula I

wherein:

R^{1a} at each occurrence independently is a bond, H, a protecting group, a saccharide, an unsubstituted or substituted C₁-C₃₀ alkyl group, an unsubstituted or substituted aralkyl (-alkylaryl) group, an unsubstituted or substituted alkoxyaryl group, or a steroid nucleus-containing group;

R^{1b}, R^{1c} and R^{1d} at each occurrence independently are a bond, H, a protecting group, a saccharide, an unsubstituted or substituted C₁-C₃₀ alkyl group, an unsubstituted or substituted aralkyl group, an unsubstituted or substituted alkoxyaryl group, or a steroid nucleus-containing group;

R² at each occurrence independently is a bond, a bond to U, H, an unsubstituted or substituted C₁-C₃₀ alkyl group, an unsubstituted or substituted aralkyl group, an unsubstituted or substituted alkoxyaryl group, a steroid nucleus-containing group, -NH-, -S-, -O-NH-, a spacer, -triazolo-, -NH(C=O)-CH₂-, or -(CH₂)_m-maleimide-;

W¹ at each occurrence independently is -CH₂-, -CH₂-O-, -CH₂-S-, -CH₂-NH-, - (C=O)-, -(C=O)-NH-, -(C=S)-, or -(C=S)-NH-;

W² at each occurrence independently is -O-, -S-, -NH-, or -CH₂-;

at least one occurrence of R^{1a}, R^{1b}, R^{1c}, R^{1d} or R² is an unsubstituted or substituted C₁-C₃₀ alkyl, aralkyl, alkoxyaryl or steroid nucleus-containing group;

m is an integer from 1 to 10; and

n is 1, 2 or 3; and

the peptide has Formula II:

aa₁-aa₂-aa₃-aa₄-aa₅-aa₆-aa₇-aa₈-aa₉-aa₁₀-aa₁₁-aa₁₂-aa₁₃-aa₁₄-aa₁₅-aa₁₆-aa₁₇-aa₁₈-aa₁₉-aa₂₀-
aa₂₁-aa₂₂-aa₂₃-aa₂₄-aa₂₅-aa₂₆-aa₂₇-aa₂₈-aa₂₉-aa₃₀-aa₃₁-aa₃₂-aa₃₃-aa₃₄-aa₃₅-aa₃₆-aa₃₇-Z

Formula II (SEQ. ID. NO. 1108)

wherein:

Z is -OH, -NHR³ or -N(R⁴)His, wherein:

R³ is H, unsubstituted or substituted C₁-C₁₂ alkyl, or a PEG-containing group of less than 10 Da; and

R⁴ is H, C₂-C₁₀ acyl (e.g., acetyl) or -C(=O)-aryl (e.g., benzoyl); aa₁ is His, N(R³)His, N(R⁴)His, or pGlu-His;

aa₂ is Ser, D-Ser, Ala, Gly, Pro, MePro, Aib, Ac4c or Ac5c;

aa₃ is Gln or Cit;

aa₄ is Gly or D-Ala;

aa₅ is Thr or Ser;

aa₆ is Phe, Trp, 2FPhe, MePhe, 2FMePhe or Nal2;

aa₇ is Thr or Ser;

aa₈ is Ser or Asp;

aa₉ is Asp or Glu;

aa₁₀ is Tyr, Leu, Met, Nal2, Bip, Bip2EtMeO, Glu, Lys or U;

aa₁₁ is absent or Ser, Asn, Bip or U;

aa₁₂ is absent or Lys, Glu, Ser, Arg or U;

aa₁₃ is absent or Tyr, Gln, Cit or U;

aa₁₄ is absent or Leu, Met, Nle, Glu, Lys or U;

aa₁₅ is absent or Asp, Glu or U;

aa₁₆ is absent or Ser, Gly, Glu, Ala, Aib, Ac5c, Lys, Arg or U;

aa₁₇ is absent or Arg, hArg, Gln, Glu, Cit, Aib, Ac4c, Ac5c, Lys or U;

aa₁₈ is absent or Arg, hArg, Ala, Aib, Ac4c, Ac5c or U;

aa₁₉ is absent or Ala, Val, Aib, Ac4c, Ac5c or U;

aa₂₀ is absent or Gln, Lys, Arg, Cit, Glu, Aib, Ac4c, Ac5c or U;

aa₂₁ is absent or Asp, Glu, Leu, Aib, Ac4c, Ac5c or U;

aa₂₂ is absent or Phe, Trp, Nal2, Aib, Ac4c, Ac5c or U;

aa₂₃ is absent or Val, Ile, Aib, Ac4c, Ac5c or U;

aa₂₄ is absent or Ala, Gln, Glu, Cit or U;

aa₂₅ is absent or Trp, Nal2 or U;

aa₂₆ is absent or Leu or U;

aa₂₇ is absent or Met, Val, Leu, Nle, Lys or U;

aa₂₈ is absent or Asn, Lys, Glu, Gln, Cit or U;

aa₂₉ is absent or Thr, Gly, Aib, Ac4c, Ac5c or U;
 aa₃₀ is absent or Lys, Aib, Ac4c, Ac5c, Arg or U;
 aa₃₁ is absent or Arg, Aib, Ac4c, Ac5c or U;
 aa₃₂ is absent or Asn, Aib, Ac4c, Ac5c or U;
 aa₃₃ is absent or Arg, Aib, Ac4c, Ac5c or U;
 aa₃₄ is absent or Asn, Aib, Ac4c, Ac5c or U;
 aa₃₅ is absent or Asn, Aib, Ac4c, Ac5c or U;
 aa₃₆ is absent or Ala, Ile, Aib, Ac4c, Ac5c or U;
 aa₃₇ is absent or U;

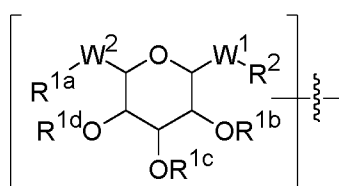
U is a natural or unnatural amino acid comprising a functional group used for covalent attachment to a surfactant X;

any two of aa₁-aa₃₇ can optionally be cyclized through their side chains to form a lactam; and provided that one, or at least one, of aa₁₀-aa₃₇ is a linker amino acid U covalently attached to a surfactant X.

[0052] A surfactant moiety can also be attached to a linker amino acid U of the peptide via R^{1a}, R^{1b}, R^{1c} or R^{1d}. For example, W² can be -O- and one occurrence of R^{1a} can be bond to a hydroxyl-bearing natural or unnatural amino acid (e.g., serine, homoserine or threonine), or W² can be -S- and one occurrence of R^{1a} can be bond to a thiol/sulfhydryl-bearing natural or unnatural amino acid (e.g., cysteine or homocysteine), or W² can be -NH- and one occurrence of R^{1a} can be bond to an amino-bearing natural or unnatural amino acid (e.g., lysine or ornithine). In certain embodiments, U attached to a surfactant moiety via R^{1a} is an unnatural amino acid. A linker amino acid U attached to a surfactant moiety via R^{1a} can be the L- or D-isomer. In certain embodiments, U is the D-isomer.

[0053] In some embodiments, n is 1. In other embodiments, n is 2, and a first glycoside is attached to a second glycoside via a bond between W² of the first glycoside and -OR^{1b}, -OR^{1c} or -OR^{1d} of the second glycoside. In yet other embodiments, n is 3, and a first glycoside is attached to a second glycoside via a bond between W² of the first glycoside and -OR^{1b}, -OR^{1c} or -OR^{1d} of the second glycoside, and the second glycoside is attached to a third glycoside via a bond between W² of the second glycoside and -OR^{1b}, -OR^{1c} or -OR^{1d} of the third glycoside.

[0054] In some embodiments of the peptide products of Formula I-A, the surfactant X is:



Formula I

wherein:

R^{1a} is H, a protecting group, a saccharide, an unsubstituted or substituted C₁-C₃₀ alkyl group, or a steroid nucleus-containing group;

R^{1b}, R^{1c} and R^{1d} independently are H, a protecting group, a saccharide, or an unsubstituted or substituted C₁-C₃₀ alkyl group;

R² is a bond to U, -NH-, -S-, -triazolo-, -NH(C=O)-CH₂- or -(CH₂)_m-maleimide-;

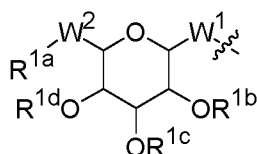
W¹ is -CH₂-, -CH₂-O-, -CH₂-S-, -(C=O)-, -(C=O)-NH-, -(C=S)-, or -(C=S)-NH-;

W² is -O- or -S-;

m is 1-10; and

at least one of R^{1a}, R^{1b}, R^{1c} and R^{1d} is an unsubstituted or substituted C₁-C₃₀ alkyl group or a steroid nucleus-containing group.

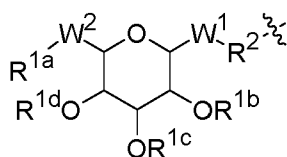
[0055] In certain embodiments, the surfactant X has the structure



in which R² is a bond to U. In certain embodiments, W¹ is -C(=O)NH- and R² is a bond between W¹ and an amino acid

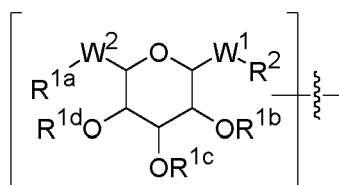
residue U (e.g., the side-chain amino group of a lysine residue) of the peptide.

[0056] In other embodiments, the surfactant X is



In certain embodiments, W^1 is $-\text{CH}_2-\text{O}-$, $-\text{CH}_2-\text{S}-$ or $-(\text{C}=\text{O})-\text{NH}-$, and R^2 is a $-(\text{CH}_2)_m$ -maleimide- group that forms a bond with a suitable functional group of an amino acid residue U of the peptide (e.g., a thiol group of a cysteine residue forms a thioether bond with the maleimide group).

[0057] In further embodiments, the surfactant X has the structure:



Formula I

wherein:

R^{1a} is H, a protecting group, a saccharide, an unsubstituted or substituted C_1 - C_{30} alkyl group, or a steroid nucleus-containing group;

R^{1b} , R^{1c} and R^{1d} independently are H, a protecting group, or an unsubstituted or substituted C_1 - C_{30} alkyl group;

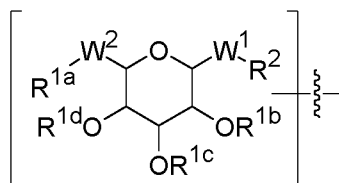
R^2 is a bond to U;

W^1 is $-(\text{C}=\text{O})-\text{NH}-$;

W^2 is $-\text{O}-$; and

at least one of R^{1a} , R^{1b} , R^{1c} and R^{1d} is an unsubstituted or substituted C_1 - C_{30} alkyl group or a steroid nucleus-containing group.

[0058] In certain embodiments, the surfactant X has the structure:



Formula I

wherein:

R^{1a} is an unsubstituted or substituted C_1 - C_{30} alkyl group;

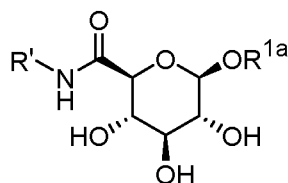
R^{1b} , R^{1c} , and R^{1d} are H;

R^2 is a bond to U;

W^1 is $-(\text{C}=\text{O})-\text{NH}-$; and

W^2 is $-\text{O}-$.

[0059] In some embodiments, the surfactant X is a 1-O-alkyl beta-D-glucuronyl moiety:



wherein R^{1a} is an unsubstituted or substituted C₁-C₃₀, C₁-C₂₀ or C₆-C₂₀ alkyl group, and R' is a peptide that is attached to the surfactant moiety via the N-terminal alpha amino group or a side-chain amino group of a natural or unnatural amino acid (e.g., lysine or ornithine). In certain embodiments, R^{1a} is an unsubstituted or substituted C₈-C₂₀, C₁₂-C₂₀ or C₁₂-C₁₆ alkyl group.

[0060] In some embodiments, an alkyl group attached to a saccharide is an unsubstituted or substituted C₁-C₃₀, C₁-C₂₀, C₆-C₃₀ or C₆-C₂₀ alkyl group. In certain embodiments, an alkyl group attached to a saccharide is an unsubstituted or substituted C₈-C₂₀, C₆-C₁₈ or C₁₂-C₁₈ alkyl group.

[0061] In some embodiments, at least one occurrence of R^{1a}, R^{1b}, R^{1c}, R^{1d} or R² is an unsubstituted or substituted C₁-C₃₀ alkyl group. In certain embodiments, an alkyl group is attached to at least one occurrence of R^{1b}, R^{1c} or R^{1d} via an ether bond (-O-alkyl). In further embodiments, an alkyl group is attached to at least one occurrence of R² via an ether bond (-O-alkyl) or an amide bond [-C(=O)NH-alkyl].

[0062] In some embodiments, at least one occurrence, or the sole occurrence, of R^{1a} is an unsubstituted or substituted C₁-C₃₀, C₆-C₃₀, C₆-C₂₀ or C₈-C₂₀ alkyl group. In certain embodiments, at least one occurrence, or the sole occurrence, of R^{1a} is an unsubstituted or substituted C₁₂-C₂₀ alkyl group.

[0063] In some embodiments, an alkyl group (e.g., a 1-alkyl group) is internally or/and terminally substituted with a carboxyl or carboxylate group. In certain embodiments, an alkyl group (e.g., a 1-alkyl group) is substituted with a carboxyl or carboxylate group at the distal end of the alkyl group.

[0064] In additional embodiments, at least one occurrence, or the sole occurrence, of R^{1a} is a saccharide. In certain embodiments, the saccharide is a galactose. The galactose can be alpha- or beta-linked. In some embodiments, the galactose is alpha-linked galactopyranose, beta-linked galactopyranose, alpha-linked galactofuranose, or beta-linked galactofuranose.

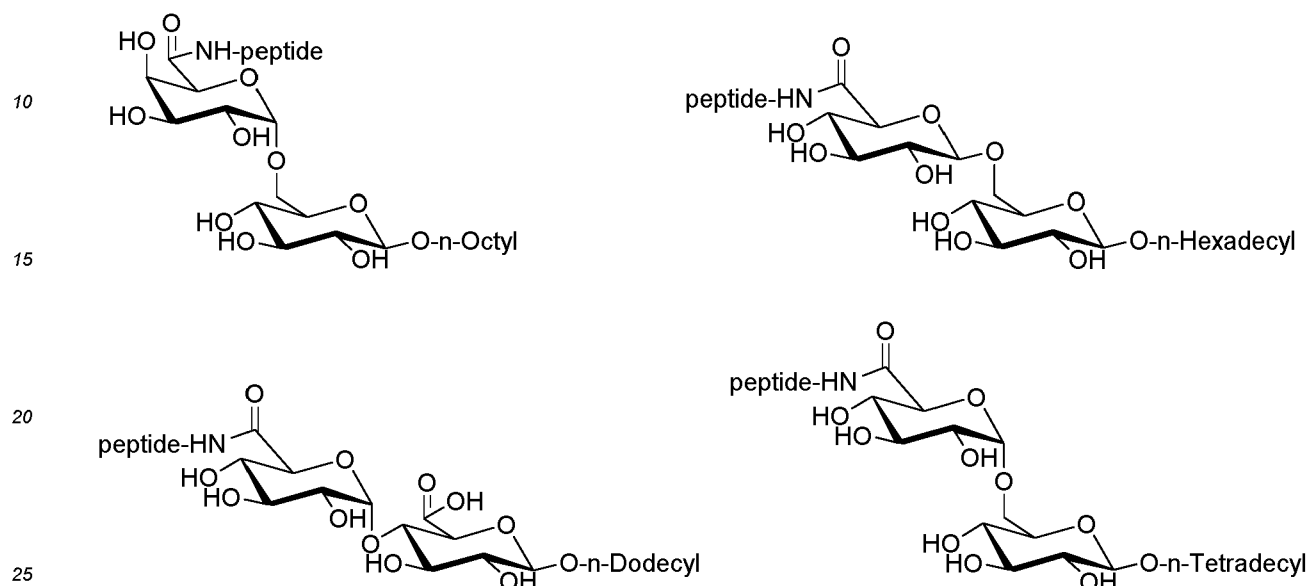
[0065] In some embodiments, the saccharide group of the surfactant moiety is a monosaccharide. In certain embodiments, the monosaccharide is a suitably functionalized glucose, galactose or mannose, such as glucuronic acid, galacturonic acid or mannouronic acid. In other embodiments, the saccharide is a disaccharide. In some embodiments, the disaccharide contains two glucose molecules, or one glucose molecule and one galactose molecule. In certain embodiments, the disaccharide is diglucuronic acid or a suitably functionalized melibiose, maltose, isomaltose, gentiobiose or lactose, such as melibiouronic acid, maltouronic acid, isomaltouronic acid, gentiobiouronic acid or lactouronic acid. The terms "-uronic acid" and "-uronyl" are used interchangeably herein in regard to a saccharide group of a surfactant moiety.

[0066] In some embodiments, the surfactant X is a 1-alkyl glycoside, wherein an unsubstituted or substituted alkyl group is attached to the C-1 position of a saccharide via a glycosidic bond. The glycosidic bond can be an O-, S-, N- or C-glycosidic bond. In certain embodiments, the glycosidic bond is an O-glycosidic bond. The 1-alkyl group can be the beta- or alpha-anomer. In certain embodiments, 1-alkyl group is the beta-anomer.

[0067] In some embodiments, the surfactant X is selected from 1-eicosyl beta-D-glucuronic acid, 1-octadecyl beta-D-glucuronic acid, 1-hexadecyl beta-D-glucuronic acid, 1-tetradecyl beta-D-glucuronic acid, 1-dodecyl beta-D-glucuronic acid, 1-decyl beta-D-glucuronic acid, 1-octyl beta-D-glucuronic acid, 1-eicosyl beta-D-diglucuronic acid, 1-octadecyl beta-D-diglucuronic acid, 1-hexadecyl beta-D-diglucuronic acid, 1-tetradecyl beta-D-diglucuronic acid, 1-dodecyl beta-D-diglucuronic acid, 1-decyl beta-D-diglucuronic acid, 1-octyl beta-D-diglucuronic acid, 1-eicosyl beta-D-isomaltouronic acid, 1-octadecyl beta-D-isomaltouronic acid, 1-hexadecyl beta-D-isomaltouronic acid, 1-tetradecyl beta-D-isomaltouronic acid, 1-dodecyl beta-D-isomaltouronic acid, 1-decyl beta-D-isomaltouronic acid, 1-octyl beta-D-isomaltouronic acid, 1-eicosyl beta-D-gentiobiouronic acid, 1-octadecyl beta-D-gentiobiouronic acid, 1-hexadecyl beta-D-gentiobiouronic acid, 1-tetradecyl beta-D-gentiobiouronic acid, 1-dodecyl beta-D-gentiobiouronic acid, 1-decyl beta-D-gentiobiouronic acid, 1-octyl beta-D-gentiobiouronic acid, 1-eicosyl beta-D-melibiouronic acid, 1-octadecyl beta-D-melibiouronic acid, 1-hexadecyl beta-D-melibiouronic acid, 1-tetradecyl beta-D-melibiouronic acid, 1-dodecyl beta-D-melibiouronic acid, 1-decyl beta-D-melibiouronic acid, 1-octyl beta-D-melibiouronic acid, functionalized 1-eicosyl beta-D-glucose, 1-octadecyl beta-D-glucose, 1-hexadecyl beta-D-glucose, 1-tetradecyl beta-D-glucose, 1-dodecyl beta-D-glucose, 1-decyl beta-D-glucose, 1-octyl beta-D-glucose, 1-eicosyl beta-D-maltoside, 1-octadecyl beta-D-maltoside, 1-hexadecyl beta-D-maltoside, 1-tetradecyl beta-D-maltoside, 1-dodecyl beta-D-maltoside, 1-decyl beta-D-maltoside, 1-octyl beta-D-maltoside, 1-eicosyl beta-D-melibioside, 1-octadecyl beta-D-melibioside, 1-hexadecyl beta-D-melibioside, 1-tetradecyl beta-D-melibioside, 1-dodecyl beta-D-melibioside, 1-decyl beta-D-melibioside, 1-octyl beta-D-melibioside, the corresponding 1-alkyl glycosides with a 6-carboxyl group or 6,6'-dicarboxyl groups, the corresponding 1-alkyl alpha-anomers, and the like. In

certain embodiments, the surfactant X is a 1-alkyl beta-D-glucuronic acid.

[0068] As illustrative examples, shown below are a 1-O-octyl beta-D-melibiouroyl moiety (upper left), a 1-O-hexadecyl beta-D-gentiobouronyl moiety (upper right), a 1-O-dodecyl beta-D-maltouronyl moiety (lower left, either or both carboxyl groups can be attached to the peptide), and a 1-O-tetradecyl beta-D-isomaltouronyl moiety (lower right) attached to an amino group of a peptide (e.g., the side-chain amino group of a lysine residue).



[0069] In some embodiments, a surfactant moiety is attached to a linker amino acid U of the peptide via an amide bond.

[0070] The peptide of a peptide product can be covalently attached to one or more surfactant moieties. In certain embodiments, a peptide product has one surfactant moiety. In further embodiments, a peptide product has two surfactant moieties, which can be the same or different. In other embodiments, a peptide product has three surfactant moieties, which can be the same or different.

[0071] A linker amino acid U can be any natural or unnatural amino acid that has a functional group suitable for covalent attachment to a surfactant moiety. In some embodiments, U is a dibasic natural or unnatural amino acid (e.g., one having a side-chain amino group such as lysine or ornithine), a diacidic natural or unnatural amino acid (e.g., one having a side-chain carboxyl group such as glutamic acid or aspartic acid), a natural or unnatural amino acid having a thiol/sulfhydryl group (e.g., cysteine), a natural or unnatural amino acid having a hydroxyl group (e.g., serine or threonine), or an unnatural amino acid having an $-N_3$ group, an acetylenic group, a haloacetyl group (e.g., $-NHC(=O)CH_2Br$) or a $-(CH_2)_m$ -maleimide group, wherein m is 1-10. A haloacetyl group or a maleimide group of a linker amino acid can couple with, e.g., a thiol group of a saccharide group of the surfactant moiety, or vice versa. An azide group or an alkyne group of a linker amino acid can do a 1,3-dipolar cycloaddition with an alkyne group or an azide group, respectively, of a saccharide group of the surfactant moiety using a copper catalyst, for example, to form a triazole. In certain embodiments, U is a lysine, ornithine (Orn), cysteine or glutamic acid residue. Like any amino acid residue of the peptide, U can be an L- or D-amino acid.

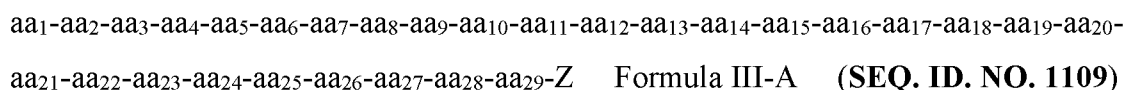
[0072] A linker amino acid U can be an internal or/and a terminal amino acid residue of the peptide. The functional group of U that forms a covalent bond with a surfactant moiety can be a side-chain functional group of an internal or terminal amino acid residue, or can be the alpha amino group of the N-terminal amino acid residue or the alpha carboxyl group of the C-terminal amino acid residue.

[0073] In some embodiments, side-chain functional groups of two amino acid residues (denoted with an asterisk), such as a lysine residue and a glutamic acid residue, of the peptide are linked to form a cyclic structure, such as a lactam. A lactam formed between the side-chain functional groups of a lysine residue and a glutamic acid residue can stabilize the α -helical structure of a peptide. A cyclic structure can also be formed by a disulfide bond between the thiol group of two cysteine residues, which can restrict conformation and promote α -helix formation. A "click reaction" between the side-chain azide and alkyne groups of two unnatural amino acid residues can also form a heterocyclic structure (a triazole) that restricts conformation and stabilizes an α -helix (Le Chevalier et al., J. Peptide Sci., 15:451-454 [2009]). Furthermore, the side-chain alkene groups of two unnatural amino acid residues can cyclize by olefin metathesis to form a C=C double bond, which can then be reduced to a C-C single bond (Verdine and Hilinski, Meth. Enzymol., 503:3-33 [2011]).

[0074] In some embodiments, peptide products of Formula I-A comprise at least amino acid residues aa_1 - aa_{17} ,

aa₁-aa₁₈, aa₁-aa₁₉ or aa₁-aa₂₀ of **SEQ. ID. NO. 1108**. In further embodiments, peptide products of Formula I-A comprise at least amino acid residues aa₁-aa₂₇, aa₁-aa₂₈, aa₁-aa₂₉ or aa₁-aa₃₀ of **SEQ. ID. NO. 1108**.

[0075] In some embodiments, peptide products of Formula I-A have Formula III-A:



wherein:

10 Z is -OH or -NHR³, wherein R³ is H, unsubstituted or substituted C₁-C₁₂ alkyl, or a PEG-containing group of less than 10 Da;

 aa₁ is His, N(R³)His, N(Ac)His, or pGlu-His;

 aa₂ is Ser, Ala, Gly, MePro, Aib, Ac4c or Ac5c;

15 aa₃ is Gln or Cit;

 aa₄ is Gly or D-Ala;

 aa₅ is Thr or Ser;

 aa₆ is Phe, Trp, 2FPhe, MePhe, 2FMePhe or Nal2;

 aa₇ is Thr or Ser;

20 aa₈ is Ser or Asp;

 aa₉ is Asp or Glu;

 aa₁₀ is Tyr, Leu, Met, Nal2, Bip, Bip2EtMeO, Glu, Lys or U(X);

 aa₁₁ is absent or Ser, Asn, Bip or U(X);

 aa₁₂ is absent or Lys, Glu, Ser, Arg or U(X);

25 aa₁₃ is absent or Tyr, Gln, Cit or U(X);

 aa₁₄ is absent or Leu, Met, Nle, Glu, Lys or U(X);

 aa₁₅ is absent or Asp, Glu or U(X);

 aa₁₆ is absent or Ser, Gly, Glu, Ala, Aib, Ac5c, Lys, Arg or U(X);

 aa₁₇ is absent or Arg, hArg, Gln, Glu, Lys, Cit, Aib, Ac4c, Ac5c or U(X);

30 aa₁₈ is absent or Arg, hArg, Ala, Aib, Ac4c, Ac5c or U(X);

 aa₁₉ is absent or Ala, Val, Aib, Ac4c, Ac5c or U(X);

 aa₂₀ is absent or Gln, Lys, Arg, Cit, Glu, Aib, Ac4c, Ac5c or U(X);

 aa₂₁ is absent or Asp, Glu, Leu, Aib, Ac4c, Ac5c or U(X);

 aa₂₂ is absent or Phe, Trp, Nal2, Aib, Ac4c, Ac5c or U(X);

35 aa₂₃ is absent or Val, Ile, Aib, Ac4c, Ac5c or U(X);

 aa₂₄ is absent or Ala, Gln, Glu, Cit or U(X);

 aa₂₅ is absent or Trp, Nal2 or U(X);

 aa₂₆ is absent or Leu or U(X);

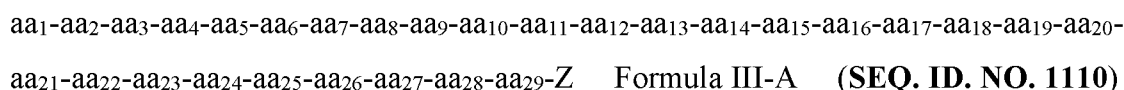
 aa₂₇ is absent or Met, Val, Leu, Nle, Lys or U(X);

40 aa₂₈ is absent or Asn, Lys, Glu, Gln or U(X);

 aa₂₉ is absent or Thr, Gly, Aib, Ac4c, Ac5c or U(X);

 any two of aa₁-aa₂₉ can optionally be cyclized through their side chains to form a lactam; and
 provided that one, or at least one, of aa₁₀-aa₁₂ and aa₁₆-aa₂₉ is a natural or unnatural amino acid U covalently attached to a surfactant X.

45 **[0076]** In certain embodiments, peptide products of Formula III-A have the structure:



wherein:

55 Z is -OH or -NHR³, wherein R³ is H, unsubstituted or substituted C₁-C₁₂ alkyl, or a PEG-containing group of less than 10 Da;

 aa₁ is His;

 aa₂ is Aib;

 aa₃ is Gln;

aa₄ is Gly;
 aa₅ is Thr;
 aa₆ is Phe;
 aa₇ is Thr;
 5 aa₈ is Ser;
 aa₉ is Asp;
 aa₁₀ is Tyr, Glu, Lys or U(X);
 aa₁₁ is Ser;
 aa₁₂ is Lys or Glu;
 10 aa₁₃ is Tyr;
 aa₁₄ is Leu, Glu or Lys;
 aa₁₅ is Asp;
 aa₁₆ is Glu or Lys;
 aa₁₇ is Gln, Glu or U(X);
 15 aa₁₈ is Ala;
 aa₁₉ is Ala;
 aa₂₀ is Glu, Lys or U(X);
 aa₂₁ is Glu;
 aa₂₂ is Phe;
 20 aa₂₃ is Ile;
 aa₂₄ is Gln, Glu or U(X);
 aa₂₅ is Trp;
 aa₂₆ is Leu;
 aa₂₇ is Leu;
 25 aa₂₈ is Glu or Gln;
 aa₂₉ is Thr;
 aa₁₀ and aa₁₄, or aa₁₂ and aa₁₆, or aa₁₆ and aa₂₀ can optionally be cyclized through their side chains to form a lactam; and
 provided that one, or at least one, of aa₁₀, aa₁₇, aa₂₀ and aa₂₄ is a natural or unnatural amino acid U covalently
 30 attached to a surfactant X.

[0077] In further embodiments, peptide products of Formula I-A have Formula III-B:

35 His₁-aa₂-aa₃-Gly₄-Thr₅-aa₆-Thr₇-Ser₈-Asp₉-aa₁₀-aa₁₁-aa₁₂-aa₁₃-aa₁₄-aa₁₅-aa₁₆-aa₁₇-aa₁₈-
 aa₁₉-aa₂₀-aa₂₁-aa₂₂-aa₂₃-aa₂₄-aa₂₅-aa₂₆-aa₂₇-aa₂₈-aa₂₉-aa₃₀-Z Formula III-B
 (SEQ. ID. NO. 1111)

40 wherein:

Z is -OH or -NHR³, wherein R³ is H, unsubstituted or substituted C₁-C₁₂ alkyl, or a PEG-containing group of less than 10 Da;
 aa₂ is Gly, MePro or Aib;
 45 aa₃ is Gln or Cit;
 aa₆ is Phe, 2FPhe, MePhe, 2FMePhe or Nal₂;
 aa₁₀ is Tyr, Nal₂, Bip, Bip2EtMeO, Glu, Lys or U(X);
 aa_n is absent or Ser, Asn, Bip or U(X);
 aa₁₂ is absent or Lys, Glu, Ser or U(X);
 50 aa₁₃ is absent or Tyr, Gln, Cit or U(X);
 aa₁₄ is absent or Leu, Nle, Glu, Lys or U(X);
 aa₁₅ is absent or Asp, Glu or U(X);
 aa₁₆ is absent or Ser, Gly, Glu, Ala, Aib, Lys, Arg or U(X);
 aa₁₇ is absent or Arg, hArg, Gln, Glu, Lys, Cit, Aib or U(X);
 55 aa₁₈ is absent or Arg, hArg, Ala, Aib, Ac4c, Ac5c or U(X);
 aa₁₉ is absent or Ala, Aib or U(X);
 aa₂₀ is absent or Gln, Lys, Arg, Cit, Glu, Aib or U(X);
 aa₂₁ is absent or Asp, Glu, Leu, Aib or U(X);

aa₂₂ is absent or Phe or U(X)
 aa₂₃ is absent or Val, Ile, Aib or U(X);
 aa₂₄ is absent or Ala, Glu, Gln or U(X);
 aa₂₅ is absent or Trp or U(X);
 aa₂₆ is absent or Leu or U(X);
 aa₂₇ is absent or Met, Val, Leu, Nle, Lys or U(X);
 aa₂₈ is absent or Asn, Glu, Gln, Cit or U(X);
 aa₂₉ is absent or Thr, Aib or U(X);
 aa₃₀ is absent or Arg or U(X);
 any two of aa₁-aa₂₃ can optionally be cyclized via their side chains to form a lactam; and
 provided that one, or at least one, of aa₁₀-aa₁₂, aa₁₆-aa₂₄ and aa₂₈ is a natural or unnatural amino acid U covalently
 attached to a surfactant X.

[0078] In some embodiments of peptide products of Formula I-A, III-A or III-B:

aa₂ is Gly, Aib or Ac4c; or
 aa₁₂ is lysine; or
 aa₁₄ is leucine; or
 aa₁₇ is glycine or homoarginine (hArg); or
 aa₁₇, aa₁₈, aa₂₀, aa₂₄ or aa₂₈, or any combination thereof, is lysine attached to a surfactant X; or
 aa₁₆ and aa₂₀ are cyclized through their side chains to form a lactam; or
 the surfactant X comprises an unsubstituted or substituted dodecyl, tetradecyl, hexadecyl or octadecyl alkyl group; or
 any combination or all of the above.

[0079] In some embodiments, the peptide of peptide products described herein comprises one or more Aib residues at or near the N-terminus, at or near the C-terminus or internally, or any combination or all thereof. An Aib residue can protect the peptide from degradation by proteases such as dipeptidyl peptidase 4 (DPP-4). In certain embodiments, aa₂ is Aib.

[0080] In some embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
 aa₁₇-Ala₁₈-Ala₁₉-aa₂₀-Glu₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂
(SEQ. ID. NO. 1126)

wherein:

aa₂ is Gly or Aib;
 aa₁₆ is Glu, Ser, Ala, Lys or Aib;
 aa₁₇ is Gln, Lys or U(X);
 aa₂₀ is Lys, Glu or Arg;
 aa₂₃ is Ile or Val;
 aa₂₄ is Ala, Gln or U(X);
 aa₂₇ is Met, Val or Leu; and
 aa₂₈ is Asn, Gln or U(X).

[0081] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
aa₁₇-Arg₁₈-Ala₁₉-aa₂₀-Asp₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂

(SEQ. ID. NO. 1127)

wherein:

aa₂ is Gly or Aib;
aa₁₆ is Glu, Ala or Aib;
aa₁₇ is Arg, hArg or Gln;
aa₂₀ is U(X) [e.g., Lys(X)];
aa₂₃ is Ile or Val;
aa₂₄ is Gln or Ala;
aa₂₇ is Leu or Val; and
aa₂₈ is Asn or Gln.

[0082] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅- aa₁₆-
aa₁₇-Ala₁₈-Ala₁₉-aa₂₀-Glu₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂

(SEQ. ID. NO. 774)

wherein:

aa₂ is Gly or Aib;
aa₁₆ is Glu, Ser, Ala, Lys or Aib;
aa₁₇ is Gln, Glu, Lys or U(X);
aa₂₀ is Lys, Glu or Arg;
aa₂₃ is Ile or Val;
aa₂₄ is Ala, Gln or U(X);
aa₂₇ is Met, Val or Leu; and
aa₂₈ is Asn, Gln or U(X).

[0083] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
aa₁₇-Ala₁₈-Ala₁₉-Lys₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-aa₂₇-Asn₂₈-Thr₂₉-NH₂ (SEQ.

ID. NO. 775)

wherein:

aa₂ is Gly or Aib;
aa₁₆ is Glu, Ala or Aib;
aa₁₇ is U(X) [e.g., Lys(X)]; and
aa₂₇ is Leu or Val.

[0084] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
aa₁₇-Arg₁₈-Ala₁₉-aa₂₀-Asp₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂

(SEQ. ID. NO. 776)

wherein:

aa₂ is Gly or Aib;
 aa₁₆ is Glu, Ser, Ala or Aib;
 aa₁₇ is Arg, hArg or Gln;
 aa₂₀ is Lys or U(X);
 aa₂₃ is Ile or Val;
 aa₂₄ is Ala, Gln or U(X);
 aa₂₇ is Leu or Val; and
 aa₂₈ is Asn, Gln or U(X).

[0085] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
 aa₁₇-Arg₁₈-Ala₁₉-aa₂₀-Asp₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂
(SEQ. ID. NO. 777)

wherein:

aa₂ is Gly or Aib;
 aa₁₆ is Glu, Ser, Ala or Aib;
 aa₁₇ is Arg, hArg or Gln;
 aa₂₀ is Lys or U(X);
 aa₂₃ is Ile or Val;
 aa₂₄ is Gln, Ala or U(X);
 aa₂₇ is Leu or Val; and
 aa₂₈ is Asn, Gln or U(X).

[0086] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 aa₁₆*-aa₁₇-Ala₁₈-Ala₁₉-aa₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega-X)₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-
 Thr₂₉-NH₂ **(SEQ. ID. NO. 778)**

wherein:

aa₂ is Aib or Gly;
 aa₁₆* and aa₂₀* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₁₇ is Arg, hArg or Gln;
 aa₂₇ is Met, Val, Leu or Nle; and
 aa₂₈ is Asn or Gln.

In some embodiments, the surfactant X is 1'-alkyl beta-D-glucuronyl. In certain embodiments, the alkyl group is linear C₈-C₂₀ alkyl.

[0087] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
 aa₁₇-Ala₁₈-Ala₁₉-Lys₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Ala₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Asn₂₈-Thr₂₉-NH₂
(SEQ. ID. NO. 779)

wherein:

aa₂ is Aib or Gly;
 aa₁₆ is Glu, Ala or Aib; and
 aa₁₇ is Lys(N-omega-X).

5 In some embodiments, the surfactant X is 1'-alkyl beta-D-glucuronyl. In certain embodiments, the alkyl group is linear C₈-C₂₀ alkyl.

[0088] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

10 His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-aa₁₆-
 aa₁₇-Arg₁₈-Ala₁₉-aa₂₀-Asp₂₁-Phe₂₂-aa₂₃-aa₂₄-Trp₂₅-Leu₂₆-aa₂₇-aa₂₈-Thr₂₉-NH₂
 (SEQ. ID. NO. 780)

15 wherein:

aa₂ is Gly or Aib;
 aa₁₆ is Glu, Ala or Aib;
 aa₁₇ is Arg or hArg;
 20 aa₂₀ is Lys(N-omega-X);
 aa₂₃ is Ile or Val;
 aa₂₄ is Gln or Ala;
 aa₂₇ is Leu or Val; and
 aa₂₈ is Asn or Gln.

25 In some embodiments, the surfactant X is 1'-alkyl beta-D-glucuronyl. In certain embodiments, the alkyl group is linear C₈-C₂₀ alkyl.

[0089] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

30 His₁-aa₂-Gln₃-Gly₄-Thr₅-aa₆-Thr₇-Ser₈-Asp₉-aa₁₀-aa₁₁-Z (SEQ. ID. NO. 781) wherein:

aa₂ is Gly, Aib or MePro;
 aa₆ is Phe, 2FPhe, MePhe or 2FMePhe;
 aa₁₀ is Tyr, Nal2, Bip, Bip2Et or Bip2EtMeO; and
 aa₁₁ is Lys(N-omega-X).

35 In some embodiments, the surfactant X is 1'-alkyl beta-D-glucuronyl. In certain embodiments, the alkyl group is linear C₈-C₂₀ alkyl.

[0090] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

40 His₁-aa₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 Glu₁₆-U(X)₁₇-Ala₁₈-Ala₁₉-Lys₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-
 NH₂ (SEQ. ID. NO. 795)

45 wherein:

aa₂ is Gly or Aib; and
 aa₂₈ is Asn or Gln.

50 [0091] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 55 aa₁₆*-Gln₁₇-Ala₁₈-Ala₁₉-aa₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega-X)₂₄-Trp₂₅-Leu₂₆-Leu₂₇-
 aa₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 796)

wherein:

aa₁₆* and aa₂₀* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₂₈ is Asn or Gln; and
 the surfactant X comprises a 1-alkyl beta-D-glucoside, 1-alkyl beta-D-maltoside, 1-alkyl beta-D-melibioside or the like, or the corresponding alpha anomer, wherein alkyl is linear C₈-C₂₀ alkyl.

[0092] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 Glu₁₆*-Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega-X)₂₄-Trp₂₅-Leu₂₆-
 Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 797)

wherein:

Glu₁₆* and Lys₂₀* are cyclized through their side chains to form a lactam; and
 the surfactant X comprises a 1-alkyl beta-D-glucoside, 1-alkyl beta-D-maltoside, 1-alkyl beta-D-melibioside or the like, or the corresponding alpha anomer, wherein alkyl is linear C₈-C₂₀ alkyl.

[0093] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-U(X)₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 aa₁₆*-aa₁₇-Ala₁₈-Ala₁₉-aa₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-aa₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-Z
 (SEQ. ID. NO. 1025)

wherein:

Z is -OH or -NHR³, wherein R³ is H or a PEG-containing group of less than 10 Da;
 aa₁₆* and aa₂₀* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₁₇ is Glu or Gln;
 aa₂₄ is Ala, Glu or Gln; and
 aa₂₈ is Asn or Gln.

[0094] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 aa₁₆*-U(X)₁₇-Ala₁₈-Ala₁₉-aa₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-aa₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-Z
 (SEQ. ID. NO. 1026)

wherein:

Z is -OH or -NHR³, wherein R³ is H or a PEG-containing group of less than 10 Da;
 aa₁₆* and aa₂₀* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₂₄ is Ala, Glu or Gln; and
 aa₂₈ is Asn or Gln.

[0095] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-aa₁₀*-Ser₁₁-Lys₁₂-Tyr₁₃-aa₁₄*-Asp₁₅-
 Ser₁₆-aa₁₇-Ala₁₈-Ala₁₉-U(X)₂₀-Glu₂₁-Phe₂₂-Ile₂₃-aa₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-Z
 (SEQ. ID. NO. 1027)

wherein:

Z is -OH or -NHR³, wherein R³ is H or a PEG-containing group of less than 10 Da;
 aa₁₀* and aa₁₄* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₁₇ is Glu or Gln;
 aa₂₄ is Ala, Glu or Gln; and
 aa₂₈ is Asn or Gln.

[0096] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-aa₁₂*-Tyr₁₃-Gln₁₄-Asp₁₅-
 aa₁₆*-aa₁₇-Ala₁₈-Ala₁₉-U(X)₂₀-Glu₂₁-Phe₂₂-Ile₂₃-aa₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-Z
 (SEQ. ID. NO. 1028)

wherein:

Z is -OH or -NHR³, wherein R³ is H or a PEG-containing group of less than 10 Da;
 aa₁₂* and aa₁₆* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₁₇ is Glu or Gln;
 aa₂₄ is Ala, Glu or Gln; and
 aa₂₈ is Asn or Gln.

[0097] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 aa₁₆*-Gln₁₇-Ala₁₈-Ala₁₉-aa₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-U(X)₂₄-Trp₂₅-Leu₂₆-Leu₂₇-aa₂₈-Thr₂₉-Z
 (SEQ. ID. NO. 1029)

wherein:

Z is -OH or -NHR³, wherein R³ is H or a PEG-containing group of less than 10 Da;
 aa₁₆* and aa₂₀* independently are Lys or Glu and are cyclized through their side chains to form a lactam;
 aa₂₈ is Asn or Gln; and
 the surfactant X comprises a 1-alkyl beta-D-glucoside, 1-alkyl beta-D-maltoside, 1-alkyl beta-D-melibioside or the like, or the corresponding alpha anomer, wherein alkyl is linear C₈-C₂₀ alkyl.

[0098] In other embodiments, peptide products of Formula I-A, III-A or III-B have the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-
 Glu₁₆*-Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega-X)₂₄-Trp₂₅-Leu₂₆-
 Leu₂₇-Gln₂₈-Thr₂₉-Z (SEQ. ID. NO. 1113)

wherein:

Z is -OH or -NHR³;
 Glu₁₆* and Lys₂₀* are cyclized through their side chains to form a lactam; and

the surfactant X comprises a 1-alkyl beta-D-glucoside, 1-alkyl beta-D-maltoside, 1-alkyl beta-D-melibioside or the like, or the corresponding alpha anomer, wherein alkyl is linear C₈-C₂₀ alkyl.

[0099] In some embodiments, a peptide product has the structure:

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-dodecyl beta-D-glucuronyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 601);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-tetradecyl beta-D-glucuronyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 602);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-hexadecyl beta-D-glucuronyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 603);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-octadecyl beta-D-glucuronyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 604);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-octyl beta-D-melibiouroyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 630);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-dodecyl beta-D-melibiouroyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 631);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-tetradecyl beta-D-melibiouroyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 632);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-hexadecyl beta-D-
melibiouroyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 633);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu₁₆*-
Gln₁₇-Ala₁₈-Ala₁₉-Lys₂₀*-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-octadecyl beta-D-melibiouroyl])₂₄-
Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 634);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-hexadecyl alpha-D-
 melibiouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 805);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-tetradecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 819);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-hexadecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 820);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-octadecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 821);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-dodecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Lys(N-omega[1-dodecyl beta-D-glucouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂
 (SEQ. ID. NO. 1114);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-tetradecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Lys(N-omega[1-tetradecyl beta-D-glucouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂
 (SEQ. ID. NO. 1115);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-hexadecyl alpha-D-melibiouronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-
 Lys(N-omega[1-hexadecyl beta-D-glucouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂
 (SEQ. ID. NO. 1116);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-(13-carboxyl-tridecyloxy) beta-D-glucuronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-
 Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1117);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-(15-carboxyl-pentadecyloxy) beta-D-glucuronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-
 Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1118);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Lys(N-omega[1-(17-carboxyl-heptadecyloxy) beta-D-glucuronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-
 Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1119);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(13-carboxyl-tridecyloxy) beta-D-
 glucuronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1120);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(15-carboxyl-pentadecyloxy) beta-
 D-glucuronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1121);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(17-carboxyl-heptadecyloxy) beta-
 D-glucuronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1122);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(13-carboxyl-tridecyloxy) beta-D-
 melibiouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1123);

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(15-carboxyl-pentadecyloxy) beta-
 D-melibiouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1124); or

His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-
 Gln₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Lys(N-omega[1-(17-carboxyl-heptadecyloxy) beta-
 D-melibiouronyl])₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ. ID. NO. 1125);

or a pharmaceutically acceptable salt thereof, wherein Glu₁₆* and Lys₂₀* denote residues that are cyclized through their side chains to form a lactam.

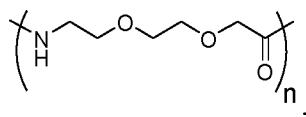
[0100] Additional peptide products are described in Table 1 in FIG. 1, Table 2 in FIG. 2, Table 3 in FIG. 3, and Table 4 in FIG. 4.

[0101] FIG. 5 illustrates the x-ray crystal structure of the binding site of the N-terminal region/ extracellular domain of the GLP-1 receptor and shows a critical hydrophobic ligand-binding region (Val^{19*}, Phe^{22*}, Trp^{25*} and Leu^{26*} of the ligand exendin-4, and the sequence of exendin-4 beyond Glu₁₅ interacts as an amphiphilic helix with this region). A 1-alkyl group of the surfactant moiety of a peptide product can engage in such a hydrophobic interaction with the GLP-1 receptor.

[0102] In some embodiments, a surfactant moiety is connected to a linker amino acid U of a peptide via a spacer. A

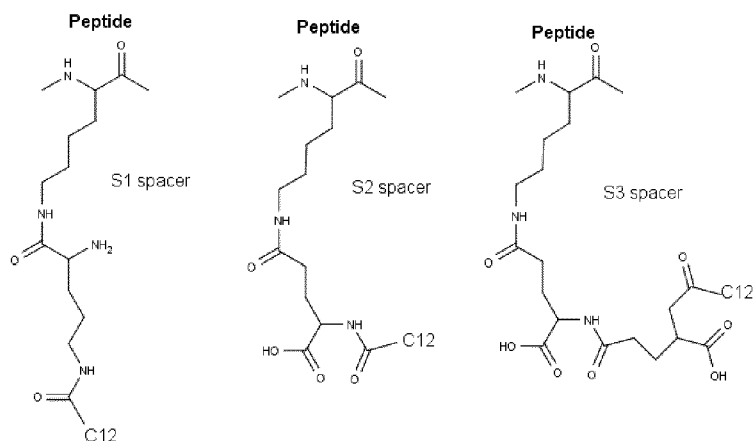
spacer can increase the aqueous solubility of the peptide product and increase the flexibility of the peptide-surfactant attachment point. In certain embodiments, the spacer is an amino acid spacer containing one or more amino acids. In some embodiments, one occurrence of R² of surfactant X is an amino acid spacer used for attachment to the peptide. In certain embodiments, an amino acid spacer is Gly_m, Glu_m or Lys_m, where m is an integer from 1 to 10. For example, W¹ can be -(C=O)- and R² can be a Gly_m spacer that is joined via the carboxyl group of the terminal glycine residue, or a Glu_m spacer that is joined via the alpha or gamma carboxyl group of the terminal glutamic acid residue, to the side-chain amino group of a lysine residue, or to the N-terminus, of the peptide, or R² can be a Lys_m spacer that is joined via the carboxyl group of the terminal lysine residue to the side-chain amino group of a lysine residue, or to the N-terminus, of the peptide.

[0103] In other embodiments, the spacer is a hydrophilic spacer that does not contain an amino acid residue. For example, such a spacer can be



where n is 1, 2 or 3. The amino group of such a spacer can be joined to, e.g., a carboxyl group at the C-6 position of a saccharide of the surfactant moiety, and the carboxyl group of such a spacer can be joined to, e.g., a side-chain amino group of an amino acid (e.g., a lysine) residue or the N-terminus of the peptide.

[0104] Three examples of attachment of a surfactant moiety to a peptide via a spacer are shown below. The peptide is at the top, the spacer is in the middle and the surfactant comprising a C₁₂ alkyl group (denoted as "C12") is at the bottom. In the example on the left, the spacer is one ornithine residue, whose carboxyl group forms an amide bond with the side-chain amino group of a lysine residue of the peptide. In the example in the middle, the spacer is one glutamic acid residue, whose gamma carboxyl group forms an amide bond with the side-chain amino group of a lysine residue of the peptide. In the example on the right, the spacer comprises one glutamic acid residue.



[0105] A peptide product can optionally have one or more additional modifications. Such modifications include without limitation acylation (e.g., acetylation) at the N-terminus, and attachment of a natural or synthetic polymer (e.g., a hydrophilic synthetic polymer such as polyethylene glycol [PEG], which can increase the aqueous solubility of the peptide product) or/and lipidation (e.g., acylation with a C₈-C₂₀ saturated or unsaturated fatty acid/di-acid or linkage to a steroid nucleus-containing group such as cholesterol) at the N-terminus, the C-terminus or/and one or more side chains.

[0106] The disclosure encompasses analogs and variants of the peptide products described herein. Such analogs and variants include without limitation those having a conservative substitution at one or more positions of the amino acid sequence of the specific peptide products disclosed herein. Reference to the peptide products described herein includes all pharmaceutically acceptable salts thereof.

[0107] Covalent attachment of a surfactant moiety to a peptide confers a unique combination of beneficial properties on the peptide products. The hydrophobic nature of the surfactant moiety promotes binding of the peptide-surfactant conjugates to hydrophobic carrier proteins such as human serum albumin (HSA), thereby increasing the half-life and duration of action of the peptide products via multiple mechanisms, including increased resistance to proteases and other types of hydrolytic enzymes, reduced renal clearance and slow release of the peptide products from the carrier proteins. Strong but reversible, non-covalent binding of the hydrophobic group of the surfactant moiety of the peptide products to a hydrophobic pocket of carrier proteins such as HSA (MW of about 67 kDa) shields the peptide products

from proteases (e.g., DPP-4) and other types of degradative enzymes circulating in the blood and expressed on the surface of cells, renders the peptide products less immunogenic, and increases the molecular weight of the peptide products above the filtration threshold of about 60-70 kDa so that the peptide products avoid renal clearance via glomerular filtration into the urine. Furthermore, binding of the peptide products to HSA increases their half-life through pH-dependent HSA recycling mediated by the neonatal Fc receptor (FcRn). In some embodiments, the peptide products have a half-life (e.g., circulation half-life or/and elimination half-life) of at least about 3 days, 1 week, 10 days or 2 weeks (e.g., at least about 1 week).

[0108] In addition, the amphiphilic nature of the surfactant moiety containing a hydrophilic saccharide group and a hydrophobic group increases the bioavailability and duration of action of the peptide products. The surfactant moiety can disrupt the tight junction between cells in mucosal membranes, thereby facilitating penetration of the peptide products across mucosal barriers. The surfactant moiety can also form micelles, which can facilitate penetration of the peptide products through membranes. Moreover, the process of breaking up of the micelles can prolong the duration of action of the peptide products. A surfactant forms micelles when its concentration is greater than its critical micelle concentration (CMC), and alkyl glycosides having the same saccharide group tend to have a lower CMC the longer the alkyl chain.

[0109] With a greatly increased plasma and elimination half-life compared to the peptides not attached to a surfactant moiety, the peptide products themselves are pharmacological agents. In other words, the stable surfactant moiety remains attached to the peptide *in vivo*, and the intact peptide-surfactant conjugate can exert biological activity by binding to the receptor(s) of the underlying class of peptide. For example, peptide products disclosed herein can exert biological activity by binding to and activating the GLP-1 receptor (GLP1R) or/and the glucagon receptor (GCGR). In some embodiments, the peptide products are dual GLP1R/GCGR agonists. The potency or/and the selectivity of receptor binding or activation can be fine-tuned by varying the surfactant component or/and the peptide component.

Pharmaceutical Compositions

[0110] The disclosure also provides pharmaceutical compositions comprising a peptide product described herein or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. A pharmaceutical composition contains a therapeutically effective amount of a peptide product or an appropriate fraction thereof. A composition can optionally contain an additional therapeutic agent. In some embodiments, a peptide product is at least about 90%, 95% or 98% pure.

[0111] Pharmaceutically acceptable excipients and carriers include pharmaceutically acceptable substances, materials and vehicles. Non-limiting examples of types of excipients include liquid and solid fillers, diluents, binders, lubricants, glidants, surfactants, dispersing agents, disintegration agents, emulsifying agents, wetting agents, suspending agents, thickeners, solvents, isotonic agents, buffers, pH adjusters, absorption-delaying agents, stabilizers, antioxidants, preservatives, antimicrobial agents, antibacterial agents, antifungal agents, chelating agents, adjuvants, sweetening agents, flavoring agents, coloring agents, encapsulating materials and coating materials. The use of such excipients in pharmaceutical formulations is known in the art. For example, conventional vehicles and carriers include without limitation oils (e.g., vegetable oils such as olive oil and sesame oil), aqueous solvents {e.g., saline, buffered saline (e.g., phosphate-buffered saline [PBS]) and isotonic solutions (e.g., Ringer's solution)}, and organic solvents (e.g., dimethyl sulfoxide and alcohols [e.g., ethanol, glycerol and propylene glycol]). Except insofar as any conventional excipient or carrier is incompatible with a peptide product, the disclosure encompasses the use of conventional excipients and carriers in formulations containing a peptide product. See, e.g., Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (Philadelphia, Pennsylvania) (2005); Handbook of Pharmaceutical Excipients, 5th Ed., Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association (2005); Handbook of Pharmaceutical Additives, 3rd Ed., Ash and Ash, Eds., Gower Publishing Co. (2007); and Pharmaceutical Pre-formulation and Formulation, Gibson, Ed., CRC Press (Boca Raton, Florida) (2004).

[0112] Appropriate formulation can depend on various factors, such as the route of administration chosen. Potential routes of administration of a pharmaceutical composition comprising a peptide product include without limitation oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intra-arterial, intraperitoneal, intracavitary and topical), and topical (including transdermal, transmucosal, intranasal [e.g., by nasal spray or drop], ocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal, sublingual, rectal [e.g., by suppository], and vaginal [e.g., by suppository]). In certain embodiments, a peptide product is administered parenterally (e.g., subcutaneously, intravenously or intramuscularly). In other embodiments, a peptide product is administered by oral inhalation or nasal inhalation or insufflation.

[0113] In some embodiments, the carrier is an aqueous-based carrier, such as in a parenteral (e.g., subcutaneous, intravenous or intramuscular) formulation. In other embodiments, the carrier is a nonaqueous-based carrier. In certain embodiments, the nonaqueous-based carrier is a hydrofluoroalkane (HFA) or HFA-like solvent that may comprise sub-micron anhydrous α -lactose or/and other excipients, such as in a formulation for administration by oral inhalation or nasal inhalation or insufflation.

[0114] In some embodiments, a peptide product is administered parenterally (e.g., subcutaneously, intravenously or intramuscularly) by injection. Parenteral administration bypasses the strongly acidic environment of the stomach, gastrointestinal (GI) absorption and first-pass metabolism. Excipients and carriers that can be used to prepare parenteral formulations include without limitation solvents (e.g., aqueous solvents such as water, saline, physiological saline, buffered saline [e.g., PBS], balanced salt solutions [e.g., Ringer's BSS] and aqueous dextrose solutions), isotonic/iso-osmotic agents (e.g., salts [e.g., NaCl, KCl and CaCl₂] and sugars [e.g., sucrose]), buffering agents and pH adjusters (e.g., sodium dihydrogen phosphate [monobasic sodium phosphate]/disodium hydrogen phosphate [dibasic sodium phosphate], citric acid/sodium citrate and L-histidine/L-histidine HCl), and emulsifiers (e.g., non-ionic surfactants such as polysorbates [e.g., polysorbate 20 and 80] and poloxamers [e.g., poloxamer 188]). Peptide formulations and delivery systems are discussed in, e.g., A. J. Banga, *Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems*, 3rd Ed., CRC Press (Boca Raton, Florida) (2015).

[0115] The excipients can optionally include one or more substances that increase peptide stability, increase peptide solubility, inhibit peptide aggregation or reduce solution viscosity, or any combination or all thereof. Such substances include without limitation hydrophilic amino acids (e.g., arginine and histidine), polyols (e.g., *myo*-inositol, mannitol and sorbitol), saccharides (e.g., glucose (including D-glucose [dextrose]), lactose, sucrose and trehalose), osmolytes (e.g., trehalose, taurine, amino acids [e.g., glycine, sarcosine, alanine, proline, serine, β -alanine and γ -aminobutyric acid], and betaines [e.g., trimethylglycine and trimethylamine N-oxide]), and non-ionic surfactants (e.g., alkyl polyglycosides, Pro-Tek® alkylsaccharides (e.g., a monosaccharide [e.g., glucose] or a disaccharide [e.g., maltose or sucrose] coupled to a long-chain fatty acid or a corresponding long-chain alcohol), and polypropylene glycol/polyethylene glycol block copolymers (e.g., poloxamers [e.g., Pluronic™ F-68], and Genapol® PF-10 and variants thereof)). Because such substances increase peptide solubility, they can be used to increase peptide concentration in a formulation. Higher peptide concentration in a formulation is particularly advantageous for subcutaneous administration, which has a limited volume of bolus administration (e.g., $\leq$ about 1.5 mL). In addition, such substances can be used to stabilize peptides during the preparation, storage and reconstitution of lyophilized peptides.

[0116] Examples of excipients of aqueous formulations, whether pre-made with a peptide therapeutic or prepared after reconstituting a peptide therapeutic in lyophilized or powder form, for parenteral (e.g., subcutaneous or intravenous) administration include without limitation those shown in Table 5. Any formulation in Table 5 for which sodium chloride (NaCl) is not explicitly listed can optionally contain NaCl. An exemplary parenteral formulation comprises a peptide product, mannitol, methionine, sodium thioglycolate, polysorbate 20, a pH adjuster (e.g., NaOH or/and HCl) and de-ionized water.

Table 5. Exemplary excipients of parenteral (e.g., intravenous and subcutaneous) formulations

	NaCl, sodium acetate and water
35	NaCl, acetic acid, sodium acetate and water
	NaCl, citric acid, sodium citrate and water
	Mannitol, histidine, glycine and water
	NaCl, sucrose, mannitol, glycine, potassium dihydrogen phosphate, disodium hydrogen phosphate and water
40	NaCl, sodium phosphate or sodium dihydrogen phosphate/disodium hydrogen phosphate, polysorbate 80 and water
	NaCl, sodium citrate, polysorbate 80 and water
45	NaCl, citric acid, sodium citrate, polysorbate 80 and water
	NaCl, glycine, citric acid, NaOH, polysorbate 80 and water
	NaCl, KCl, potassium dihydrogen phosphate, disodium hydrogen phosphate, polysorbate 80, disodium edetate and water
50	Sucrose, lactic acid, polysorbate and water
	NaCl, sucrose, sodium dihydrogen phosphate, disodium hydrogen phosphate, polysorbate 20 or 80, and water
	NaCl, sucrose, citric acid, sodium citrate, polysorbate 80 and water
	NaCl, sucrose, glycine, citric acid, sodium citrate, polysorbate 80 and water
55	NaCl, trehalose, sodium phosphate, polysorbate 20 and water
	NaCl, trehalose, citric acid, sodium citrate, polysorbate 80 and water

(continued)

5	NaCl, mannitol, sodium dihydrogen phosphate/disodium hydrogen phosphate or/and citric acid/sodium citrate, polysorbate 80 and water, and optionally NaOH to adjust pH
	NaCl, mannitol, sodium citrate, polysorbate 80, pentetic acid and water, and optionally HCl or/and NaOH to adjust pH
	NaCl, mannitol, Tris HCl, polysorbate 80, pentetic acid and water
10	Mannitol or sorbitol, acetic acid, NaOH, polysorbate 20 and water
	NaCl, sucrose, L-histidine, polysorbate 80 and water, and optionally HCl or/and NaOH to adjust pH
	NaCl, sucrose, L-histidine, acetic acid, polysorbate 20 and water
	Sucrose, L-histidine, L-histidine HCl, polysorbate 20 or 80 and water
15	Trehalose, L-histidine, L-histidine HCl, polysorbate 20 and water
	NaCl, trehalose, L-histidine, L-histidine HCl, poloxamer 188 and water
	Trehalose, L-histidine, L-histidine HCl, polysorbate 20 and water, and optionally a bacteriostat (e.g., benzyl alcohol)
20	Trehalose, L-histidine, L-histidine HCl, L-methionine, polysorbate 80 and water
	Sorbitol, L-histidine, L-histidine HCl, polysorbate 80 and water
	NaCl, glycine, L-histidine, L-histidine HCl, polysorbate 80 and water
	NaCl, sucrose, L-arginine HCl, L-histidine, L-histidine HCl, polysorbate 80 and water
25	Sucrose, sodium acetate, optionally acetic acid, L-arginine HCl, L-histidine, polysorbate 80 and water
	L-Arginine, L-arginine HCl, L-histidine, L-histidine HCl, L-methionine, polysorbate 80 and water
	Proline, glutamate, polysorbate 20 and water
30	Propylene glycol, phenol, disodium hydrogen phosphate and water, and optionally HCl or/and NaOH to adjust pH
	NaCl, sucrose or maltose, sodium dihydrogen phosphate and water
	Sucrose, sodium dihydrogen phosphate, disodium hydrogen phosphate, poloxamer 188 and water
	NaCl, sucrose, sodium phosphate, L-arginine HCl and water
35	Sucrose, glycine, L-arginine HCl, L-histidine, L-histidine HCl, PEG 3350 and water
	Mannitol, trehalose, sodium phosphate, polysorbate 80 and water
	Mannitol, citric acid, trisodium citrate, polysorbate 80 and water
40	NaCl, CaCl ₂ , sucrose, L-histidine, polysorbate 20 and water
	Sucrose, mannitol, L-histidine, HCl, polysorbate 20 and water
	NaCl, sucrose, mannitol, L-histidine, HCl, NaOH, polysorbate 20 and water

45 **[0117]** For parenteral (e.g., subcutaneous, intravenous or intramuscular) administration, a sterile solution or suspension of a peptide product in an aqueous solvent containing one or more excipients can be prepared beforehand and can be provided in, e.g., a pre-filled syringe of a single-use pen or a pen with a dose counter. Alternatively, a peptide product can be dissolved or suspended in an aqueous solvent that can optionally contain one or more excipients prior to lyophilization (freeze-drying). Shortly prior to parenteral administration, the lyophilized peptide product stored in a suitable container (e.g., a vial) can be reconstituted with, e.g., sterile water that can optionally contain one or more excipients.

50 **[0118]** In other embodiments, a peptide product is administered intranasally. The nasal mucosa provides a big surface area, a porous endothelium, a highly vascular subepithelial layer and a high absorption rate, and hence allows for high bioavailability. An intranasal formulation can comprise a peptide product along with excipients, such as a solubility enhancer (e.g., propylene glycol), a humectant (e.g., mannitol or sorbitol), a buffer and water, and optionally a preservative (e.g., benzalkonium chloride), a mucoadhesive agent (e.g., hydroxyethylcellulose) or/and a penetration enhancer. An intranasal solution or suspension formulation can be administered to the nasal cavity by any suitable means, including but not limited to a dropper, a pipette, or spray using, e.g., a metering atomizing spray pump. Table 6 shows exemplary excipients of nasal-spray formulations.

Table 6. Exemplary excipients and carriers of nasal and pulmonary formulations

Dosage Form	Ingredients in Addition to a Peptide Product
nasal spray	microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, water, and optionally a pH adjuster (e.g., HCl)
nasal spray	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, disodium edetate, potassium sorbate, a pH adjuster (e.g., HCl), water, and optionally an alcohol (e.g., ethanol)
nasal spray	microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose, polysorbate 80, benzalkonium chloride, phenylethyl alcohol, water, and optionally an alcohol (e.g., ethanol)
nasal spray	hypromellose, benzalkonium chloride, NaCl, EDTA, citric acid, sodium phosphate dibasic, water, and optionally an alcohol (e.g., ethanol)
inhalation (DPI)	mannitol, glycine, sodium citrate and NaOH
inhalation (DPI)	lactose, starch, a starch derivative (e.g., hydroxypropylmethyl cellulose) or polyvinylpyrrolidone, and optionally magnesium stearate or/and leucine
inhalation (MDI)	a propellant (e.g., 1,1,1,2-tetrafluoroethane), a surfactant (e.g., lecithin or oleic acid), and a co-solvent (e.g., ethanol)
inhalation (nebulizer)	polysorbate 80, edetate disodium, sodium chloride, pH buffering agents (e.g., citric acid/sodium citrate), and water

[0119] In further embodiments, a peptide product is administered pulmonarily, such as by oral inhalation or nasal inhalation. A pulmonarily administered drug can treat a lung disorder or/and a systemic disorder, as the lungs serve as a portal to the systemic circulation. Advantages of pulmonary drug delivery include, for example: 1) avoidance of first-pass metabolism; 2) fast drug action; 3) large surface area of the alveolar region for absorption, high permeability of the lungs (thin air-blood barrier), and profuse vasculature of the airways; and 4) reduced extracellular enzyme levels compared to the GI tract due to the large alveolar surface area. An advantage of oral inhalation over nasal inhalation includes deeper penetration/deposition of the drug into the lungs, although nasal inhalation can deliver the drug into systemic circulation transmucosally in the nasal cavity as well as in the lungs.

[0120] Oral or nasal inhalation can be achieved by means of, e.g., a metered-dose inhaler (MDI), a nebulizer or a dry powder inhaler (DPI). For example, a peptide product can be formulated for aerosol administration to the respiratory tract by oral or nasal inhalation. The drug is delivered in a small particle size (e.g., between about 0.5 micron and about 5 microns), which can be obtained by micronization, to improve, e.g., drug deposition in the lungs and drug suspension stability. The drug can be provided in a pressurized pack with a suitable propellant, such as a hydrofluoroalkane (HFA, e.g., 1,1,1,2-tetrafluoroethane [HFA-134a]), a chlorofluorocarbon (CFC, e.g., dichlorodifluoromethane, trichlorofluoromethane or dichlorotetrafluoroethane), or a suitable gas (e.g., oxygen, compressed air or carbon dioxide). The drug in the aerosol formulation is dissolved, or more often suspended, in the propellant for delivery to the lungs. The aerosol can contain excipients such as a surfactant (which enhances penetration into the lungs by reducing the high surface tension forces at the air-water interface within the alveoli, may also emulsify, solubilize or/and stabilize the drug, and can be, e.g., a phospholipid such as lecithin) or/and a stabilizer, although the surfactant moiety of the peptide product can perform functions of a surfactant. For example, an MDI formulation can comprise a peptide product, a propellant (e.g., an HFA such as 1,1,1,2-tetrafluoroethane) and a co-solvent (e.g., an alcohol such as ethanol), and optionally a surfactant (e.g., a fatty acid such as oleic acid). The MDI formulation can optionally contain a dissolved gas (e.g., CO₂). After device actuation, the bursting of CO₂ bubbles within the emitted aerosol droplets breaks up the droplets into smaller droplets, thereby increasing the respirable fraction of drug. As another example, a nebulizer formulation can comprise a peptide product, a chelator or preservative (e.g., edetate disodium), an isotonicity agent (e.g., NaCl), pH buffering agents (e.g., citric acid/sodium citrate) and water, and optionally a surfactant (e.g., a Tween® such as polysorbate 80). The drug can be delivered by means of, e.g., a nebulizer or an MDI with or without a spacer, and the drug dose delivered can be controlled by a metering chamber (nebulizer) or a metering valve (MDI). Table 6 shows exemplary MDI, nebulizer and DPI formulations.

[0121] Metered-dose inhalers (also called pressurized metered-dose inhalers [pMDI]) are the most widely used inhalation devices. A metering valve delivers a precise amount of aerosol (e.g., about 20-100 µL) each time the device is actuated. MDIs typically generate aerosol faster than the user can inhale, which can result in deposition of much of the aerosol in the mouth and the throat. The problem of poor coordination between device actuation and inhalation can be

addressed by using, e.g., a breath-actuated MDI or a coordination device. A breath-actuated MDI (e.g., Easibreathe®) is activated when the device senses the user's inspiration and discharges a drug dose in response. The inhalation flow rate is coordinated through the actuator and the user has time to actuate the device reliably during inhalation. In a coordination device, a spacer (or valved holding chamber), which is a tube attached to the mouthpiece end of the inhaler, serves as a reservoir or chamber holding the drug that is sprayed by the inhaler and reduces the speed at which the aerosol enters the mouth, thereby allowing for the evaporation of the propellant from larger droplets. The spacer simplifies use of the inhaler and increases the amount of drug deposited in the lungs instead of in the upper airways. The spacer can be made of an anti-static polymer to minimize electrostatic adherence of the emitted drug particles to the inner walls of the spacer.

[0122] Nebulizers generate aerosol droplets of about 1-5 microns. They do not require user coordination between device actuation and inhalation, which can significantly affect the amount of drug deposited in the lungs. Compared to MDIs and DPIs, nebulizers can deliver larger doses of drug, albeit over a longer administration time. Examples of nebulizers include without limitation human-powered nebulizers, jet nebulizers (e.g., AeroEclipse® II BAN [breath-actuated], CompAIR™ NE-C801 [virtual valve], PARI LC® Plus [breath-enhanced] and SideStream Plus [breath-enhanced]), ultrasonic wave nebulizers, and vibrating mesh nebulizers (e.g., Akita2® Apixneb, I-neb AAD System with metering chambers, MicroAir® NE-U22, Omron U22 and PARI eFlow® rapid). As an example, a pulsed ultrasonic nebulizer can aerosolize a fixed amount of the drug per pulse, and can comprise an opto-acoustical trigger that allows the user to synchronize each breath to each pulse.

[0123] For oral or nasal inhalation using a dry powder inhaler (DPI), a peptide product can be provided in the form of a dry micronized powder, where the drug particles are of a certain small size (e.g., between about 0.5 micron and about 5 microns) to improve, e.g., aerodynamic properties of the dispersed powder and drug deposition in the lungs. Particles between about 0.5 micron and about 5 microns deposit by sedimentation in the terminal bronchioles and the alveolar regions. By contrast, the majority of larger particles (> 5 microns) do not follow the stream of air into the many bifurcations of the airways, but rather deposit by impaction in the upper airways, including the oropharyngeal region of the throat. A DPI formulation can contain the drug particles alone or be blended with a powder of a suitable larger base/carrier, such as lactose, starch, a starch derivative (e.g., hydroxypropylmethyl cellulose) or polyvinylpyrrolidone. The carrier particles enhance flow, reduce aggregation, improve dose uniformity and aid in dispersion of the drug particles. A DPI formulation can optionally contain an excipient such as magnesium stearate or/and leucine that improves the performance of the formulation by interfering with inter-particle bonding (by anti-adherent action). The powder formulation can be provided in unit dose form, such as a capsule (e.g., a gelatin capsule) or a cartridge in a blister pack, which can be manually loaded or pre-loaded in an inhaler. The drug particles can be drawn into the lungs by placing the mouthpiece or nosepiece of the inhaler into the mouth or nose, taking a sharp, deep inhalation to create turbulent airflow, and holding the breath for a period of time (e.g., about 5-10 seconds) to allow the drug particles to settle down in the bronchioles and the alveolar regions. When the user actuates the DPI and inhales, airflow through the device creates shear and turbulence, inspired air is introduced into the powder bed, and the static powder blend is fluidized and enters the user's airways. There, the drug particles separate from the carrier particles due to turbulence and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. Thus, the user's inspiratory airflow achieves powder de-agglomeration and aeroionisation, and determines drug deposition in the lungs. (While a passive DPI requires rapid inspiratory airflow to deagglomerate drug particles, rapid inspiration is *not* recommended with an MDI or nebulizer, since it creates turbulent airflow and fast velocity which increase drug deposition by impaction in the upper airways.) Compared to an MDI, a DPI (including a breath-activated DPI) may be able to deliver larger doses of drug, and larger-size drugs (e.g., macromolecules), to the lungs.

[0124] Lactose (e.g., alpha-lactose monohydrate) is the most commonly used carrier in DPI formulations. Examples of grades/types of lactose monohydrate for DPI formulations include without limitation DCL 11, Flowlac® 100, Inhalac® 230, Lactohale® 300, Lactopress® SD 250 (spray-dried lactose), Respitose® SV003 and Sorbolac® 400. A DPI formulation can contain a single lactose grade or a combination of different lactose grades. For example, a fine lactose grade like Lactohale® 300 or Sorbolac® 400 may not be a suitable DPI carrier and may need to be blended with a coarse lactose grade like DCL 11, Flowlac® 100, Inhalac® 230 or Respitose® SV003 (e.g., about a 1:9 ratio of fine lactose to coarse lactose) to improve flow. Tables 7 and 8 show non-limiting examples of grades/types of lactose that can be used in DPI formulations. The distribution of the carrier particle sizes affects the fine particle fraction/dose (FPF or FPD) of the drug, with a high FPF being desired for drug delivery to the lungs. FPF/FPD is the respirable fraction/dose mass out of the DPI device with an aerodynamic particle size ≤ 5 microns in the inspiration air. High FPF, and hence good DPI performance, can be obtained from, e.g., DPI formulations having an approximately 1:9 ratio of fine lactose (e.g., Lactohale® 300) to coarse lactose (e.g., Respitose® SV003) and about 20% w/w overages to avoid deposition of the drug in the capsule shell or the DPI device and to deliver essentially all of the drug to the airways.

Table 7

Product	Type	Range of Particle Sizes (μm)		
		10%	50%	90%
Lactohale®	LH200	<9	<69	<141
InhaLac®	230	<35	<93	<138
Respitose®	ML001	<4	<43	<146
	ML003	<4	<35	<106
	SV003	<30	<59	<90
	SV004	<32	<61	<93

Table 8

Product	Type	Range of Particle Sizes			
		<45 μm	<100 μm	<150 μm	<250 μm
Respitose®	ML003	65%	98%	100%	NA
Respitose®	ML002	65%	98%	NA	100%

[0125] Other carriers for DPI formulations include without limitation glucose, mannitol (e.g., crystallized mannitol [Pearlitol 110 C] and spray-dried mannitol [Pearlitol 100 SD]), maltitol (e.g., crystallized maltitol [Maltisorb P90]), sorbitol and xylitol.

[0126] Most DPIs are breath-activated ("passive"), relying on the user's inhalation for aerosol generation. Examples of passive DPIs include without limitation Airmax®, Novolizer® and Otsuka DPI (compact cake). The air classifier technology (ACT) is an efficient passive powder dispersion mechanism employed in DPIs. In ACT, multiple supply channels generate a tangential airflow that results in a cyclone within the device during inhalation. There are also power-assisted ("active") DPIs (based on, e.g., pneumatics, impact force or vibration) that use energy to aid, e.g., particle de-agglomeration. For example, the active mechanism of Exubera® inhalers utilizes mechanical energy stored in springs or compressed-air chambers. Examples of active DPIs include without limitation Actispire® (single-unit dose), Aspirair® (multi-dose), Exubera® (single-unit dose), MicroDose® (multi-unit dose and electronically activated), Omnihaler® (single-unit dose), Pfeiffer DPI (single-unit dose), and Spiros® (multi-unit dose).

[0127] A peptide product can also be administered by other routes, such as orally. An oral formulation can contain a peptide product and conventional excipients known in the art, and optionally an absorption enhancer such as sodium *N*-[8-(2-hydroxybenzoyl)aminocaprylate] (SNAC). SNAC protects against enzymatic degradation via local buffering action and enhances GI absorption. An oral dosage form (e.g., a tablet, capsule or pill) can optionally have an enteric coating to protect its content from the strong acids and proteolytic enzymes of the stomach.

[0128] In some embodiments, a peptide product is delivered from a sustained-release composition. As used herein, the term "sustained-release composition" encompasses sustained-release, prolonged-release, extended-release, delayed-release, slow-release and controlled-release compositions, systems and devices. In some embodiments, a sustained-release composition delivers a peptide product over a period of at least about 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months or longer.

[0129] In some embodiments, a sustained-release composition is formulated as nanoparticles or microparticles composed of a biodegradable polymer and incorporating a peptide product. In certain embodiments, the biodegradable polymer comprises lactic acid or/and glycolic acid [e.g., an L-lactic acid-based copolymer, such as poly(L-lactide-co-glycolide) or poly(L-lactic acid-coD,L-2-hydroxyoctanoic acid)].

[0130] In further embodiments, a sustained-release composition is in the form of a depot that is generated when a mixture of a peptide product and a polymer is injected into a subject intramuscularly or subcutaneously. In certain embodiments, the polymer is or comprises PEG, polylactic acid (PLA) or polyglycolic acid (PGA), or a copolymer thereof (e.g., PLGA or PLA-PEG).

[0131] A pharmaceutical composition can be presented in unit dosage form as a single dose wherein all active and inactive ingredients are combined in a suitable system, and components do not need to be mixed to form the composition to be administered. A unit dosage form generally contains a therapeutically effective dose of the drug, but can contain an appropriate fraction thereof so that taking multiple unit dosage forms achieves the therapeutically effective dose.

Examples of a unit dosage form include a tablet, capsule or pill for oral uptake; a solution in a pre-filled syringe of a single-use pen or a pen with a dose counter for parenteral (e.g., intravenous, subcutaneous or intramuscular) injection; and a capsule, cartridge or blister pre-loaded in or manually loaded into an inhaler.

[0132] Alternatively, a pharmaceutical composition can be presented as a kit in which the active ingredient, excipients and carriers (e.g., solvents) are provided in two or more separate containers (e.g., ampules, vials, tubes, bottles or syringes) and need to be combined to form the composition to be administered. The kit can contain instructions for storing, preparing and administering the composition (e.g., a solution to be injected parenterally).

[0133] A kit can contain all active and inactive ingredients in unit dosage form or the active ingredient and inactive ingredients in two or more separate containers, and can contain instructions for administering or using the pharmaceutical composition to treat a medical condition disclosed herein. A kit can further contain a device for delivering the composition, such as an injection pen or an inhaler.

[0134] In some embodiments, a kit contains a peptide product or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same, and instructions for administering or using the peptide product or the composition to treat a medical condition disclosed herein, such as insulin resistance, diabetes, obesity, metabolic syndrome or a cardiovascular disease, or a condition associated therewith (e.g., NASH or PCOS). In certain embodiments, the kit further contains a device for delivering the peptide product or the composition, such as an injection pen or an inhaler.

Therapeutic Uses of Peptide Products

[0135] The disclosure further provides uses of the peptide products described herein to treat, e.g., insulin resistance, diabetes, obesity, metabolic syndrome and cardiovascular diseases, and conditions associated therewith, such as NASH and PCOS.

[0136] In some embodiments, the peptide products are used to treat hyperglycemia, insulin resistance, hyperinsulinemia, prediabetes, diabetes (including types 1 and 2, gestational and juvenile diabetes), diabetic complications, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, elevated blood levels of free fatty acids, obesity, metabolic syndrome, syndrome X, cardiovascular diseases (including coronary artery disease), atherosclerosis, acute cardiovascular syndrome, ischemia (including myocardial ischemia and cerebral ischemia/stroke), ischemia-reperfusion injury (including myocardial and cerebral IRI), infarction (including myocardial and cerebral infarction), angina, heart failure (e.g., congestive heart failure), peripheral vascular disease, thrombosis (e.g., deep vein thrombosis), embolism (e.g., pulmonary embolism), systemic inflammation (e.g., one characterized by elevated C-reactive protein blood level), and hypertension. The peptide products can achieve their therapeutic effects through various mechanisms, including stimulation of blood glucose-dependent insulin secretion, increase in insulin sensitivity, stimulation of fat burning and reduction of body weight. The peptide products can also promote, e.g., pancreatic beta-cell protection, cardioprotection and wound healing.

[0137] The peptide products described herein can be used to treat other conditions associated with insulin resistance or/and obesity. Other conditions associated with insulin resistance or/and obesity include without limitation arthritis (e.g., osteoarthritis), low back pain, breathing disorders (e.g., asthma, obesity hypoventilation syndrome [Pickwickian syndrome] and obstructive sleep apnea), dermatological disorders (e.g., diabetic ulcers, acanthosis nigricans, cellulitis, hirsutism, intertrigo and lymphedema), gastroenterological disorders (e.g., cholelithiasis [gallstone], gastroesophageal reflux disease [GERD] and gastroparesis), gout, hypercortisolism (e.g., Cushing's syndrome), kidney disorders (e.g., chronic kidney disease), liver disorders (e.g., fatty liver disease [FLD] including alcoholic and non-alcoholic FLD), neurological disorders (e.g., carpal tunnel syndrome, dementias [e.g., Alzheimer's disease and vascular dementia], meralgia paresthetica, migraines and multiple sclerosis), urological disorders (e.g., erectile dysfunction, hypogonadism and urinary incontinence), polycystic ovary syndrome, infertility, menstrual disorders, mood disorders (e.g., depression), and cancers (e.g., cancers of the endometrium, esophagus, colorectum, gallbladder, kidney, liver [e.g., hepatocellular carcinoma], pancreas and skin [e.g., melanoma], and leukemia).

[0138] In certain embodiments, a peptide product described herein is used to treat polycystic ovary syndrome (PCOS). In other embodiments, a peptide product is used to treat chronic kidney disease (CKD), also known as chronic kidney/renal failure (CKF/CRF). The most common causes of CKD are diabetes and long-term, uncontrolled hypertension.

[0139] In further embodiments, a peptide product described herein is used to treat fatty liver disease (FLD). In some embodiments, the FLD is non-alcoholic fatty liver disease (NAFLD). In certain embodiments, the NAFLD is non-alcoholic steatohepatitis (NASH). FLD, also known as hepatic steatosis, is characterized by excessive fat accumulation in the liver. FLD includes alcoholic fatty liver disease (AFLD) and NAFLD. Chronic alcoholism causes fatty liver due to production of toxic metabolites such as aldehydes during metabolism of alcohol in the liver. NAFLD is described below. FLD is associated with diabetes, obesity and metabolic syndrome. Fatty liver can develop into cirrhosis or a liver cancer (e.g., hepatocellular carcinoma [HCC]). Less than about 10% of people with cirrhotic AFLD develop HCC, but up to about 45% of people with NASH without cirrhosis may develop HCC. HCC is the most common type of primary liver cancer in adults and occurs in the setting of chronic liver inflammation.

[0140] NAFLD is characterized by fatty liver that occurs when fat, in particular free fatty acids and triglycerides, accumulates in liver cells (hepatic steatosis) due to causes other than excessive alcohol consumption, such as nutrient overload, high caloric intake and metabolic dysfunction (e.g., dyslipidemia and impaired glucose control). A liver can remain fatty without disturbing liver function, but a fatty liver can progress to become NASH, a condition in which steatosis is accompanied by inflammation, hepatocyte ballooning and cell injury with or without fibrosis of the liver. Fibrosis is the strongest predictor of mortality from NASH. NAFLD can be characterized by steatosis alone; steatosis with lobular or portal inflammation but without ballooning; steatosis with ballooning but without inflammation; or steatosis with inflammation and ballooning.

[0141] NASH is the most extreme form of NAFLD. NASH is a progressive disease, with about 20% of patients developing cirrhosis of the liver and about 10% dying from a liver disease, such as cirrhosis or a liver cancer (e.g., HCC). NAFLD is the most common liver disorder in developed countries, and NASH is projected to supplant hepatitis C as the major cause of liver transplant in the U.S. by 2020. About 12-25% of people in the U.S. have NAFLD, with NASH affecting about 2-5% of people in the U.S.

[0142] NAFLD, including NASH, is associated with insulin resistance, obesity and metabolic syndrome. For instance, insulin resistance contributes to progression of fatty liver to hepatic inflammation and fibrosis and thus NASH. Furthermore, obesity drives and exacerbates NASH, and weight loss can alleviate NASH. Therefore, the peptide products described herein, including GLP-1 receptor (GLP1R) agonists, glucagon receptor (GCGR) agonists and dual GLP1R/GCGR agonists, can be used to treat NAFLD, including NASH.

[0143] In some embodiments, the peptide products used to treat a condition associated with insulin resistance or/and obesity disclosed herein, such as NAFLD (e.g., NASH) or PCOS, are selected from the peptide products of **SEQ. ID. NOs. 601, 602, 603, 604, 630, 631, 632, 633, 634, 805, 819, 820, 821, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125**, and pharmaceutically acceptable salts thereof.

[0144] A peptide product can be administered by any suitable route for treatment of a condition disclosed herein. Potential routes of administration of a peptide product include without limitation oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intra-arterial, intraperitoneal, intracavitary and topical), and topical (including transdermal, transmucosal, intranasal [e.g., by nasal spray or drop], ocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal, sublingual, rectal [e.g., by suppository], and vaginal [e.g., by suppository]). In some embodiments, a peptide product is administered parenterally, such as subcutaneously, intravenously or intramuscularly. In other embodiments, a peptide product is administered by oral inhalation or nasal inhalation or insufflation.

[0145] The therapeutically effective amount and the frequency of administration of, and the length of treatment with, a peptide product to treat a condition disclosed herein may depend on various factors, including the nature and severity of the condition, the potency of the compound, the route of administration, the age, body weight, general health, gender and diet of the subject, and the response of the subject to the treatment, and can be determined by the treating physician.

[0146] In some embodiments, a peptide product is administered parenterally (e.g., subcutaneously [sc], intravenously [iv] or intramuscularly [im]) in a dose from about 0.1 mg to about 1, 5 or 10 mg, or about 0.1-1 mg or 1-10 mg, over a period of about one week for treatment of a condition disclosed herein (e.g., one associated with insulin resistance or/and obesity, such as NASH or PCOS). In further embodiments, a peptide product is administered parenterally (e.g., sc, iv or im) in a dose of about 0.1-0.5 mg, 0.5-1 mg, 1-5 mg or 5-10 mg over a period of about one week. In certain embodiments, a peptide product is administered parenterally (e.g., sc, iv or im) in a dose of about 0.1-1 mg, or about 0.1-0.5 mg or 0.5-1 mg, over a period of about one week.

[0147] A peptide product can be administered in any suitable frequency for treatment of a condition disclosed herein (e.g., one associated with insulin resistance or/and obesity, such as NASH or PCOS). In some embodiments, a peptide product is administered, e.g., sc or iv once a day, once every two days, once every three days, twice a week, once a week or once every two weeks. In certain embodiments, a peptide product is administered, e.g., sc or iv once a week.

[0148] A peptide product can be administered at any time of day convenient to the patient. A peptide product can be taken substantially with food (e.g., with a meal or within about 1 hour or 30 minutes before or after a meal) or substantially without food (e.g., at least about 1 or 2 hours before or after a meal).

[0149] The length of treatment of a medical condition with a peptide product can be based on, e.g., the nature and severity of the condition and the response of the subject to the treatment, and can be determined by the treating physician.

In some embodiments, a peptide product is administered chronically to treat a condition disclosed herein, such as at least about 2 months, 3 months, 6 months, 1 year, 1.5 years, 2 years, 3 years, 5 years, 10 years or longer. A peptide product can also be taken *pro re nata* (as needed) until clinical manifestations of the condition disappear or clinical targets are achieved, such as blood glucose level, blood pressure, blood levels of lipids, body weight or body mass index, waist-to-hip ratio or percent body fat, or any combination thereof. If clinical manifestations of the condition reappear or the clinical targets are not maintained, administration of the peptide product can resume.

[0150] The disclosure further provides a peptide product described herein or a pharmaceutically acceptable salt thereof, or a composition comprising the same, for use as a medicament. In addition, the disclosure provides for the use of a peptide product described herein or a pharmaceutically acceptable salt thereof in the preparation of a medicament. The

medicament containing a peptide product can be used to treat any medical condition described herein. A peptide product can optionally be used in combination with one or more additional therapeutic agents.

Combination Therapies

[0151] A peptide product described herein can optionally be used in combination with one or more additional therapeutic agents to treat any disorder disclosed herein, such as insulin resistance, diabetes, obesity, metabolic syndrome or a cardiovascular disease, or any condition associated therewith, such as NASH or PCOS. In some embodiments, the one or more additional therapeutic agents are selected from antidiabetic agents, anti-obesity agents (including lipid-lowering agents and pro-satiety agents), anti-atherosclerotic agents, anti-inflammatory agents, antioxidants, antifibrotic agents, anti-hypertensive agents, and combinations thereof.

[0152] Antidiabetic agents include without limitation:

AMP-activated protein kinase (AMPK) agonists, including biguanides (e.g., buformin and metformin);

peroxisome proliferator-activated receptor gamma (PPAR- γ) agonists, including thiazolidinediones (e.g., balaglitazone, ciglitazone, darglitazone, englitazone, lobeglitazone, netoglitazone, pioglitazone, rivoglitazone, rosiglitazone and troglitazone) and saroglitazar (dual PPAR- α/γ agonist);

glucagon-like peptide-1 (GLP-1) receptor agonists, including exendin-4, albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, taspoglutide, CNTO736, CNTO3649, HM11260C (LAPS-Exendin), NN9926 (OG9S7GT), TT401 and ZY0G1;

dipeptidyl peptidase 4 (DPP-4) inhibitors, including alogliptin, anagliptin, dutogliptin, evogliptin, gemigliptin, gossogliptin, linagliptin, omarigliptin, saxagliptin, septagliptin, sitagliptin, teneligliptin, trelagliptin and vildagliptin;

sodium-glucose transport protein 2 (SGLT2) inhibitors, including canagliflozin (also inhibits SGLT1), dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin etabonate, sotagliflozin (also inhibits SGLT1) and tofogliflozin;

blockers of ATP-dependent K⁺ (K_{ATP}) channels on pancreatic beta cells, including meglitinides (e.g., mitiglinide, nateglinide and repaglinide) and sulfonylureas {including first generation (e.g., acetohexamide, carbutamide, chlorpropamide, glycyclamide [tolhexamide], metahexamide, tolazamide and tolbutamide) and second generation (e.g., glibenclamide [glyburide], glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide and glycopyramide)};

insulin and analogs thereof, including fast-acting insulin (e.g., insulin aspart, insulin glulisine and insulin lispro), intermediate-acting insulin (e.g., NPH insulin), and long-acting insulin (e.g., insulin degludec, insulin detemir and insulin glargine); and

analogs, derivatives and salts thereof.

[0153] In certain embodiments, the antidiabetic agent is or includes a biguanide (e.g., metformin), a thiazolidinedione (e.g., pioglitazone or rosiglitazone) or a SGLT2 inhibitor (e.g., empagliflozin or tofogliflozin), or any combination thereof.

[0154] Anti-obesity agents include, but are not limited to:

appetite suppressants (anorectics), including amphetamine, dexamphetamine, amfepramone, clobenzorex, mazindol, phentermine (with or without topiramate) and lorcaserin;

pro-satiety agents, including ciliary neurotrophic factor (e.g., axokine) and longer-acting analogs of amylin, calcitonin, cholecystokinin (CCK), GLP-1, leptin, oxyntomodulin, pancreatic polypeptide (PP), peptide YY (PYY) and neuropeptide Y (NPY);

lipase inhibitors, including caulerpenyne, cetilistat, ebelactone A and B, esterastin, lipstatin, orlistat, percyquinin, panclicin A-E, valilactone and vibrilactone;

antihyperlipidemic agents; and

analogs, derivatives and salts thereof.

[0155] Antihyperlipidemic agents include without limitation:

HMG-CoA reductase inhibitors, including statins {e.g., atorvastatin, cerivastatin, fluvastatin, mevastatin, monacolins (e.g., monacolin K [lovastatin]), pitavastatin, pravastatin, rosuvastatin and simvastatin} and flavanones (e.g., naringenin);

5 squalene synthase inhibitors, including lapaquistat, zaragozic acid and RPR-107393;

acetyl-CoA carboxylase (ACC) inhibitors, including anthocyanins, avenaciolides, chloroacetylated biotin, cycloclim, diclofop, haloxyfop, soraphens (e.g., soraphen A_{1α}), 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA), CP-640186, GS-0976, NDI-010976; 7-(4-propyloxy-phenylethynyl)-3,3-dimethyl-3,4 dihydro-2H-benzo[b][1,4]dioxepine; N-ethyl-N'-{(3-[[4-(3,3-dimethyl-1-oxo-2-oxa-7-azaspiro[4.5]dec-7-yl)piperidin-1-yl]-carbonyl]-1-benzothien-2-yl)urea; 5-(3-acetamidobut-1-ynyl)-2-(4-propyloxyphenoxy)thiazole; and 1-(3-[[4-(3,3-dimethyl-1-oxo-2-oxa-7-aza-spiro[4.5]dec-7-yl)piperidin-1-yl]-carbonyl]-5-(pyridin-2-yl)-2-thienyl)-3-ethylurea;

15 PPAR-α agonists, including fibrates (e.g., bezafibrate, ciprofibrate, clinofibrate, clofibric acid, clofibrate, aluminum clofibrate [alfibrate], clofibrade, etofibrate, fenofibric acid, fenofibrate, gemfibrozil, ronifibrate and simfibrate), isoflavones (e.g., daidzein and genistein), and perfluoroalkanoic acids (e.g., perfluorooctanoic acid and perfluorononanoic acid);

20 PPAR-δ agonists, including elafibranor (dual PPAR-α/δ agonist), GFT505 (dual PPAR-α/δ agonist), GW0742, GW501516 (dual PPAR-β/δ agonist), sodelglitazar (GW677954), MBX-8025, and isoflavones (e.g., daidzein and genistein);

25 PPAR-γ agonists, including thiazolidinediones (*supra*), saroglitazar (dual PPAR-α/γ agonist), 4-oxo-2-thioxothiazolines (e.g., rhodanine), berberine, honokiol, perfluorononanoic acid, cyclopentenone prostaglandins (e.g., cyclopentenone 15-deoxy-Δ-prostaglandin J₂ [15d-PGJ₂]), and isoflavones (e.g., daidzein and genistein);

liver X receptor (LXR) agonists, including endogenous ligands (e.g., oxysterols such as 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 27-hydroxycholesterol and cholestenoic acid) and synthetic agonists (e.g., acetyl-podocarpic dimer, hypocholamide, N,N-dimethyl-3β-hydroxy-cholenamide [DMHCA], GW3965 and T0901317);

30 retinoid X receptor (RXR) agonists, including endogenous ligands (e.g., 9-cis-retinoic acid) and synthetic agonists (e.g., bexarotene, AGN 191659, AGN 191701, AGN 192849, BMS649, LG100268, LG100754 and LGD346);

35 inhibitors of acyl-CoA cholesterol acyltransferase (ACAT, aka sterol O-acyltransferase [SOAT], including ACAT1 [SOAT1] and ACAT2 [SOAT2]), including avasimibe, pactimibe, pellitorine, terpendole C and flavanones (e.g., naringenin);

40 inhibitors of stearoyl-CoA desaturase-1 (SCD-1, aka stearoyl-CoA delta-9 desaturase) activity or expression, including aramchol, CAY-10566, CVT-11127, SAR-224, SAR-707, XEN-103; 3-(2-hydroxyethoxy)-4-methoxy-N-[5-(3-trifluoromethylbenzyl)thiazol-2-yl]benzamide and 4-ethylamino-3-(2-hydroxyethoxy)-N-[5-(3-trifluoromethylbenzyl)thiazol-2-yl]benzamide; 1'-{6-[5-(pyridin-3-ylmethyl)-1,3,4-oxadiazol-2-yl]pyridazin-3-yl}-5-(trifluoromethyl)-3,4-dihydrospiro[chromene-2,4'-piperidine]; 5-fluoro-1'-{6-[5-(pyridin-3-ylmethyl)-1,3,4-oxadiazol-2-yl]pyridazin-3-yl}-3,4-dihydrospiro[chromene-2,4'-piperidine]; 6-[5-(cyclopropylmethyl)-4,5-dihydro-1'H,3H-spiro[1,5-benzoxazepine-2,4'-piperidin]-1'-yl]-N-(2-hydroxy-2-pyridin-3-ylethyl)pyridazine-3-carboxamide; 6-[4-(2-methylbenzoyl)piperidin-1-yl]pyridazine-3-carboxylic acid (2-hydroxy-2-pyridin-3-ylethyl)amide; 4-(2-chlorophenoxy)-N-[3-(methyl carbamoyl)phenyl]piperidine-1-carboxamide; the cis-9,trans-11 isomer and the trans-10,cis-12 isomer of conjugated linoleic acid, substituted heteroaromatic compounds disclosed in WO 2009/129625 A1, anti-sense polynucleotides and peptide-nucleic acids (PNAs) that target mRNA for SCD-1, and SCD-1-targeting siRNAs;

50 cholesterylester transfer protein (CETP) inhibitors, including anacetrapib, dalcetrapib, evacetrapib, torcetrapib and AMG 899 (TA-8995);

55 inhibitors of microsomal triglyceride transfer protein (MTTP) activity or expression, including implitapide, lomitapide, dirilotapide, mitratapide, CP-346086, JTT-130, SLX-4090, anti-sense polynucleotides and PNAs that target mRNA for MTTP, MTTP-targeting microRNAs (e.g., miRNA-30c), and MTTP-targeting siRNAs;

GLP-1 receptor agonists (*supra*);

fibroblast growth factor 21 (FGF21) and analogs and derivatives thereof, including BMS-986036 (pegylated FGF21);

inhibitors of pro-protein convertase subtilisin/kexin type 9 (PCSK9) activity or expression, including berberine (reduces PCSK9 level), annexin A2 (inhibits PCSK9 activity), anti-PCSK9 antibodies (e.g., alirocumab, bococizumab, evolocumab, LGT-209, LY3015014 and RG7652), peptides that mimic the epidermal growth factor-A (EGF-A) domain of the LDL receptor which binds to PCSK9, PCSK9-binding adnectins (e.g., BMS-962476), anti-sense polynucleotides and PNAs that target mRNA for PCSK9, and PCSK9-targeting siRNAs (e.g., inclisiran [ALN-PCS] and ALN-PCS02);

apolipoprotein mimetic peptides, including apoA-I mimetics (e.g., 2F, 3F, 3F-1, 3F-2, 3F-14, 4F, 4F-P-4F, 4F-IHS-4F, 4F2, 5F, 6F, 7F, 18F, 5A, 5A-C1, 5A-CH1, 5A-CH2, 5A-H1, 18A, 37pA [18A-P-18A], ELK [name], ELK-1A, ELK-1F, ELK-1K1A1E, ELK-1L1K, ELK-1W, ELK-2A, ELK-2A2K2E, ELK-2E2K, ELK-2F, ELK-3E3EK, ELK-3E3K3A, ELK-3E3LK, ELK-PA, ELK-P2A, ELKA [name], ELKA-CH2, ATI-5261, CS-6253, ETC-642, FAMP [name], FREL [name] and KRES [name]) and apoE mimetics (e.g., Ac-hE18A-NH₂ [AEM-28], Ac-[R]hE18A-NH₂, AEM-28-14, EpK, hEp, mR18L, COG-112, COG-133 and COG-1410);

omega-3 fatty acids, including docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), eicosapentaenoic acid (EPA), α -linolenic acid (ALA), fish oils (which contain, e.g., DHA and EPA), and esters (e.g., glyceryl and ethyl esters) thereof; and

analogs, derivatives and salts thereof.

[0156] In certain embodiments, the anti-obesity agent is or includes a lipase inhibitor (e.g., orlistat) or/and an antihyperlipidemic agent (e.g., a statin such as atorvastatin, or/and a fibrate such as fenofibrate).

[0157] Antihypertensive agents include without limitation:

antagonists of the renin-angiotensin-aldosterone system (RAAS), including renin inhibitors (e.g., aliskiren), angiotensin-converting enzyme (ACE) inhibitors (e.g., benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril andtrandolapril), angiotensin II receptor type 1 (AT₁) antagonists (e.g., azilsartan, candesartan, eprosartan, fimasartan, irbesartan, losartan, olmesartan medoxomil, olmesartan, telmisartan and valsartan), and aldosterone receptor antagonists (e.g., eplerenone and spironolactone);

diuretics, including loop diuretics (e.g., bumetanide, ethacrynic acid, furosemide and torsemide), thiazide diuretics (e.g., bendroflumethiazide, chlorothiazide, hydrochlorothiazide, epitizide, methyclothiazide and polythiazide), thiazide-like diuretics (e.g., chlorthalidone, indapamide and metolazone), cicletanine (an early distal tubular diuretic), potassium-sparing diuretics (e.g., amiloride, eplerenone, spironolactone and triamterene), and theobromine;

calcium channel blockers, including dihydropyridines (e.g., amlodipine, levamlodipine, cilnidipine, clevidipine, felodipine, isradipine, lercanidipine, nicardipine, nifedipine, nimodipine, nisoldipine and nitrendipine) and non-dihydropyridines (e.g., diltiazem and verapamil);

α_2 -adrenoreceptor agonists, including clonidine, guanabenz, guanfacine, methyl dopa and moxonidine;

α_1 -adrenoreceptor antagonists (alpha blockers), including doxazosin, indoramin, nicergoline, phenoxybenzamine, phentolamine, prazosin, terazosin and tolazoline;

β -adrenoreceptor (β_1 or/and β_2) antagonists (beta blockers), including atenolol, betaxolol, bisoprolol, carteolol, carvedilol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol and timolol;

mixed alpha/beta blockers, including bucindolol, carvedilol and labetalol;

endothelin receptor antagonists, including selective ET_A receptor antagonists (e.g., ambrisentan, atrasentan, edonantan, sitaxentan, zibotentan and BQ-123) and dual ET_A/ET_B antagonists (e.g., bosentan, macitentan and tezosentan);

other vasodilators, including hydralazine, minoxidil, theobromine, sodium nitroprusside, organic nitrates (e.g., isosorbide mononitrate, isosorbide dinitrate and nitroglycerin, which are converted to nitric oxide in the body), endothelial nitric oxide synthase (eNOS) stimulators (e.g., cicletanine), activators of soluble guanylate cyclase (e.g., cinaciguat

and riociguat), phosphodiesterase type 5 (PDE5) inhibitors (e.g., avanafil, benzamidenafil, dasantafil, dynafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil, vardenafil, dipyridamole, papaverine, propentofylline, zaprinast and T-1032), prostaglandin E₁ (alprostadil) and analogs thereof (e.g., limaprost and misoprostol), prostacyclin and analogs thereof (e.g., ataprost, beraprost [e.g., esuberaprost], 5,6,7-trinor-4,8-inter-*m*-phenylene-9-fluoro-PGI₂, carbacyclin, isocarbacyclin, clinprost, ciprostone, eptalprost, cicaprost, iloprost, pimilprost, SM-10906 (des-methyl pimilprost), naxaprostene, taprostene, treprostinil, CS-570, OP-2507 and TY-11223), non-prostanoid prostacyclin receptor agonists (e.g., 1-phthalazinol, ralinepag, selexipag, ACT-333679 [MRE-269, active metabolite of selexipag], and TRA-418), phospholipase C (PLC) inhibitors, and protein kinase C (PKC) inhibitors (e.g., BIM-1, BIM-2, BIM-3, BIM-8, chelerythrine, cicletanine, gossypol, miyabenol C, myricitrin, ruboxistaurin and verbascoside;

minerals, including magnesium and magnesium sulfate; and

analogs, derivatives and salts thereof.

[0158] In certain embodiments, the antihypertensive agent is or includes a thiazide or thiazide-like diuretic (e.g., hydrochlorothiazide or chlorthalidone), a calcium channel blocker (e.g., amlodipine or nifedipine), an ACE inhibitor (e.g., benazepril, captopril or perindopril) or an angiotensin II receptor antagonist (e.g., olmesartan medoxomil, olmesartan, telmisartan or valsartan), or any combination thereof.

[0159] In some embodiments, a peptide product described herein is used in combination with one or more additional therapeutic agents to treat NAFLD, such as NASH. In some embodiments, the one or more additional therapeutic agents are selected from antidiabetic agents, anti-obesity agents, anti-inflammatory agents, antifibrotic agents, antioxidants, anti-hypertensive agents, and combinations thereof.

[0160] Therapeutic agents that can be used to treat NAFLD (e.g., NASH) include without limitation:

PPAR agonists, including PPAR- δ agonists (e.g., MBX-8025, elafibranor [dual PPAR- α/δ agonist] and GW501516 [dual PPAR- β/δ agonist]) and PPAR- γ agonists (e.g., thiazolidinediones such as pioglitazone, and saroglitazar [dual PPAR- α/γ agonist]) - PPAR- δ and - γ agonism increases insulin sensitivity, PPAR- α agonism reduces liver steatosis and PPAR- δ agonism inhibits activation of macrophages and Kupffer cells;

farnesoid X receptor (FXR) agonists, such as obeticholic acid and GS-9674 - FXR agonists reduce liver gluconeogenesis, lipogenesis, steatosis and fibrosis;

fibroblast growth factor 19 (FGF19) and analogs and derivatives thereof, such as NGM-282 - FGF19 analogs reduce liver gluconeogenesis and steatosis;

fibroblast growth factor 21 (FGF21) and analogs and derivatives thereof, such as BMS-986036 (pegylated FGF21) - FGF21 analogs reduce liver steatosis, cell injury and fibrosis;

HMG-CoA reductase inhibitors, including statins (e.g., rosuvastatin) - statins reduce steatohepatitis and fibrosis;

ACC inhibitors, such as NDI-010976 (liver-targeted) and GS-0976 - ACC inhibitors reduce *de novo* lipogenesis and liver steatosis;

SCD-1 inhibitors, such as aramchol - SCD-1 inhibitors reduce liver steatosis and increase insulin sensitivity;

SGLT2 inhibitors, such as canagliflozin, ipragliflozin and luseogliflozin - SGLT2 inhibitors reduce body weight, liver ALT level and fibrosis;

antagonists of CCR2 or/and CCR5, such as cenicriviroc - antagonists of CCR2 (binds to CCL2 [MCP1]) and CCR5 (binds to CCL5 [RANTES]) inhibit activation and migration of inflammatory cells (e.g., macrophages) to the liver and reduce liver fibrosis;

apoptosis inhibitors, including apoptosis signal-regulating kinase 1 (ASK1) inhibitors (e.g., selonsertib) and caspase inhibitors (e.g., emricasan [pan-caspase inhibitor]) - apoptosis inhibitors reduce liver steatosis and fibrosis;

lysyl oxidase-like 2 (LOXL2) inhibitors, such as simtuzumab - LOXL2 is a key matrix enzyme in collagen formation and is highly expressed in the liver;

galectin-3 inhibitors, such as GR-MD-02 and TD139 - galectin-3 is critical for development of liver fibrosis;

antioxidants, including vitamin E (e.g., α -tocopherol) and scavengers of reactive oxygen species (ROS) and free radicals (e.g., cysteamine, glutathione, melatonin and pentoxifylline [also anti-inflammatory via inhibition of TNF- α and phosphodiesterases]) - vitamin E reduces liver steatosis, hepatocyte ballooning and lobular inflammation; and

analogs, derivatives and salts thereof.

[0161] In some embodiments, a peptide product described herein is used in conjunction with a PPAR agonist (e.g., a PPAR- δ agonist such as elafibranor or/and a PPAR- γ agonist such as pioglitazone), a HMG-CoA reductase inhibitor (e.g., a statin such as rosuvastatin), an FXR agonist (e.g., obeticholic acid) or an antioxidant (e.g., vitamin E), or any combination thereof, to treat NAFLD (e.g., NASH). In certain embodiments, the one or more additional therapeutic agents for treatment of NAFLD (e.g., NASH) are or include vitamin E or/and pioglitazone.

Preparation of Peptide Products

[0162] WO 2015/184177 A1 describes the synthesis of peptide products. The Examples below also describe the synthesis of representative peptide products.

EXAMPLES

[0163] The following examples are intended only to illustrate the disclosure. Other processes, assays, studies, protocols, procedures, methodologies, reagents and conditions may alternatively be used as appropriate. Examples 6 to 9 are not according to the present invention and are present for illustration purposes only.

Example 1. Reagents such as N- α -Fmoc, N- ϵ -(1-octyl B-D-glucuronide-6-yl)-L-lysine

[0164] In an oven-dried 250 mL Erlenmeyer flask is placed 1-octyl β -D-glucuronic acid (3.06 g, 10 mmol, Carbosynth Ltd.), 50 mL anhydrous DMF, and anhydrous 1-hydroxybenzotriazole (1.62 g, 12 mmol). A chilled (4 °C) solution of N, N'-dicyclohexylcarbodiimide (2.48g, 12 mmol) in 50 mL of DMF is added with stirring, and the reaction is allowed to proceed for 5 min. The copious white precipitate of N, N'-dicyclohexylurea is filtered on a fritted glass funnel and the filtrate is added to a solution of N- α -Fmoc-L-lysine (3.68g, 10 mmol) in 25 ml anhydrous DMF. The reaction is allowed to proceed for 25 min with warming to room temp or until the ninhydrin color is very faint. The reaction mixture is filtered, stripped to dryness and crystallized from MeOH/Et₂O by dissolution in MeOH and slow dilution to the cloud point with Et₂O, followed by refrigeration. Further purification can be achieved by silica gel chromatography using a solvent gradient from EtOAc to EtOAc/EtOH/AcOH.

[0165] A similar reaction using N- α -Boc-L-lysine yields N- α -Boc,N- ϵ -(1-octyl β -D-glucuronide-6-yl)-L-lysine, which is suitable for N-terminal incorporation and cleavage to a free N-terminus. A similar reaction using N- α -Ac-L-lysine yields N- α -Ac,N- ϵ -(1-octyl β -D-glucuronide-6-yl)-L-lysine, which is suitable for incorporation at the N-terminus of a peptide with a blocked N-terminus. A similar reaction using an appropriate amount of N- α -Fmoc-L-ornithine yields N- α -Fmoc,N- δ -(1-octyl (3-D-glucuronide-6-yl)-L-ornithine. Similar reactions using other N-mono-protected diamino acids furnish the corresponding reagents. Alternatively, use of a transient Me₃Si ester protecting group during the coupling and without pre-activation of the 1-octyl β -D-glucuronic acid provides a facile route to the formation of the reagents. The transient Me₃Si ester is produced by reaction of the Fmoc-Lys-OH with an equimolar amount of N,O-bis(trimethylsilyl)acetamide in dichloromethane (CH₂Cl₂). The organic layer contains the desired reagent as a solution in CH₂Cl₂ ready for coupling with the 1-alkyl glucuronide as above. The filtered reaction mixture is washed with aqueous NaHSO₄ to hydrolyze the Me₃Si ester and then is dried over MgSO₄, and then the solvent is removed.

[0166] Similarly, but using peracetyl or perbenzoyl 1-octyl β -D-glucuronic acid, one obtains the Ac- or Bz-protected form of the reagents (e.g. 2,3,4-trisacetyl 1-octyl β -D-glucuronic acid and the like, formed by treatment with Ac₂O). Such reagents have increased stability during acid cleavage from the resin and are used when instability during deprotection is detected. Final deprotection of such products is carried out by base-catalyzed transesterification after cleavage, by use of MeOH/NH₃, MeOH/NaOMe or MeOH/NH₂NH₂, as described above.

Example 2. Synthetic peptides

[0167] In general, peptide synthesis methods involve the sequential addition of protected amino acids to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid and any reactive side chain group are protected. This protected amino acid is then either attached to an inert solid support or utilized in solution, and the next amino acid in the sequence, also suitably protected, is added under conditions amenable to formation of the amide linkage. After all the desired amino acids have been linked in the proper sequence, protecting groups and any solid support are removed to afford the crude peptide. The peptide is desalted and purified chromatographically.

[0168] One method of preparing peptides having fewer than about fifty amino acids involves solid-phase peptide synthesis. In this method, the α -amino (N α) group and any reactive side-chain functional groups are protected by acid- or base-sensitive groups. The protecting group should be stable to the conditions of peptide linkage formation, while being readily removable without affecting the extant peptide chain. Suitable α -amino protecting groups include, but are not limited to, t-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz), o-chlorobenzyloxycarbonyl, biphenylisopropylloxycarbonyl, t-amylloxycarbonyl (Amoc), isobornyloxycarbonyl, α,α -dimethyl-3,5-dimethoxybenzyloxy-carbonyl, o-nitrophenylsulfenyl, 2-cyano-t-butyloxycarbonyl, 9-fluorenyl-methoxycarbonyl (Fmoc) and the like, preferably Boc or Fmoc. Suitable side-chain protecting groups include, but are not limited to, acetyl, benzyl (Bzl or Bn), benzyloxymethyl (Bom), Boc, t-butyl, o-bromobenzyloxycarbonyl, t-butyl, t-butyl dimethylsilyl, 2-chlorobenzyl (Cl-z), 2,6-dichlorobenzyl, cyclohexyl, cyclopentyl, isopropyl, pivalyl, tetrahydropyran-2-yl, tosyl (Tos), 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf), trimethylsilyl and trityl. A preferred No-protecting group for synthesis of the compounds is Fmoc. Preferred side-chain

protecting groups include -O-t-butyl for Glu, Tyr, Thr, Asp and Ser; Boc for Lys and Trp side chains; Pbf for Arg; and Trt for Asn, Gln and His. For selective modification of a Lys residue, orthogonal protection with a protecting group not removed by reagents that cleave the Fmoc or t-butyl-based protecting groups is preferred. Preferred examples for modification of the Lys side chain include, but are not limited to, those removed by hydrazine but not piperidine - e.g., 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl (ivDde), 1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl (Dde) and allyloxycarbonyl (Alloc).

[0169] The Fmoc-Lys(ivDde) or Fmoc-Lys(Dde) protecting group scheme is preferred in cases where side-chain lactam formation is desired because Fmoc-Glu(O-allyl) and Fmoc-Lys(Alloc) can be incorporated and used to provide transient protection, and then deprotected for lactam formation while the Lys(Dde) protecting group remains for later removal and reaction with the functionalized surfactant. The side-chain lactam between acidic and basic residues (e.g. Glu and Lys) is carried out after removal of the allyl-based protecting group by activation of the carboxyl side-chain function with N,N'-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate (HBTU)/N,N-di-isopropylethylamine (DIEA), using standard protocols in the art.

[0170] In solid-phase synthesis, the C-terminal amino acid is first attached to a suitable resin support. Suitable resin supports are those materials which are inert to the reagents and reaction conditions of the stepwise condensation and deprotection reactions, as well as being insoluble in the media used. Examples of commercially available resins include styrene/divinylbenzene resins modified with a reactive group, e.g., chloromethylated co-poly-(styrene-divinylbenzene), hydroxymethylated co-poly-(styrene-divinylbenzene), and the like. Benzylated, hydroxymethylated phenylacetamidomethyl (PAM) resin and hydroxymethylphenoxycetylamidomethyl (HMPA) are preferred for the preparation of peptide C-terminal acids. When the C-terminus of the compound is an amide, preferred resins are p-methylbenzhydrylamino-co-poly(styrene-divinylbenzene) resin and 2,4-dimethoxybenzhydrylamino-based resin ("Rink amide"), and the like. A preferred support for the synthesis of larger peptides is commercially available resins containing PEG sequences grafted onto other polymeric matrices, such as the Rink Amide-PEG and PAL-PEG-PS resins (Applied Biosystems) and similar resins designed for peptide amide synthesis using the Fmoc protocol. Thus, in certain cases it may be desirable to have an amide linkage to a PEG chain. In such cases it is convenient to link an N-Fmoc-amino-PEG-carboxylic acid to the amide-forming resin above (e.g. Rink amide resin and the like). The first amino acid of the chain can be coupled as an N-Fmoc-amino acid to the amino function of the PEG chain. Final deprotection yields the desired Peptide-NH-PEG-CO-NH₂ product.

[0171] Attachment to the PAM or HMPA resin may be accomplished by reaction of the N α -protected amino acid, such as the Boc-amino acid, as its ammonium, cesium, triethylammonium, 1,5-diazabicyclo-[5.4.0]undec-5-ene, tetramethylammonium, or similar salt in ethanol, acetonitrile, N,N-dimethylformamide (DMF), and the like, preferably the cesium salt in DMF, with the resin at an elevated temperature, such as between about 40 °C and about 60 °C, preferably about 50 °C, for about 12 to 72 hours, preferably about 48 hours. This eventually yields the peptide acid product following acid cleavage or an amide following aminolysis.

[0172] The N α -Boc-amino acid may be attached to the benzhydrylamine resin by means of, e.g., a DIC/HOBt-mediated coupling for about 2 to 24 hours, preferably about 2 hours, at a temperature between about 10° and about 50 °C, preferably about 25 °C, in a solvent such as CH₂Cl₂ or DMF, preferably CH₂Cl₂.

[0173] For Boc-based protocols, the successive coupling of protected amino acids may be carried out by methods known in the art, typically in an automated peptide synthesizer. Following neutralization with triethylamine, DIEA, N-methylmorpholine (NMM), collidine or similar base, each protected amino acid is introduced in approximately about 1.5- to 2.5-fold molar excess and the coupling carried out in an inert, nonaqueous, polar solvent such as CH₂Cl₂, DMF, N-methylpyrrolidone (NMP), N,N-dimethylacetamide (DMA), or a mixture thereof, preferably in dichloromethane at ambient temperature. For Fmoc-based protocols no acid is used for deprotection, but a base, preferably DIEA or NMM, is usually incorporated into the coupling mixture. Couplings are typically done in DMF, NMP, DMA or mixed solvents, preferably DMF. Representative coupling agents are N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC) and other carbodiimides, either alone or in the presence of HOBt, O-acyl ureas, benzotriazol-1-yl-oxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBop), N-hydroxysuccinimide, other N-hydroxyimides, or oximes. Alternatively, protected amino acid active esters (e.g. p-nitrophenyl, pentafluorophenyl and the like) or symmetrical anhydrides may be used. Preferred coupling agents are of the aminium/uronium class, such as HBTU, O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU), 2-(6-Chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate (HCTU), and the like.

[0174] A preferred method of attachment to the Fmoc-PAL-PEG-PS resin may be accomplished by deprotection of the resin linker with 20% piperidine in DMF, followed by reaction of the N- α -Fmoc protected amino acid, about a 5-fold molar excess of the N- α -Fmoc-amino acid, using HBTU: di-isopropylethylamine (DIEA) (1:2) in DMF in a microwave-assisted peptide synthesizer with a 5 min, 75 °C max. coupling cycle.

[0175] Peptides of the disclosure may contain a PEG group (dPEG) at the C-terminus. Such PEG groups can be short chains of polyethylene glycol with an amino terminus and a carboxyl terminus. Thus, they are essentially unnatural amino acids and are treated similarly to the other amino acids for synthesis. For example, Fmoc-amidooxy-dPEG4-acid is

commercially available from Quanta Biodesign (#10213) and is attached to the Rink or HMPA resin at the first step of the synthesis in a manner similar to that used for the N-Fmoc or N-Boc amino acids described above. Deprotection with the standard strong acid conditions provides the corresponding short dPEG C-terminally modified peptide with the corresponding acid or amide C-terminus.

[0176] For an Fmoc-based protocol in a microwave-assisted peptide synthesizer, the N- α -Fmoc amino acid protecting group is removed with 20% piperidine in DMF containing 0.1 M 1-hydroxybenzotriazole (HOBt), in a double-deprotection protocol for 30 sec and then for 3 min with a temperature maximum set at 75 °C. HOBt is added to the deprotection solution to reduce aspartimide formation. Coupling of the next amino acid then employs a 5-fold molar excess using HBTU:DIEA (1:2) with a 5 min, 75 °C max. double-coupling cycle.

[0177] At the end of the solid-phase synthesis, the fully protected peptide is removed from the resin. When the linkage to the resin support is of the benzyl ester type, cleavage may be effected by means of aminolysis with an alkylamine or fluoroalkylamine for peptides with an alkylamide C-terminus, or by ammonolysis using, e.g., ammonia/methanol or ammonia/ethanol for peptides with an unsubstituted amide C-terminus, at a temperature between about -10 °C and about 50 °C, preferably at about 25 °C, for about 12 to 24 hours, preferably about 18 hours. Peptides with a hydroxy C-terminus may be cleaved by HF or other strongly acidic deprotection regimen or by saponification. Alternatively, the peptide may be removed from the resin by transesterification using methanol for example, followed by aminolysis or saponification. The protected peptide may be purified by silica gel or reverse-phase HPLC.

[0178] The side-chain protecting groups may be removed from the peptide by treating the aminolysis product with, e.g., anhydrous liquid HF in the presence of anisole or other carbonium ion scavenger, treatment with HF/pyridine complex, treatment with tris(trifluoroacetyl)boron and trifluoroacetic acid, by reduction with hydrogen and palladium on carbon or polyvinylpyrrolidone, or by reduction with sodium in liquid ammonia, preferably with liquid HF and anisole at a temperature between about -10 °C and 10 °C, preferably at about 0 °C, for about 15 minutes to 2 hours, preferably about 1.5 hours.

[0179] For peptides on the benzhydrylamine-type resins, the resin cleavage and deprotection steps may be combined in a single step utilizing liquid HF and anisole as described above or preferably through the use of milder cleavage cocktails. For example, for the PAL-PEG-PS resin, a preferred method is the use of a double-deprotection protocol in a microwave-assisted peptide synthesizer using one of the mild cleavage cocktails known in the art, such as TFA/water/tri-iso-propylsilane/3,6-dioxo-1,8-octanedithiol (DODT) (92.5/2.5/2.5/2.5) for 18 min at 38 °C each time. Cleavage of alkyl glycoside-containing materials has shown survival of the alkyl glycoside linkage using protocols with TFA/water ratios in the 9/1 to 19/1 range. A typical cocktail is 94% TFA:2% EDT; 2% H₂O; 2% TIS. Typically the fully deprotected product is precipitated and washed with cold (-70 °C to 4 °C) Et₂O, dissolved in deionized water and lyophilized.

[0180] The peptide solution may be desalted (e.g. with BioRad AG-3[®] anion-exchange resin) and the peptide purified by a sequence of chromatographic steps employing any or all of the following types: ion exchange on a weakly basic resin in the acetate form; hydrophobic adsorption chromatography on underivatized co-poly(styrene-divinylbenzene) such as Amberlite[®] XAD; silica gel adsorption chromatography; ion-exchange chromatography on carboxymethylcellulose; partition chromatography on Sephadex[®] G-25 for example; countercurrent distribution; supercritical fluid chromatography; and HPLC, especially reversed-phase HPLC on octyl- or octadecylsilylsilica (ODS) bonded phase column packing.

[0181] Provided herein are processes for preparing covalently modified peptides described herein and pharmaceutically acceptable salts thereof, which comprise sequentially condensing protected amino acids on a suitable resin support, removing the protecting groups and resin support, and purifying the product, to afford the covalently modified peptides. The processes can employ any protocol for peptide synthesis known in the art, such as microwave-assisted solid-phase synthesis. In some embodiments, the peptides are attached to an alkyl glycoside.

Example 3. Oxidation method to make uronic acids

[0182] To a solution of 1-dodecyl β -D-glucopyranoside (2.0 g, 5.74 mmol, Carbosynth) in 20 mL of acetonitrile and 20 mL of de-ionized (DI) water was added (diacetoxyiodo)benzene (4.4 g, 13.7 mmol, Fluka) and TEMPO (0.180 g, 1.15 mmol). The resulting mixture was stirred at room temperature for 20 hr. The reaction was followed by mass spectrometry (e.g., LCQ ESI) and upon completion, the reaction mixture was diluted with water and lyophilized to dryness to give 1.52 g (73% crude yield) of the crude product, 1-dodecyl β -D-glucuronic acid, as a white powder, which was used directly for the solid-phase synthesis without further purification. For longer alkyl groups, 1,4-dioxane was used instead of acetonitrile and the temperature was raised to as high as 30 °C. In a similar manner are prepared the desired alkyl saccharide uronic acids used to make the products and reagents described herein.

[0183] In a like manner, but using, e.g., the corresponding 1-octyl, 1-decyl, 1-undecyl, 1-tetradecyl, 1-hexadecyl and 1-octadecyl glycosides (Anatrace, Maumee, Ohio), were prepared the desired 1-alkyl saccharide uronic acids which were used to make the products and reagents described herein. In a like manner, but using, e.g., the corresponding 1-octyl, 1-decyl, 1-undecyl, 1-tetradecyl, 1-hexadecyl and 1-octadecyl β -D-melibiosides or β -D-maltosides (Anatrace),

were prepared the desired 1-alkyl disaccharide uronic acids which were used to make the products and reagents described herein.

Example 4. Preparation of peptide product with C-terminal amide (EU-A387)

[0184] A sample of Fmoc-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Bip-Ser-Lys-Tyr-Leu-Glu-Ser-Lys(Alloc)-Rink amide resin (**SEQ ID NO: 782**) was prepared by sequential addition of N α -Fmoc-protected amino acids as described in Example 1 and deprotected at the Lys-N-epsilon position by incubation with Pd(PPh₃)₄ (0.5 eq.) and DMBA (20 eq.) in DMF/CH₂Cl₂ (1:1) overnight in the dark at room temperature. Following washing by DMF/CH₂Cl₂, the Lys side chain was acylated with 1'-dodecyl β -D-glucuronic acid in DMF/CH₂Cl₂ using DIC/HOBt. Completion of the coupling was checked by ninhydrin, and the product was washed extensively with CH₂Cl₂.

[0185] The product resin was submitted to final deprotection and cleavage from the resin by treatment with a cleavage cocktail (94% TFA, 2% EDT, 2% H₂O, 2% TIS) for a period of 240 min at room temperature. The mixture was treated with Et₂O to precipitate the product and washed extensively with Et₂O to yield the crude title peptide product after drying in vacuo.

[0186] Purification was carried out in two batches by reverse-phase (C18) HPLC. The crude peptide was loaded on a 4.1x25 cm HPLC column at a flow rate of 15 mL/min (15% organic modifier, acetic acid buffer) and eluted with a gradient from 15-45% buffer B in 60 min at 50 °C. The product fraction was lyophilized to yield the title peptide product with a purity of 98% by analytical HPLC (18.6 min; 30-60% CH₃CN in 0.1% TFA)/mass spectrometry (M+1 peak = 2382.14). In a similar manner were prepared other peptide products of the disclosure, the characterization of which is shown below.

[0187] The corresponding 1-methyl and 1-octyl analogs of the title compound are prepared in a similar manner, but using the reagents 1'-methyl β -D-glucuronic acid and 1'-octyl β -D-glucuronic acid (Carbosynth). The corresponding 1-decyl, 1-dodecyl, 1-tetradecyl, 1-hexadecyl, 1-octadecyl, 1-eicosyl and higher analogs are prepared using the corresponding monosaccharide and disaccharide uronic acids, prepared as described above. Alternatively, the 1-alkyl glucuronyl, or other uronic acylated analogs, may be prepared by initial purification of the deprotected or partially deprotected peptide followed by acylation by the desired uronic acid.

Example 5. Preparation of peptide products with C-terminal acid

[0188] A sample of Boc-His(Trt)-Aib-Gln(Trt)-Gly-Thr(tBu)-Phe-Thr(tBu)-Ser(tBu)-Asp(OtBu)-Tyr(tBu)-Ser(tBu)-Lys(Boc)-Tyr(tBu)-Leu-Asp(OtBu)-Glu(O-Allyl)-Gln(Trt)-Ala-Ala-Lys(Alloc)-Glu(O-tBu)-Phe-Ile-Lys(Dde)-Trp(Boc)-Leu-Leu-Gln(Trt)-Thr(tBu)-HMPA (**SEQ ID NO: 783**) resin (started from Fmoc-Thr(tBu)-HMPA resin, substitution 0.45mmol/g) was prepared by sequential addition of N α -Fmoc-protected amino acids as described in Example 1. The allyl-protected side chains of Glu and Lys residues were deprotected by incubation with Pd(PPh₃)₄ (0.5 eq.) and DMBA (20 eq.) in DMF/CH₂Cl₂ (1:1) overnight in the dark at room temperature. The resin was washed with 0.5% DIEA in DMF (twice), 0.5% sodium diethyldithiocarbamate in DMF (twice), and DMF/CH₂Cl₂ until a light yellow resin was obtained. A side-chain lactam was formed by coupling the Glu and Lys residues with DIC/HOBT (5 eq.) in DMF. The reaction was checked for completeness with ninhydrin and recoupled if necessary. Following washing with DMF/CH₂Cl₂, the Lys side chain was deprotected by incubation with 5% hydrazine hydrate in DMF (10 eq.) twice, in each case for 15 min. Following washing with DMF/CH₂Cl₂, the side-chain amino group of the deprotected Lys residue was reacted with 1'-tetradecyl β -D-melibouronic acid in DMF/CH₂Cl₂ using DIC/HOBt. Completion of the coupling was checked by ninhydrin, and the product was washed extensively with CH₂Cl₂. Any coupling which was not complete by ninhydrin was rerun. In general, 10-12 g of peptide product resin was obtained from a 2 mmole synthesis.

[0189] The product resin was submitted to final deprotection and cleavage from the resin by treatment with a cleavage cocktail (94% TFA, 2% EDT, 2% H₂O, 2% TIS) for a period of 240 min at room temperature. The mixture was treated with Et₂O to precipitate the product and washed extensively with Et₂O to yield the crude title peptide product after drying in vacuo. In general, 5-8 g of crude peptide product was obtained.

[0190] Purification was carried out in two batches by reverse-phase (C18) HPLC. The crude peptide (1-1.5g) was loaded on a 4.1x25 cm HPLC column at a flow rate of 15 mL/min (15% organic modifier, 0.1% TFA buffer) and eluted with a gradient from 35-55% buffer B in 70 min at room temperature. Repurification of the less pure fractions was done for the fractions with a purity of > 70%. The product fraction was lyophilized to yield EU-A1077 with a purity of 98.7% by analytical HPLC (10.3 min, 45-75% CH₃CN in 0.1% TFA)/mass spectrometry (1317.67, +3 charged; 1976.13, +2 charged; molecular weight 3950.44). In a similar manner were prepared other peptide products of the disclosure, whose characterization is shown below.

[0191] The corresponding 1-methyl and 1-octyl analogs of the title compound are prepared in a similar manner, but using the reagents 1'-methyl β -D-glucuronic acid and 1'-octyl β -D-glucuronic acid (Carbosynth). In a like manner, but using the corresponding 1-octyl, 1-decyl, 1-undecyl, 1-tetradecyl, 1-hexadecyl and 1-octadecyl β -D-glucouronic acids

(prepared as described above), were prepared peptide products of the disclosure. In a like manner, but using the corresponding 1-octyl, 1-decyl, 1-undecyl, 1-tetradecyl, 1-hexadecyl and 1-octadecyl β -D-melibouronic acids or β -D-maltouronic acids (prepared as described above), were prepared peptide products of the disclosure. Alternatively, the 1-alkyl glucuronyl, or other uronic acylated analogs, may be prepared by initial purification of the deprotected or partially deprotected peptide followed by acylation by the desired uronic acid reagent. Alternatively, ammonolysis of the HMPA resin-bound intermediate yields the corresponding C-terminal amide.

[0192] Analysis and characterization was done by HPLC/mass spectrometry in positive ion mode using the eluent gradients given in the table below.

Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
EU-A387	2379.66	2380.14	18.6[b]
EU-A388	2393.69	2393.74	16.0 [a]
EU-A391	2317.62	2318.26	11.2 [b]
EU-A455	2988.36	2988.00	11.5 [b]
EU-A474	2570.86	2570.54	11.3 [b]
EU-A478	2459.75	2459.74	11.1 [b]
EU-A484	2544.86	2545.06	9.6 [b]
EU-A501	2904.2	2903.34	7.9 [b]
EU-A502	2776.07	2776.14	8.0 [b]
EU-A503	2704.98	2704.40	8.0 [b]
EU-A504	2548.80	2548.00	9.1 [b]
EU-A505	2392.61	2392.40	10.5 [b]
EU-A506	2305.53	2305.06	10.7 [b]
EU-A507	3763.23	3762.66	9.0 [b]
EU-A521	2303.56	2303.60	8.2 [c]
EU-A522	2315.60	2315.60	14.2 [d]
EU-A523	2615.94	2616.00	8.1 [b]
EU-A524	2459.75	2459.74	12.7 [d]
EU-A525	2459.75	2459.06	6.0 [c]
EU-A526	2473.75	2473.60	12.7 [d]
EU-A527	2390.64	2390.40	14.6 [d]
EU-A529	2546.83	2546.80	9.5 [b]
EU-A531	2546.83	2546.80	9.5 [b]
EU-A532	2559.00	2558.66	9.6 [b]
EU-A533	2560.96	2560.66	9.5 [b]
EU-A534	2544.99	2544.94	9.7 [b]
EU-A535	2573.05	2574.00	12.0 [b]
EU-A536	2602.96	2603.46	14.3 [b]
EU-A538	2516.99	2516.40	10.3 [b]
EU-A539	2657.20	2656.80	10.8 [b]
EU-A540	2685.20	2684.94	9.8 [c]
EU-A541	2713.20	2712.80	13.0 [c]
EU-A544	2631.94	2632.26	10.8 [b]

(continued)

	Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
5	EU-A546	2687.94	2688.80	9.1 [c]
	EU-A549	2388.67	2388.66	6.3 [e]
	EU-A551	2444.67	2445.20	11.4 [e]
	EU-A552	2472.67	2473.14	10.7 [f]
10	EU-A554	2560.86	2560.40	10.3 [c]
	EU-A556	2616.86	2616.40	11.7 [e]
	EU-A557	2644.86	2645.74	10.4 [f]
15	EU-A560	2570.86	2571.06	8.3 [c]
	EU-A562	2626.86	2626.66	9.9 [e]
	EU-A563	2654.86	2655.06	8.7 [f]
	EU-A565	2542.80	2542.54	9.5 [c]
20	EU-A567	2598.80	2599.06	12.0 [e]
	EU-A568	2626.80	2626.54	10.1 [f]
25	HPLC gradients in 0.1% TFA: [a] 35 to 65% CH ₃ CN over 30 min [b] 30 to 60% CH ₃ CN over 20 min [c] 35 to 65% CH ₃ CN over 20 min [d] 25 to 55% CH ₃ CN over 20 min [e] 40 to 70% CH ₃ CN over 20 min [f] 45 to 75% CH ₃ CN over 20 min HPLC was carried out on a Phenomenex Luna C18 5 micron 250x4.6 mm analytical column.			
30				

[0193] The following table lists other compounds synthesized and analyzed as described above:

	Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
35	EU-A570	2656.16	2656.00	10.4 [b]
	EU-A571	2684.16	2683.34	11.2 [c]
40	EU-A575	2670.16	2670.94	11.8 [b]
	EU-A576	2698.16	2697.20	11.2 [c]
	EU-A580	2668.20	2667.20	12.3 [b]
45	EU-A581	2696.20	2695.46	11.1 [c]
	EU-A592	2724.20	2724.58	9.9 [e]
	EU-A595	2682.20	2682.40	9.7 [c]
	EU-A596	2710.20	2710.46	10.4 [c]
50	EU-A597	2738.20	2738.18	10.9 [e]
	EU-A721	2461.85	2461.74	10.3 [b]
	EU-A722	2475.85	2475.34	10.8 [b]
55	EU-A723	2459.88	2459.86	7.7 [c]
	EU-A724	2473.88	2473.34	11.1 [b]
	EU-A725	2471.92	2472.00	10.8 [b]

(continued)

	Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
5	EU-A726	2557.03	2556.80	11.0 [b]
	EU-A727	2485.92	2485.74	10.9 [b]
	EU-A728	2513.92	2513.86	10.6 [c]
	EU-A729	2541.92	2541.86	9.7 [e]
10	EU-A730	2569.92	2569.74	9.4 [f]
	EU-A731	2425.88	2425.32	10.6 [d]
	EU-A732	2476.95	2476.40	9.4 [c]
	EU-A733	2381.83	2382.02	11.4 [b]
15	EU-A734	2616.09	2616.18	11.4 [b]
	EU-A750	1611.89	1611.56	9.4 [c]
	EU-A751	1625.89	1625.35	9.7 [c]
	EU-A752	1709.93	1709.41	11.7 [g]
20	EU-A753	1637.84	1637.46	12.5 [b]
	EU-A754	1651.84	1651.18	9.9 [c]
	EU-A755	1711.93	1711.46	10.3 [h]
	EU-A756	1671.98	1671.37	9.8 [e]
25	EU-A757	1770.02	1769.17	14.9 [g]
	EU-A770	3333.61	3334.65	9.5 [b]
	EU-A771	3678.25	3677.96	11.3 [c]
	EU-A772	3762.25	3763.35	14.9 [e]
30	EU-A773	3790.31	3791.31	11.1 [f]
	EU-A774	3475.74	3477.15	10.5 [d]
	EU-A775	3820.38	3821.52	10.4 [c]
	EU-A776	3904.38	3905.76	10.2 [f]
35	EU-A777	3932.44	3933.69	9.7 [f]
	EU-A792	3793.43	3793.52	8.9 [f]
	EU-A793	3821.43	3821.60	10.8 [f]
	EU-A794	3849.43	3848.78	10.5 [g]
40	EU-A945	3777.18	3777.54	12.2 [e]
	EU-A948	3861.18	3862.14	13.0 [f]
	EU-A993	3759.22	3759.00	9.3 [f]
	EU-A994	3787.22	3787.44	11.4 [f]
45	EU-A995	3815.22	3815.52	14.5 [g]
	EU-A996	3843.22	3843.12	12.3 [g]
	EU-A999	3935.35	3934.66	13.4 [e]
	EU-A1011	3854.21	3854.38	14.2 [c]
50	EU-A1017	3896.26	3895.77	12.3 [c]
	EU-A1023	3921.35	3921.15	10.5 [e]

(continued)

	Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
5	EU-A1024	3949.42	3950.22	5.8 [g]
	EU-A1025	3977.47	3976.84	7.96 [g]
	EU-A1026	4005.55	4004.64	12.8 [g]
	EU-A1029	3939.31	3939.06	10.7 [e]
10	EU-A1032	4023.51	4025.22	13.9 [f]
	EU-A1035	3840.21	3838.21	9.8 [e]
	EU-A1041	3882.26	3880.50	9.6 [e]
15	EU-A1044	3966.46	3965.46	12.6 [f]
	EU-A1167	3731.15	3731.42	8.9 [f]
	EU-A1168	3745.15	3745.20	10.8 [i]
	EU-A1173	3978.49	3977.00	12.9 [f]
20	EU-A1576	3922.37	3922.08	10.2 [e]
	EU-A1577	3950.44	3949.95	10.3 [f]
	EU-A1581	3923.35	3921.21	13.1 [i]
25	EU-A1587	3949.42	3949.92	9.6 [f]
	EU-A1588	3977.47	3977.97	8.3 [f]
	EU-A1589	4005.55	4005.18	9.2 [g]
	EU-A1590	3922.37	3923.01	12.5 [j]
30	EU-A1591	3922.33	3922.80	12.4 [j]
	EU-A1592	3923.35	3921.74	13.0 [i]
	EU-A1595	3914.38	3915.45	11.5 [e]
35	EU-A1596	3942.43	3942.48	7.1 [g]
	EU-A1598	3887.29	3886.80	12.4 [i]
	EU-A1599	3888.31	3888.00	12.5 [i]
40	EU-A1601	4049.52	4051.35	10.1[e]
	EU-A1602	4077.59	4075.41	12.4 [n]
	EU-A1606	4050.46	4051.77	10.4[e]
	EU-A1607	4078.53	4077.99	12.7 [n]
45	EU-A1611	4050.54	4051.44	10.1[e]
	EU-A1612	4078.61	4078.86	12.3 [e]
	EU-A1617	4079.55	4079.55	13.0 [j]
50	EU-A1620	4180.59	4181.49	11.0 [e]
	EU-A1622	4208.66	4208.31	12.9 [i]
	EU-A1627	4207.64	4208.28	12.8 [i]
	EU-A1634	4035.78	4037.34	13.9 [e]
55	EU-A1635	4063.78	4065.54	9.5 [g]
	EU-A1639	4169.54	4167.99	7.7 [k]
	EU-A1645	4183.76	4182.60	13.2 [e]

(continued)

	Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
5	EU-A1646	4211.99	4213.32	23.5 [l]
	EU-A1647	4239.74	4239.21	12.2 [m]
	EU-A1651	4345.89	4345.41	10.8 [o]
	EU-A1679	3704.17	3704.85	9.0 [e]
10	EU-A1680	3732.17	3732.45	7.0 [f]
	EU-A1681	3760.24	3761.31	8.8 [f]
	EU-A1682	3788.24	3788.52	11.9 [f]
15	EU-A1710	3859.32	3859.71	6.4 [f]
	EU-A1711	3887.39	3888.12	8.0 [f]
	EU-A1712	3915.39	3915.72	12.1 [e]
	EU-A1713	3943.39	3943.32	11.2 [f]
20	EU-A1716	3860.26	3860.49	9.8 [e]
	EU-A1717	3888.33	3889.23	8.4 [f]
	EU-A1718	3916.33	3916.98	12.6 [i]
25	EU-A1719	3944.33	3944.31	9.0 [g]
	EU-A1722	3989.37	3990.03	6.1 [f]
	EU-A1723	4017.44	4017.54	7.8 [f]
	EU-A1730	3916.35	3917.76	7.8 [f]
30	EU-A1734	3726.10	3726.63	14.0 [e]
	EU-A1735	3754.10	3754.26	12.9 [f]
	EU-A1739	3949.38	3950.31	13.0 [f]
35	EU-A1740	3977.43	3978.30	8.9 [g]
	EU-A1745	3815.18	3815.10	13.8 [g]
	EU-A1784	3915.35	3917.31	11.0 [f]
	EU-A1785	3943.35	3944.40	14.6 [i]
40	EU-A1787	3916.25	3917.46	9.1 [g]
	EU-A1788	3944.29	3945.45	10.8 [f]
	EU-A1841	3788.20	3789.36	6.6 [f]
45	EU-A1842	3816.20	3817.80	11.3 [m]
	EU-A1847	3727.08	3728.46	10.9 [f]

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(continued)

Compound Number	Molecular Wt Expected	Molecular Wt Found	HPLC (min; elution)
EU-A1848	3755.08	3756.96	10.2 [g]
HPLC gradients in 0.1% TFA: [a] 35 to 65% CH₃CN over 30 min [b] 30 to 60% CH₃CN over 20 min [c] 35 to 65% CH₃CN over 20 min [d] 25 to 55% CH₃CN over 20 min [e] 40 to 70% CH₃CN over 20 min [f] 45 to 75% CH₃CN over 20 min [g] 50 to 80% CH₃CN over 20 min [h] 10 to 40% CH₃CN over 20 min [i] 30 to 90% CH₃CN over 20 min [j] 10 to 90% CH₃CN over 20 min [k] 30 to 95% CH₃CN over 20 min [l] 30 to 60% CH₃CN over 30 min [m] 20 to 100% CH₃CN over 20 min [n] 20 to 80% CH₃CN over 20 min [o] 30 to 50% CH₃CN over 20 min HPLC was carried out on a Phenomenex Luna C18 5 micron 250x4.6 mm analytical column.			

Example 6. *In vitro* stability of peptide products in human plasma

[0194] One mg/mL stock solution was prepared in DMSO/CH₃CN (1/1). Standard working solutions in 50% CH₃CN were prepared with the stock solution. The concentrations of the working solutions were 20, 50, 100, 200, 500, 1000, 2000, 5000, 10000 and 20000 ng/mL. Ten μ L of the working solutions was spiked into 90 μ L blank plasma, and the mixture was vortexed. 300 μ L of internal standard solution (verapamil, 20 ng/mL in 100% CH₃CN) was added, and the mixture was vortexed and centrifuged. The supernatant was transferred to an HPLC injection plate for loading onto the HPLC column. The standard samples were at 2, 5, 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL. The QC samples were at 5 (LQC), 50 (MQC) and 500 (HQC) ng/mL. For the plasma-stability study, samples of EU-A993, EU-A1023 and human GLP-1(7-36) (Bachem) were prepared in human plasma (about 6-20 ng/mL or similar concentrations above the limit of quantitation) and sampled at time points $t = 0, 0.5, 1, 2, 4$ and 8 hr during incubation at 30 °C. Samples were treated with internal standard solution (100% CH₃CN) as described above in order to precipitate the peptides, and supernatants were loaded into an injection plate for loading into the HPLC column for quantitation by mass spectrometry.

[0195] Instruments used were: API-4000 Mass Spectrometer, ESI positive, MRM scan; and Shimadzu HPLC/CTC Autosampler with ACE C8 column (2.1x50 mm, 5 μ m), mobile phase A: 0.1% formic acid and 5mM NH₄OA_C in water, mobile phase B: 0.1% formic acid in CH₃CN, 10 μ L of sample was injected.

[0196] A plot of compound signal (amount) versus time shows essentially complete cleavage of GLP-1(7-36) in 4 hours, but no detectable change in the amount of intact peptide products in human plasma over a period of at least 8 hours (**FIG. 8**). Both peptide products exhibited protection from proteolysis and a long plasma half-life in the *in vitro* assay.

Example 7. Cell assay of activity of peptide products at GLP-1 and glucagon receptors

[0197] Compounds were weighed precisely in an amount of about 1 mg and assayed in standard cellular assays (Cerep SA). The readout was the amount of cAMP generated in the cells treated with the test compounds, in either agonist or antagonist mode. The assay used was the stimulation of cAMP levels in the glucagon (human, cloned into CHO cells) and GLP-1 (murine cell line) cellular assays. The assays are described in Chicchi et al., J. Biol. Chem., 272:7765-7769 (1997) and Runge et al., Br. J. Pharmacol., 138:787-794 (2003).

[0198] For EU-A391, the GCGR cellular response did not change, and the GLP1R cellular response rose steeply with an EC₅₀ of 420 nM.

Compound Number	1-Alkyl	EC ₅₀ GLP-1 R (nM)	EC ₅₀ Glucagon R (nM)
EU-A391	1-dodecyl	420	n.c.
EU-A455	1-dodecyl	59	770
EU-A474	1-dodecyl	3000	n.c.
EU-A478	1-dodecyl	n.c.	n.c.
EU-A484	1-dodecyl	n.c.	n.c.
EU-A501	1-dodecyl	20000	12000
EU-A502	1-dodecyl	9400	n.c.
EU-A503	1-dodecyl	n.c.	n.c.
EU-A504	1-dodecyl	3100	1100
EU-A505	1-dodecyl	8500	6100
EU-A506	1-dodecyl	4600	1300
EU-A507	1-dodecyl	18	1
EU-A521	1-dodecyl	n.c.	n.c.
EU-A522	1-dodecyl	n.c.	9000
EU-A523	1-dodecyl	n.c.	n.c.
EU-A524	1-dodecyl	n.c.	n.c.
EU-A525	1-dodecyl	n.c.	n.c.
EU-A526	1-dodecyl	n.c.	n.c.
EU-A527	1-dodecyl	n.c.	5000
EU-A529	1-dodecyl	n.c.	7000
EU-A531	1-dodecyl	2100	1100
EU-A532	1-dodecyl	5000	2600
EU-A533	1-dodecyl	770	780
EU-A534	1-dodecyl	290	1900
EU-A535	1-tetradecyl	§4800	2100
EU-A536	1-hexadecyl	>10000	4400
EU-A538	1-dodecyl	270	n.c.
EU-A539	1-dodecyl	860	2300
EU-A540	1-tetradecyl	n.c.	8800
EU-A541	1-hexadecyl	800	5000
n.c. means EC ₅₀ not calculable § means superagonist			

[0199] A further series of cellular assays was carried out with standard cellular assays (DiscoverX, LeadHunter assays) using readout of cAMP stimulation or arrestin activation. Compounds were weighed precisely in an amount of about 1 mg and shipped to DiscoverX for dilution and assay. The cellular assays used human glucagon receptor cloned into CHO cells and human GLP-1 receptor cloned into CHO cells.

	Compound Number	EC ₅₀ cAMP GLP-1 R (nM)	EC ₅₀ Arrestin GLP-1R (nM)	EC ₅₀ cAMP GlucagonR (nM)	EC ₅₀ Arrestin Glucagon R (nM)
5	EU-A507	0.01	9	0.02	100
	EU-A534	87		1100	
	EU-A538	55		3500	
	EU-A750	>1000		>1000	
10	EU-A751	>1000		>1000	
	EU-A752	146		>1000	
	EU-A753	>1000		>1000	
15	EU-A754	360		>1000	
	EU-A755	486		471	
	EU-A756	611		>1000	
	EU-A757	6.7		>1000	
20	EU-A770	0.01	2.3	0.5	>100
	EU-A771	0.07	14.2	0.4	>100
	EU-A772	0.07	8.4	5.4	>100
25	EU-A773	0.08	8.3	1.5	>100
	EU-A774	0.009	6.8	0.15	22.7
	EU-A775	0.16	17	0.3	33.6
	EU-A776	1.2	>100	6.5	>100
30	EU-A777	0.1	34.5	0.6	73
	EU-A792	<0.05	27.9	<0.05	
	EU-A793	<0.05	23.8	<0.05	
35	EU-A794	0.05	59.4	0.18	
	EU-A945	<0.05	9.4	0.06	
	EU-A948	0.08	25.6	9.1	
	EU-A992	0.009		0.019	
40	EU-A993	<0.05	12.3	<0.05	
	EU-A994	0.05	10.2	<0.05	
	EU-A995	0.035	59.5	0.15	
45	EU-A996	0.05	>100	0.87	
	EU-A999	0.05		0.015	
	EU-A1011	0.16		0.51	
	EU-A1017	0.44		0.10	
50	EU-A1023	0.028		0.035	
	EU-A1024	0.005		0.035	
	EU-A1025	0.008		0.240	
55	EU-A1026	0.034		0.486	
	EU-A1029	0.019		0.06	
	EU-A1032	0.03		5.4	

(continued)

	Compound Number	EC ₅₀ cAMP GLP-1 R (nM)	EC ₅₀ Arrestin GLP-1R (nM)	EC ₅₀ cAMP GlucagonR (nM)	EC ₅₀ Arrestin Glucagon R (nM)
5	EU-A1035	0.02		0.19	
	EU-A1041	0.02		0.13	
	EU-A1044	0.07		0.57	
10	EU-A1167	0.013		0.019	
	EU-A1168	0.07		0.14	
	EU-A1173	0.021		0.463	
15	EU-A1576	0.032		0.070	
	EU-A1577	0.007		0.069	
	EU-A1578	0.008		0.355	
	EU-A1581	0.086		1.032	
20	EU-A1586	0.029		0.107	
	EU-A1587	0.081		0.253	
	EU-A1588	0.023		0.043	
25	EU-A1589	0.236		0.655	
	EU-A1590	0.094		0.343	
	EU-A1591	0.073		0.286	
	EU-A1592	0.25		0.78	
30	EU-A1594	0.011		0.068	
	EU-A1595	0.021		0.113	
	EU-A1596	0.493		1.230	
35	EU-A1598	0.026		0.199	
	EU-A1599	0.061		0.317	
	EU-A1601	0.007		0.048	
	EU-A1602	0.035		0.162	
40	EU-A1606	0.017		0.058	
	EU-A1607	0.022		0.126	
	EU-A1611	0.015		0.16	
45	EU-A1612	0.011		0.059	
	EU-A1616	0.079		0.204	
	EU-A1617	0.119		0.598	
	EU-A1620	0.051		0.24	
50	EU-A1622	0.774		2.08	
	EU-A1627	0.304		0.705	
	EU-A1633	0.008		0.053	
55	EU-A1634	0.052		0.493	
	EU-A1635	0.071		1.983	
	EU-A1639	0.385		2.292	

(continued)

	Compound Number	EC ₅₀ cAMP GLP-1 R (nM)	EC ₅₀ Arrestin GLP-1R (nM)	EC ₅₀ cAMP GlucagonR (nM)	EC ₅₀ Arrestin Glucagon R (nM)
5	EU-A1645	0.029		0.091	
	EU-A1646	0.029		0.332	
	EU-A1647	0.113		1.895	
10	EU-A1651	0.033		0.149	
	EU-A1679	0.009		0.14	
	EU-A1680	0.026		0.114	
15	EU-A1681	0.009		0.132	
	EU-A1682	0.21		1.263	
	EU-A1710	0.026		0.065	
	EU-A1711	0.009		0.026	
20	EU-A1712	0.037		0.175	
	EU-A1713	0.308		2.509	
	EU-A1716	0.013		0.032	
25	EU-A1717	0.011		0.035	
	EU-A1718	0.043		0.097	
	EU-A1719	0.095		0.746	
	EU-A1722	0.006		0.012	
30	EU-A1723	0.028		0.062	
	EU-A1729	0.006		0.558	
	EU-A1730	0.008		1.172	
35	EU-A1734	0.006		0.387	
	EU-A1735	0.008		0.931	
	EU-A1739	0.056		2.223	
	EU-A1740	0.077		3.825	
40	EU-A1745	1.017		10.	
	EU-A1784	0.048		1.907	
	EU-A1785	0.239		5.145	
45	EU-A1787	0.246		10.0	
	EU-A1788	0.232		10.0	
	EU-A1841	0.316		0.475	
	EU-A1842	1.209		2.109	
50	EU-A1847	0.032		1.95	
	EU-A1848	0.060		3.064	

Example 8. Glucose-lowering activity of peptide products in db/db mice

[0200] The 60 female db/db B6BKS (D) Leprdb/J (strain 000697) mice for this study were about 8-9 weeks old at arrival (Jackson Laboratory, Bar Harbor, Maine). The mice were randomized by weight, and two treatment groups of 8 female mice each were administered the test compound EU-A994, EU-A995 or EU-A1026 at a dose level of 100 or 300

nmoles/kg. One group of 8 female mice served as the vehicle control and received the vehicle, 0.2% BSA in saline, pH 7.4. One additional group of 8 female mice received the positive-control compound, liraglutide, at a dose level of 50 nmoles/kg. The test compounds, vehicle and positive-control compound were subcutaneously injected at a dose volume of 6 mL/kg on day 1 at about 0, 7 and 24 hours.

[0201] Clinical observations were conducted at receipt, prior to randomization, and daily from days 1 to 5. Body weights were measured and recorded at receipt, prior to randomization, and daily from days 1 to 5. Food consumption was measured and recorded daily from days 1 to 5. Blood samples for glucose analysis were collected pre-study (day -3) and at 0, 1, 2, 4, 8, 10, 24, 48, 72 and 96 hours following the first dose on day 1. At study termination all animals were euthanized, and the carcasses were discarded without further evaluation.

[0202] Significant body weight changes versus vehicle were noted for liraglutide and high-dose EU-A994 and high-dose EU-A1026 on days 2 and 3 and for low-dose EU-A1026 on days 3 and 4. Regarding food consumption, liraglutide-treated animals were significantly different from vehicle on days 1 and 2, and high-dose EU-A994 at day 1, low-dose EU-A995 at days 1 and 2, high-dose EU-A994 at day 1, and low- and high-dose EU-A1026 at day 2 were significantly different from liraglutide. Glucose levels for liraglutide at 10 hr and for high-dose EU-A994 at 10 and 24 hr were significantly different from vehicle. In a similar manner, other peptide products were tested for their effects on blood glucose, body weight and food consumption.

Compound	Dose (nmole/kg)	db/db Mice - Mean Blood Glucose (mg/dL)			
		0 hr	10 hr	24 hr	48 hr
liraglutide	50	595	265	347	377
EU-A994	300	554	242	209	385
EU-A995	300	503	471	493	527
EU-A1026	300	531	399	438	505
liraglutide	50	528	286	404	477
EU-A993	250	503	305	324	426

Compound	Dose	db/db Mice - Mean Blood Glucose (mg/dL)			
EU-A995	250	539	584	548	546
EU-A1023	50	507	310	355	375
EU-A1023	250	508	264	194	375
liraglutide	50	442	174	244	439
EU-A992	250	405	104	112	130
EU-A1167	250	379	171	117	113
EU-A1168	250	380	133	169	164

[0203] FIG. 9 shows that EU-A992 (250 nmol/kg), EU-A1167 (250 nmol/kg) and EU-A1168 (250 nmol/kg) subcutaneously injected at t = 0 and 7 hr reduced the mice's elevated blood glucose level to the normal range for around 72 hr in the diabetic db/db mouse model.

Example 9. Activity of peptide products in DIO mice

[0204] Fifty diet-induced obese (DIO) C57BL/6J male mice (JAX Labs) were received at 6 wks of age. The mice were ear notched for identification and housed individually in positively ventilated polycarbonate cages with HEPA-filtered air at a density of 5 mice per cage. The animal room was lit entirely with artificial fluorescent lighting, with a controlled 12 hr light/dark cycle. The normal temperature and relative humidity ranges in the animal rooms were $22 \pm 4^\circ\text{C}$ and $50 \pm 15\%$, respectively. Filtered tap water, acidified to a pH of 2.8-3.1, and a high-fat diet (Research Diets D12492, 60 kcal %) were provided *ad libitum*.

[0205] Following a 2 week acclimation, the 50 mice were randomized into groups (n = 10): Group 1: treated with vehicle; Group 2: low-dose EU-A994; Group 3: high-dose EU-A594; Group 4: low-dose EU-A1024; and Group 5: high-

dose EU-A1024. Mice were dosed subcutaneously on days 1 (at 0 and 7 hr), 3, 6, 9, 12, 15, 18, 21 and 24. Body weight and cage-side observations were recorded daily. Food and water intake was recorded weekly. Mice underwent NMR measurements for determination of whole-body fat and lean composition on days 1 (pre-dose) and 26. On day 26, mice were fasted overnight for an oral glucose tolerance test. Next day, the first blood sample was collected via tail nick ($t = 0$). Mice were then administered a bolus of 1.0 g/kg glucose. Blood samples were obtained via tail nick at 0, 15, 30, 60, 90 and 120 min after glucose dosing, and plasma glucose was immediately determined using a glucometer.

[0206] Mice were sacrificed on day 28. Terminal blood was processed to serum/plasma, and aliquots were sent for analysis of glucose, insulin and lipid profile. Body composition was determined by NMR. EU-A1024 reduced glucose excursion in the oral glucose tolerance test (OGTT), reduced basal insulin secretion but increased glucose-dependent insulin secretion, reduced weight gain (Fig. 10), and reduced fat mass with little effect on lean mass (Fig. 11).

Example 10. Efficacy of SP-1373 in a mouse model of NASH

[0207] In a biopsy-proven DIO-NASH mouse model, SP-1373, a peptide-surfactant conjugate and a dual GLP-1 receptor/glucagon receptor agonist, demonstrated superior outcome measures in liver histopathology and metabolic parameters compared to semaglutide (a GLP-1 agonist) and elafibranor (a PPAR- α/δ agonist). Non-alcoholic steatohepatitis (NASH) was induced in male C57BL/6JRj mice (about 20 g, 5 weeks old at arrival, 37 weeks old at study start) by feeding them an AMLN diet comprising 40% fat (18% trans-fat), 2% cholesterol and 40% carbohydrates (20% fructose) for 32 weeks prior to study start and during the study period.

[0208] All mice entering the study were stratified based on liver pre-biopsy at week -3. Only mice with a fibrosis score ≥ 1 and a steatosis score ≥ 2 were included in the study. The stratified mice were randomized into treatment groups based on liver collagen type 1 alpha 1 (col1 α 1) quantification at week -3. The groups of the NASH study were: 1) vehicle (0.05% Tween 80, 50 mM Na₂HPO₄, pH 8) given subcutaneously (SC) once a day (QD) for 12 weeks ($n = 12$); 2) low dose (5 nmole/kg) of SP-1373 given SC QD for 12 weeks ($n = 11$); 3) high dose (10 nmole/kg) of SP-1373 given SC QD for 12 weeks ($n = 11$); 4) 78 μ mole/kg of elafibranor given orally (PO) QD for 12 weeks ($n = 12$); and 5) 10 nmole/kg of semaglutide given SC QD for 12 weeks ($n = 12$).

[0209] Body weight was measured daily for the entire study period. Food intake was measured daily for the first 14 days, and then weekly until study end. EchoMRI whole-body scanning was performed in week 11. At study end were measured plasma levels of alanine transaminase (ALT), aspartate transaminase (AST), γ -glutamyltransferase (GGT), triglycerides (TG) and total cholesterol (TC), liver levels of TG, TC, col1 α 1 and galectin-3, the expression levels of a wide variety of mRNAs in the liver, and the liver weight, and were performed liver biopsy/necropsy to assess steatosis, inflammation, ballooning and fibrosis of the liver.

[0210] For blood and plasma assays, blood samples were collected in heparinized tubes and plasma was separated and stored at -80°C until analysis. ALT, AST, GGT, TG and TC levels were measured using commercial kits (Roche Diagnostics, Germany) and the Cobas™ C-501 autoanalyzer according to the manufacturer's instructions.

[0211] For liver tissue assays, the triglycerides and cholesterol content in the liver was measured using the Triglyceride and Cholesterol reagents (Cat. No. 22-045-795 and Cat. No. 22-045-780, respectively, Roche Diagnostics, Germany) and the Cobas™ C-501 autoanalyzer. Homogenized liver tissue was heated to 80-100 °C twice and centrifuged in a microcentrifuge, and the triglycerides and cholesterol content in the resulting supernatant was measured.

[0212] The body composition of the mice was assessed by an EchoMRI 3-1 body composition analyzer (EchoMRI, U.S.). Unanesthetised mice were placed in a plastic tube inside the MRI scanner for about 80 seconds. The body composition was expressed as fat tissue mass, fat-free tissue mass (lean tissue mass) and water.

[0213] For liver biopsy, mice were anesthetized by inhalation of isoflurane (2-3%). A small abdominal incision was made in the midline, and the left lateral lobe of the liver was exposed. A cone-shaped wedge of liver tissue (about 50 mg) was excised from the distal portion of the lobe and fixated in 10% neutral-buffered formalin (4% formaldehyde) for histology. The cut surface of the liver was instantly electro-coagulated using bipolar coagulation (ERBE VIO 100 electrosurgical unit). After pre-biopsy, the liver was returned to the abdominal cavity, the abdominal wall was sutured, and the skin was closed with staples. For post-operative recovery, the mice were administered carprofen (5 mg/kg) subcutaneously on the day of operation and on days 1 and 2 post-operation.

[0214] For histological staining, in brief, slides with paraffin-embedded sections were deparaffinated in xylene and then rehydrated in a series of graded ethanol. For hematoxylin and eosin (H&E) staining, the slides were incubated in Mayer's Hematoxylin (Dako), washed in tap water, stained in Eosin Y solution (Sigma-Aldrich), hydrated, mounted with Pertex and then allowed to dry before scanning. For picosirius red (PSR) staining, the slides were incubated in Weigert's iron hematoxylin (Sigma-Aldrich), washed in tap water, stained in picosirius red (Sigma-Aldrich) and then washed twice in acidified water. Excess water was removed by shaking the slides, and the slides were dehydrated in three changes of 99% ethanol, cleared in xylene, mounted with Pertex and then allowed to dry before scanning.

[0215] For collagen type 1 alpha 1 (col1 α 1) and galectin-3 (GAL3) immunohistochemical (IHC) staining, after antigen retrieval and blocking of endogenous peroxidase activity, slides were incubated with the primary antibody (Cat. No.

1310-01 from Southern Biotech for col1 α 1, or Cat. No. 125402 from Biolegend for galectin-3). The anti-col1 α 1 primary antibody was detected using a polymeric horseradish peroxidase (HRP)-linker antibody conjugate, and the anti-GAL3 primary antibody was detected using a linker secondary antibody followed by amplification using a polymeric HRP-linker antibody conjugate. Next, the primary antibody was visualized with 3,3'-diaminobenzidine (DAB) as the chromogen.

Finally, sections were counterstained in hematoxylin and cover-slipped.

[0216] To assess steatosis, inflammation, ballooning and fibrosis of the liver, liver samples were fixed in formalin and embedded in paraffin, and sections were stained with hematoxylin and eosin or picrosirius red. Samples were scored for steatosis, inflammation, ballooning and fibrosis as summarized in **Table 9**.

[0217] SP-1373 (high dose) significantly reduced body weight of the obese mice to the low normal range, while semaglutide and elafibranor caused less body weight decrease (**FIGS. 12A and 12B** [high-dose SP-1373 was inadvertently administered to the vehicle group on day 62]). SP-1373 caused a marked decrease in whole-body fat tissue mass (**FIGS. 13A and 13B**), with minimal effect on whole-body lean tissue mass. Plasma levels of total cholesterol (TC, **FIG. 14B**), alanine transaminase (ALT, **FIG. 15A**), and aspartate transaminase (AST, **FIG. 15B**) were also markedly reduced in SP-1373-treated animals. Plasma ALT and AST levels and the AST/ALT ratio are clinical biomarkers for liver health. The beneficial effects of SP-1373 demonstrate the advantages of dual GLP-1 receptor/glucagon receptor agonism. GLP-1 receptor agonism stimulates insulin production and blood glucose-dependent insulin secretion, lowers blood glucose levels, suppresses appetite and causes weight loss. Glucagon receptor agonism has anti-hyperlipidemic and satiating effects, stimulates fat burning and energy expenditure, and reduces body weight.

[0218] SP-1373 caused a large decrease in liver weight, more so than semaglutide, whereas elafibranor actually increased liver weight (**FIG. 16**). Histology of the liver using hematoxylin and eosin stain revealed a nearly complete absence of liver steatosis in the animals treated with high-dose SP-1373 (**FIG. 17C** [the large white elliptical structure is a vein]), in contrast to the semaglutide-treated animals (**FIG. 17E**), which showed a moderate decrease in hepatosteatosis. **FIGS. 18A and 18B** show the post-biopsy liver steatosis in terms of % area affected and total liver lipid content in the different groups of animals as determined by histological quantitative assessment, confirming a nearly complete absence of liver steatosis in the animals treated with high-dose SP-1373. SP-1373 greatly reduced liver triglycerides (TG) and total cholesterol (TC) levels, more so than semaglutide, whereas elafibranor had little or no effect on liver TG and TC levels (**FIGS. 19A and 19B**). SP-1373 also greatly reduced total liver collagen type 1 alpha 1 staining with an anti-col1 α 1 antibody (a measure of liver fibrosis), more so than semaglutide, while elafibranor had a modest effect (**FIG. 20**). Likewise, SP-1373 greatly reduced total liver galectin-3 staining with an anti-GAL3 antibody (a biomarker for liver inflammation and fibrosis), more so than semaglutide, whereas elafibranor had essentially no effect (**FIG. 21**).

[0219] High-dose SP-1373 greatly reduced or eliminated liver steatosis in all of the treated animals (**FIG. 22C**). In **FIGS. 22A-22E**, for each animal the change from pre-study to post-study biopsy is indicated by a line, and liver steatosis is scored 0-3 in terms of surface area with steatosis. The majority of treated animals exhibited less liver inflammation (**FIGS. 23A-23E**). In **FIGS. 23A-23E**, for each animal the change from pre-study to post-study biopsy is indicated by a line, and liver inflammation is scored 0-3 in severity. Nearly all of the animals that initially exhibited hepatocyte ballooning showed no ballooning after treatment with SP-1373, elafibranor or semaglutide (**FIGS. 24A-24E**). In **FIGS. 24A-24E**, for each animal the change from pre-study to post-study biopsy is indicated by a line, and hepatocyte ballooning is scored 0-2 in severity. The liver steatosis, inflammation and ballooning scores are explained in Table 9.

[0220] NAS (non-alcoholic fatty liver disease [NAFLD] activity score) score, a clinical measure of NASH activity, improved in most of the treated animals and was reduced to the greatest extent by high-dose SP-1373 (**FIGS. 25A-25E**). In **FIGS. 25A-25E**, for each animal the change from pre-study to post-study biopsy is indicated by a line. The NAS score is the sum of the scores for liver steatosis (0-3), inflammation (0-3) and ballooning (0-2), with a maximum score of 8. A human with a NAS score of 5 or greater is diagnosed as having NASH, while a human with a NAS score of 3 or less is diagnosed as not having NASH. If translated to the mouse model of NASH, high-dose SP-1373 reversed NASH in all of the treated animals (**FIG. 25C**).

[0221] SP-1373 and elafibranor reduced liver fibrosis in the majority of animals (**FIGS. 26B-26D**). Liver fibrosis was assessed using picrosirius red, which stains types 1 and 3 collagen. In **FIGS. 26A-26E**, for each animal the change from pre-study to post-study biopsy is indicated by a line, and liver fibrosis is scored 0-4, as explained in Table 9.

Table 9. Liver steatosis, inflammation, ballooning and fibrosis scores

Feature	Score	Degree
Liver steatosis	0	< 5% surface area affected
	1	5-33%
	2	> 33-66%
	3	> 66%

(continued)

Feature	Score	Degree
Lobular inflammation¹	0	No foci
	1	< 2 foci/200x magnification
	2	2-4 foci/200x
	3	> 4 foci/200x
Ballooning degeneration²	0	None
	1	Few balloon hepatocytes
	2	Many balloon cells/prominent ballooning
Liver fibrosis	0	None
	1	Perisinusoidal or periportal
	2	Perisinusoidal and portal/periportal
	3	Bridging fibrosis
	4	Cirrhosis
¹ Lobular inflammation was evaluated by counting the number of inflammatory foci per field using 200x magnification (minimum of 5 fields per animal). A focus was defined as a cluster, not a row, of > 3 inflammatory cells. Acidophil bodies were not included in the assessment. ² Ballooning degeneration was degenerated hepatocytes with a cleared cytoplasm, enlargement, swelling, rounding and reticulated cytoplasm.		

[0222] SP-1373 reduced the expression of NASH-related mRNAs in the liver, including mRNAs encoding proteins involved in fibrosis {e.g., collagen type 1 alpha 1 (col1 α 1), transforming growth factor- β 1 (TGF β 1) and galectin-3 (GAL3, aka MAC2)}, inflammation {e.g., interleukin-1 α (IL-1 α), IL-1 β , tumor necrosis factor- α (TNF- α), GAL3, CD14, toll-like receptor 4 (TLR4), p38 mitogen-activated protein (MAP) kinase 11 and NF- κ B}, monocyte recruitment {e.g., chemokine (C-C motif) ligand 5 (CCL5, aka RANTES), monocyte chemoattractant protein 1 (MCP1, aka CCL2), chemokine (C-C motif) receptor 1 (CCR1) and CCR2}, and monocyte differentiation into, e.g., macrophages {e.g., GAL3, EGF-like module-containing mucin-like hormone receptor-like 1 (EMR1, aka F4/80), CD14, CD68 and CD86} (**FIGS. 27A-27F** and **FIGS. 28A-28F**). More specifically with respect to fibrosis, SP-1373 reduced hepatic expression of mRNAs encoding proteins involved in fibrotic fiber formation (**FIGS. 29A-29I**) and activation of hepatic stellate cells (the major cell type involved in liver fibrosis) and myofibroblast proliferation (**FIGS. 30A-30F**). Furthermore, SP-1373 reduced hepatic expression of mRNAs encoding proteins involved in pyroptosis, a highly inflammatory form of programmed cell death (**FIGS. 31A-31F**). For the **FIGS.** referred to in this paragraph, the expression level of a particular mRNA is the average plus SEM, and *P < 0.05, **P < 0.01 and ***P < 0.001 compared to vehicle after correction for gene-wise multiple testing. SP-1373 also reduced hepatic expression of mRNAs encoding proteins involved in lipid synthesis (e.g., fatty acid synthase [FAS], stearoyl-CoA desaturase-1 [SCD1] and 3-hydroxy-3-methylglutaryl-CoA synthase 1 [HMGCS1]) and lipid uptake (e.g., CD36). Moreover, SP-1373 increased hepatic expression of farnesoid X receptor (FXR) mRNA. In addition, SP-1373 modulated the expression of genes encoding proteins involved in, e.g., insulin signaling and glucose homeostasis.

[0223] In summary, SP-1373 reversed liver steatosis, reduced liver inflammation and fibrosis, and markedly improved NAS score, while also addressing metabolic and glucoregulatory deficits, in a well-recognized translational mouse model of NASH. SP-1373 is a potent, balanced and full agonist at the GLP-1 and glucagon receptors and has anti-diabetic and anti-obesity effects. Compared to the GLP-1 agonist semaglutide, SP-1373 has a stronger antihyperglycemic effect, reduces body weight, fat tissue mass and food intake to a greater extent, and has a longer duration of action. In the DIO-NASH mouse model, compared to treatment with semaglutide or elafibranor (a dual PPAR- α/δ agonist), treatment with SP-1373 resulted in greater reduction in body weight, plasma total cholesterol (TC) and alanine transaminase (ALT) levels, NAS score, hepatosteatosis, liver triglycerides (TG) and TC levels, liver weight, liver collagen type I alpha 1 content (a measure of liver fibrosis), and liver galectin-3 content (a measure of liver inflammation and fibrosis). Therefore, SP-1373 is useful for treating, e.g., insulin resistance, diabetes (including types 1 and 2), hyperlipidemia, obesity, metabolic syndrome and cardiovascular diseases, and conditions associated therewith, such as NAFLD (including NASH).

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Peptidprodukt eller et farmaceutisk acceptabelt salt deraf til anvendelse til behandling af en leverlidelse, hvor
5 peptidproduktet er: His₁-Aib₂-Gln₃-Gly₄-Thr₅-Phe₆-Thr₇-Ser₈-Asp₉-Tyr₁₀-Ser₁₁-Lys₁₂-Tyr₁₃-Leu₁₄-Asp₁₅-Glu*₁₆-Lys (N-omega[1-(17-carboxylheptadecyloxy)beta-D-glucuronyl])₁₇-Ala₁₈-Ala₁₉-Lys*₂₀-Glu₂₁-Phe₂₂-Ile₂₃-Gln₂₄-Trp₂₅-Leu₂₆-Leu₂₇-Gln₂₈-Thr₂₉-NH₂ (SEQ ID NO: 1119), hvor Glu₁₆* og Lys₂₀* angiver rester, der er cykliseret
10 via deres sidekæder til frembringelse af et lactam.
2. Peptidprodukt til anvendelse ifølge krav 1, hvor leverlidelsen er fedtleversygdom, såsom non-alkoholisk fedtleversygdom (NAFLD).
- 15 3. Peptidprodukt til anvendelse ifølge krav 1 eller 2, hvor NAFLD er non-alkoholisk steatohepatitis (NASH).
4. Peptidprodukt til anvendelse ifølge et hvilket som helst
20 af kravene 1 til 3, hvor behandlingen omfatter parenteral (f.eks. subkutan, intravenøs eller intramuskulær) administration af peptidproduktet.
5. Peptidprodukt til anvendelse ifølge et hvilket som helst
25 af kravene 1 til 4, hvor behandlingen omfatter administration af peptidproduktet ved oral inhalation eller nasal inhalation eller insufflation.
6. Peptidprodukt til anvendelse ifølge et hvilket som helst
30 af kravene 1 til 5, hvor behandlingen omfatter parenteral (f.eks. subkutan [s.c.], intravenøs [i.v.] eller intramuskulær [i.m.]) administration af peptidproduktet i en dosis fra ca. 0,1 mg til ca. 1, 5 eller 10 mg eller ca. 0,1-1 mg eller 1-10 mg over et tidsrum på ca. én uge.
- 35 7. Peptidprodukt til anvendelse ifølge krav 6, hvor behandlingen omfatter parenteral (f.eks. s.c., i.v. eller i.m.) administration af peptidproduktet i en dosis på ca. 0.1-1 mg

eller ca. 0,1-0,5 mg eller 0,5-1 mg over et tidsrum på ca. én uge.

8. Peptidprodukt til anvendelse ifølge et hvilket som helst af kravene 1 til 7, hvor behandlingen omfatter parenteral (f.eks. s.c., i.v. eller i.m.) administration af peptidproduktet én gang om ugen.

9. Peptidprodukt til anvendelse ifølge et hvilket som helst af kravene 1 til 8, hvor behandlingen endvidere omfatter administration af et eller flere yderligere terapeutiske midler.

10. Peptidprodukt til anvendelse ifølge krav 9, hvor det ene eller de flere yderligere terapeutiske midler er valgt blandt antidiabetika, antiobesitasmidler, antiinflammatoriske midler, antifibrosemidler, antioxidanter, antihypertensiva og kombinationer deraf.

11. Peptidprodukt til anvendelse ifølge krav 9 eller 10, hvor leverlidelsen er NAFLD (f.eks. NASH), og det ene eller de flere yderligere terapeutiske midler er eller indbefatter en peroxisomproliferatoraktiveret receptor (PPAR)-agonist (f.eks. en PPAR- δ -agonist, såsom elafibranor, og/eller en PPAR- γ -agonist, såsom pioglitazon), en HMG-CoA-reductasehæmmer (f.eks. en statin, såsom rosuvastatin), en farnesoid-X-receptor (FXR)-agonist (f.eks. obeticholinsyre) eller en antioxidant (f.eks. E-vitamin) eller en hvilken som helst kombination deraf.

12. Kit til anvendelse til behandling af en leverlidelse, som omfatter:
et peptidprodukt eller et farmaceutisk acceptabelt salt deraf ifølge krav 1 eller en farmaceutisk sammensætning, der omfatter samme; og
anvisninger i administrering eller anvendelse af peptidproduktet eller den farmaceutiske sammensætning til behandling af en leverlidelse.

13. Kit til anvendelse ifølge krav 12, hvor leverlidelsen er

fedtleverssygdom, såsom NAFLD (f.eks. NASH).

14. Kit til anvendelse ifølge krav 12 eller 13, hvor
peptidproduktet eller den farmaceutiske sammensætning er
5 formuleret til parenteral administration, såsom subkutan,
intravenøst eller intramuskulært, eller ved oral inhalation
eller nasal inhalation eller insufflation.

15. Kit til anvendelse ifølge et hvilket som helst af kravene
10 12 til 14, som yderligere omfatter en anordning til
administrering af peptidproduktet eller den farmaceutiske
sammensætning, såsom en injektionspen eller en inhalator.

DRAWINGS

Drawing

FIG. 1
Table 1

	SEQ. ID. NO.	1			5				10						15			20	
EU-A300	4	H	Alb	Q	G	T	F	T	S	D	L	Lys(C8)-#							
EU-A301	5	H	Alb	Q	G	T	F	T	S	D	L	Lys(C12)-#							
EU-A302	6	H	Alb	Q	G	T	F	T	S	D	L	Lys(C16)-#							
EU-A303	7	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C8)-#							
EU-A304	8	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C12)-#							
EU-A305	9	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C16)-#							
EU-A306	10	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C8)-#							
EU-A307	11	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C12)-#							
EU-A308	12	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C16)-#							
EU-A309	13	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	Lys(C8)-#							
EU-A310	14	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	Lys(C12)-#							
EU-A311	15	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	Lys(C16)-#							
EU-A312	16	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	Lys(C8)-#			
EU-A313	17	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	Lys(C12)-#			
EU-A314	18	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	Lys(C16)-#			
EU-A315	19	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	Lys(C8)-#			
EU-A316	20	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	Lys(C12)-#			
EU-A317	21	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	Lys(C16)-#			
EU-A318	22	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	Lys(C8)-#			
EU-A319	23	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	Lys(C12)-#			
EU-A320	24	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	Lys(C16)-#			
EU-A321	25	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	S	K	Y	L	Lys(C8)-#			
EU-A322	26	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	S	K	Y	L	Lys(C12)-#			
EU-A323	27	H	Alb	Q	G	T	26FF	T	S	D	Bip2Et4MeO	S	K	Y	L	Lys(C16)-#			
EU-A324	28	H	Alb	Q	G	T	F	T	S	D	V	S	K	Y	L	D	G	R	Lys(C8)-#
EU-A325	29	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	D	G	R	Lys(C8)-#
EU-A326	30	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	D	G	R	Lys(C12)-#
EU-A327	31	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	D	G	R	Lys(C16)-#
EU-A328	32	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	G	R	Lys(C8)-#
EU-A329	33	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	G	R	Lys(C12)-#
EU-A330	34	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	G	R	Lys(C16)-#

FIG. 1 (Continued)
Table 1 (Continued)

SEQ. ID. NO.	1			5					10					15			20		
EU-A331	35	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	D	G	R	Lys(C8)-#
EU-A332	36	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	D	G	R	Lys(C12)-#
EU-A333	37	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	D	G	R	Lys(C16)-#
EU-A334	38	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	S	K	Y	L	D	G	R	Lys(C8)-#
EU-A335	39	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	S	K	Y	L	D	G	R	Lys(C12)-#
EU-A336	40	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	S	K	Y	L	D	G	R	Lys(C16)-#
EU-A337	41	H	Alb	Q	G	T	F	T	S	D	L	Lys(C8)-#							
EU-A338	42	H	Alb	Q	G	T	F	T	S	D	L	Lys(C12)-#							
EU-A339	43	H	Alb	Q	G	T	F	T	S	D	L	Lys(C16)-#							
EU-A340	44	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C8)-#							
EU-A341	45	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C12)-#							
EU-A342	46	H	Alb	Q	G	T	F	T	S	D	Bip	Lys(C16)-#							
EU-A343	47	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C8)-#							
EU-A344	48	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C12)-#							
EU-A345	49	H	Alb	Q	G	T	F	T	S	D	Nal(2)	Lys(C16)-#							
EU-A346	50	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	Lys(C8)-#							
EU-A347	51	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	Lys(C12)-#							
EU-A348	52	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2Et4MeO	Lys(C16)-#							
EU-A349	53	H	Alb	Q	G	T	2,6MeF	T	S	D	Bip	Lys(C8)-#							
EU-A350	54	H	Alb	Q	G	T	2,6MeF	T	S	D	Bip	Lys(C12)-#							
EU-A351	55	H	Alb	Q	G	T	2,6MeF	T	S	D	Bip	Lys(C16)-#							
EU-A352	56	H	Alb	Q	G	T	MeF	T	S	D	L	S	K	Y	L	Lys(C8)-#			
EU-A353	57	H	Alb	Q	G	T	MeF	T	S	D	L	S	K	Y	L	Lys(C12)-#			
EU-A354	58	H	Alb	Q	G	T	MeF	T	S	D	L	S	K	Y	L	Lys(C16)-#			
EU-A355	59	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	K	Y	L	Lys(C8)-#			
EU-A356	60	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	K	Y	L	Lys(C12)-#			
EU-A357	61	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	K	Y	L	Lys(C16)-#			
EU-A358	62	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	S	K	Y	L	Lys(C8)-#			
EU-A359	63	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	S	K	Y	L	Lys(C12)-#			
EU-A360	64	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	S	K	Y	L	Lys(C16)-#			
EU-A361	65	H	Alb	Q	G	T	MeF	T	S	D	Bip2Et4MeO	S	K	Y	L	Lys(C8)-#			

FIG. 1 (Continued)
Table 1 (Continued)

SEQ. ID. NO.	1			5					10					15			20
EU-A362	66	H	Alb	Q	G	T	MeF	T	S	D	Bip2E4MeO	S	K	Y	L	Lys(C12)-#	
EU-A363	67	H	Alb	Q	G	T	MeF	T	S	D	Bip2E4MeO	S	K	Y	L	Lys(C15)-#	
EU-A364	68	H	Alb	Q	G	T	F	T	S	D	V	S	K	Y	L	E	
EU-A365	69	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	S	Lys(C8)-#
EU-A366	70	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	E	S
EU-A367	71	H	Alb	Q	G	T	F	T	S	D	L	S	K	Y	L	E	S
EU-A368	72	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	E	S
EU-A369	73	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	E	S
EU-A370	74	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	E	S
EU-A371	75	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	E	S
EU-A372	76	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	E	S
EU-A373	77	H	Alb	Q	G	T	F	T	S	D	Nal(2)	S	K	Y	L	E	S
EU-A374	78	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2E4MeO	S	K	Y	L	E	S
EU-A375	79	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2E4MeO	S	K	Y	L	E	S
EU-A376	80	H	Alb	Q	G	T	2,6FF	T	S	D	Bip2E4MeO	S	K	Y	L	E	S
EU-A377	81	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A378	82	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A379	83	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A380	84	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A381	85	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A382	86	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	D	S
EU-A383	87	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S
EU-A384	88	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S
EU-A385	89	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S
EU-A386	90	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S
EU-A387	91	H	Alb	Q	G	T	F	T	S	D	Bip	S	K	Y	L	E	S
EU-A388	92	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	K	Y	L	E	S
EU-A389	93	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	Alb	Y	L	E	S
EU-A390	94	H	Alb	Q	G	T	MeF	T	S	D	Bip	S	K	Y	L	E	Alb
EU-A391	95	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	Alb
EU-A392	96	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Y	L	D	Alb

FIG. 1 (Continued)
Table 1 (Continued)

SEQ. ID. NO.	1	5						10					15			20
EU-A393	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	Lys(C12)#				
EU-A394	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	Alb	Lys(C12)#				
EU-A395	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C12)	Alb-#	
EU-A396	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	S	K	Alb	Lys(C12)	Alb-#	
EU-A397	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)#		
EU-A398	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)	Alb-#	
EU-A399	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C12)	Alb-#	
EU-A400	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C12)	Alb-#	
EU-A401	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)	Alb-#	
EU-A402	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)	Ac5c-#	
EU-A403	H	Alb	Q	G	T	MeF	T	S	D	Nal(2)	Alb	K	Alb	Lys(C12)#		
EU-A404	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C8)	Alb-#	
EU-A405	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C12)	Alb-#	
EU-A406	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C16)	Alb-#	
EU-A407	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)#		
EU-A408	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)		
EU-A409	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)		
EU-A410	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)		
EU-A411	H	Alb	Q	G	T	MeF	T	S	D	Y	Alb	K	Alb	Lys(C12)		
EU-A412	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C8)-#		
EU-A413	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C16)#		
EU-A414	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C8)#		
EU-A415	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C12)#		
EU-A416	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C16)#		
EU-A417	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C8)	Alb-#	
EU-A418	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C12)	Alb-#	
EU-A419	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C16)	Alb-#	
EU-A420	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C8)	Ac5c-#	
EU-A421	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C12)	Ac5c-#	
EU-A422	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Alb	Lys(C16)	Ac5c-#	
EU-A423	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Alb	Lys(C8)	Ac5c-#	

FIG. 1 (Continued)
Table 1 (Continued)

	SEQ. ID. NO.	1				5					10					15				20
EU-A424	128	H	Alb	Q	G	T	F	T	S	D	Y	L				D	S	Alb	Lys(C12)	Ac5c-#
EU-A425	129	H	Alb	Q	G	T	F	T	S	D	Y	L				D	S	Alb	Lys(C16)	Ac5c-#

MeF means C-alphaMe-Phe; Har means homoArg; 2,6F-F means 2',6'-difluoro-Phe; Bip2Et4MeO means 2'-ethyl-4'-MeO-biphenylalanine.

Lys(C12) means N-epsilon-(1'-dodecyl beta-D-glucuronyl)-L-lysine and other C numbers mean the corresponding 1'-alkyl glucoronide.

means amide C-terminus.

FIG. 2
Table 2

SEQ. ID. NO.	1			5				10			15				20			25
EU-A426	130	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A427	131	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A428	132	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A429	133	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A430	134	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A431	135	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A432	136	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	
EU-A433	137	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	
EU-A434	138	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	
EU-A435	139	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A436	140	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A437	141	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A438	142	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A439	143	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A440	144	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A441	145	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A442	146	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A443	147	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	S	
EU-A435	148	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A436	149	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A437	150	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A438	151	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A439	152	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A440	153	H	Alb	Q	G	T	MeF	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A441	154	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A442	155	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A443	156	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A444	157	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A445	158	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A446	159	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	
EU-A447	160	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	E*	
EU-A448	161	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	E*	
EU-A449	162	H	Alb	Q	G	T	MeF	T	S	D	Y	S	K	Y	L	D	E*	

FIG. 2 (Continued)
Table 2 (Continued)

SEQ. ID NO.	1	5	10	15	20	25
EU-A450	163	H Alb Q G T MeF	T S D Y S K Y L D E*	R Alb	K* Lys(C8)	F Ac5c-#
EU-A451	164	H Alb Q G T MeF	T S D Y S K Y L D K*	R Alb	K* Lys(C12)	F Ac5c-#
EU-A452	165	H Alb Q G T MeF	T S D Y S K Y L D K*	R Alb	K* Lys(C16)	F Ac5c-#
EU-A457	166	H Alb Q G T MeF	T S D Y S K Y L D E*	R Alb	K* Lys(C8)	F Alb-#
EU-A448	167	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	K* Lys(C12)	F Alb-#
EU-A449	168	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	K* Lys(C16)	F Alb-#
EU-A450	169	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	K* Lys(C8)	F Ac5c-#
EU-A451	170	H Alb Q G T F	T S D Y S K Y L D K*	R Alb	K* Lys(C12)	F Ac5c-#
EU-A452	171	H Alb Q G T F	T S D Y S K Y L D K*	R Alb	K* Lys(C16)	F Ac5c-#
EU-A453	172	H Alb Q G T F	T S D Y S K Y L D E*	Q A	K* Lys(C12)	F Alb-#
EU-A454	173	H Alb Q G T F	T S D Y S K Y L D E*	Q A	K* Lys(C16)	F Alb-#
EU-A455	174	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C12)	F Alb-#
EU-A456	175	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C16)	F Alb-#
EU-A457	176	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C12)	F Ac5c-#
EU-A458	177	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C16)	F Ac5c-#
EU-A459	178	H Alb Q G T F	T S D Y S K Y L D E*	Q A	K* Lys(C12)	F Ac5c-#
EU-A460	179	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C12)	F Alb-#
EU-A461	180	H Alb Q G T F	T S D Y S K Y L D E*	R A	K* Lys(C16)	F Alb-#
EU-A462	181	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C12)	
EU-A463	182	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C12)	
EU-A464	183	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C8)	
EU-A465	184	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C16)	
EU-A466	185	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C12)	
EU-A467	186	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C8)	
EU-A468	187	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C1)	
EU-A469	188	H Alb Q G T F	T S D Y S K Y L D S	R Alb	Lys(C16)	
EU-A470	189	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C16)	
EU-A471	190	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C12)	
EU-A472	191	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C8)	
EU-A473	192	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C16)	
EU-A474	193	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C12)	
EU-A475	194	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C8)	
EU-A476	195	H Alb Q G T F	T S D Y S K Y L D E*	R Alb	Lys(C12)	
EU-A477	196	H Alb Q G T F	T S D Y S K Y L D R	R Alb	Lys(C8)	
EU-A478	197	H Alb Q G T F	T S D Y S K Y L D R	R Alb	Lys(C12)	
EU-A479	198	H Alb Q G T F	T S D Y S K Y L D R	R Alb	Lys(C16)	

FIG. 2 (Continued)
Table 2 (Continued)

	SEQ. ID. NO.	1				5				10				15					20					25	
EU-A480	199	H	Alb	Q	C	T	F	T	S	D	Y	S	K	Y	L	D	S	R	Alb	Lys(C8)	#				
EU-A481	200	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	Alb	Lys(C12)	#				
EU-A482	201	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	R	Alb	Lys(C16)	#				
EU-A483	202	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	R	Alb	Lys(C8)	#				
EU-A484	203	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	R	Alb	Lys(C12)	#				
EU-A485	204	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	R	Alb	Lys(C16)	#				
EU-A486	205	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	R	Alb	Lys(C8)	#					
EU-A487	206	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	R	Alb	Lys(C12)	#					
EU-A488	207	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	R	Alb	Lys(C16)	#					
EU-A489	208	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	Alb	R	Lys(C8)	Lys(C8)	#				
EU-A490	209	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	Alb	R	Lys(C12)	Lys(C12)	#				
EU-A491	210	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	Alb	R	Lys(C16)	Lys(C16)	#				
EU-A492	211	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	hArg	Alb	Lys(C8)	#					
EU-A493	212	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	hArg	Alb	Lys(C12)	#					
EU-A494	213	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	hArg	Alb	Lys(C16)	#					
EU-A495	214	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	hArg	Alb	Lys(C8)	#				
EU-A496	215	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	hArg	Alb	Lys(C12)	#				
EU-A497	216	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	hArg	Alb	Lys(C16)	#				
EU-A498	217	H	Alb	Q	G	T	F	T	S	D	V	S	S	Y	L	E	hArg	Alb	Lys(C8)	#					
EU-A499	218	H	Alb	Q	C	T	F	T	S	D	V	S	S	Y	L	E	hArg	Alb	Lys(C12)	#					

FIG. 2 (Continued)
Table 2 (Continued)

SEQ. ID. NO.	1			5					10					15				20		25
EU-A534	251	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	Alb	#
EU-A535	252	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C14)	Alb	#
EU-A536	253	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C16)	Alb	#
EU-A537	254	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C18)	Alb	#
EU-A538	255	I	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	Alb	#
EU-A539	256	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C12)	A	ζ*
EU-A540	257	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C14)	A	ζ*
EU-A541	258	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C16)	A	ζ*
EU-A542	259	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C18)	A	ζ*
EU-A543	260	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C20)	A	ζ*
EU-A544	261	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C12)	Alb	#
EU-A545	262	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C14)	Alb	#
EU-A546	263	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C16)	Alb	#
EU-A547	264	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C18)	Alb	#
EU-A548	265	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C20)	Alb	#
EU-A549	267	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	#	
EU-A550	268	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C14)	#	
EU-A551	269	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C16)	#	
EU-A552	270	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C18)	#	
EU-A553	271	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C20)	#	
EU-A554	272	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C12)	Alb	#
EU-A555	273	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C14)	Alb	#
EU-A556	274	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C16)	Alb	#
EU-A557	275	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C18)	Alb	#
EU-A558	276	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C20)	Alb	#
EU-A559	277	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	S	Lys(C22)	Alb	#
EU-A560	278	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C12)	Alb	#
EU-A561	279	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C14)	Alb	#
EU-A562	280	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C16)	Alb	#
EU-A563	281	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C18)	Alb	#
EU-A564	282	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C20)	Alb	#
EU-A565	283	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C12)	Alb	#
EU-A566	284	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C14)	Alb	#
EU-A567	285	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C16)	Alb	#
EU-A568	286	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C18)	Alb	#
EU-A569	287	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(C20)	Alb	#

FIG. 2 (Continued)
Table 2 (Continued)

SEQ. ID. NO.	1			5				10			15					20		25			
EU-A570	288	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C12)	Alb	#
EU-A571	289	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C14)	Alb	#
EU-A572	290	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C16)	Alb	#
EU-A573	291	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C18)	Alb	#
EU-A574	292	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C20)	Alb	#
EU-A575	293	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C12)	Alb	#
EU-A576	294	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C14)	Alb	#
EU-A577	295	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C16)	Alb	#
EU-A578	296	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C18)	Alb	#
EU-A579	297	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C20)	Alb	#
EU-A580	298	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C12)	Alb	#
EU-A581	299	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C14)	Alb	#
EU-A582	300	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C16)	Alb	#
EU-A583	301	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C18)	Alb	#
EU-A584	302	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C20)	Alb	#
EU-A585	303	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	hArg	Lys(C12)	Alb	#
EU-A586	304	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	hArg	Lys(C14)	Alb	#
EU-A587	305	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	hArg	Lys(C16)	Alb	#
EU-A588	306	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	hArg	Lys(C18)	Alb	#
EU-A589	307	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	hArg	Lys(C20)	Alb	#
EU-A590	308	H	Ac4c	Q	G	T	F	T	S	D	Y	S	K*	Y	L	D	E*	R	Lys(C12)	Alb	#
EU-A591	309	H	Ac4c	Q	C	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C14)	Alb	#
EU-A592	310	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C16)	Alb	#
EU-A593	311	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C18)	Alb	#
EU-A594	312	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	R	Lys(C20)	Alb	#
EU-A595	313	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C12)	Alb	#
EU-A596	314	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C14)	Alb	#
EU-A597	315	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C16)	Alb	#
EU-A598	316	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C18)	Alb	#
EU-A599	317	H	Ac4c	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	hArg	Lys(C20)	Alb	#

MeF means C-alpha/Me-Phe.

Lys(C12) means N-epsilon-(1'-dodecyl beta-D-glucuronyl)-L-lysine and other C numbers mean the corresponding 1'-alkyl glucuronide. The pair of amino acids E*, K* or K*, E* separated by 4 residues denotes a side chain lactam linkage formed between the side chain functional groups on these amino acids.

means amide C-terminus.

Seq. ID.	1		5		10		15		20		25	30
NO.												
EU-A700	318	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A701	319	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A702	320	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A703	321	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A704	322	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A705	323	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A706	324	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A707	325	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A708	326	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A709	327	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A710	328	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A711	329	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A712	330	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A713	331	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A714	332	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A715	333	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A716	334	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A717	335	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A718	336	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A719	337	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A720	338	H	Ac3c	Q	G	T	F	T	S	D	Y	
EU-A721	339	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A722	340	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A723	341	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A724	342	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A725	343	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A726	344	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A727	345	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A728	346	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A729	347	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A730	348	H	Ac4c	Q	G	T	F	T	S	D	Y	
EU-A731	349	H	Alb	Q	G	T	F	T	S	D	Y	
EU-A732	350	H	Ac4c	Q	G	T	F	T	S	D	Y	

[illegible]

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1	5	10	15	20	25	30																								
EU-A768	386	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A769	387	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A770	388	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	K	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A771	389	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A772	390	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A773	391	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A774	392	H	G	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A775	393	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C12)	D	F	V	Q	W	L	L	N	T	#	
EU-A776	394	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#
EU-A777	395	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#	
EU-A778	396	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C8)	D	F	V	Q	W	L	L	N	T	#
EU-A779	397	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C12)	D	F	V	Q	W	L	L	N	T	#
EU-A780	398	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C14)	D	F	V	Q	W	L	L	N	T	#
EU-A781	399	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C16)	D	F	V	Q	W	L	L	N	T	#
EU-A782	400	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#
EU-A783	401	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	N	T	#
EU-A784	402	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C8)	D	F	V	Q	W	L	L	N	T	#
EU-A785	403	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C12)	D	F	V	Q	W	L	L	N	T	#
EU-A786	404	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C14)	D	F	V	Q	W	L	L	N	T	#
EU-A787	405	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C16)	D	F	V	Q	W	L	L	N	T	#
EU-A788	406	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#
EU-A789	407	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	N	T	#
EU-A790	408	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C8)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A791	409	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A792	410	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C14)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A793	411	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A794	412	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A795	413	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A796	414	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C8)	W	L	L	N	T	#
EU-A797	415	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C12)	W	L	L	N	T	#
EU-A798	416	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C14)	W	L	L	N	T	#
EU-A799	417	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C16)	W	L	L	N	T	#
EU-A800	418	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C18)	W	L	L	N	T	#
EU-A801	419	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C20)	W	L	L	N	T	#
EU-A802	420	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C8)	W	L	L	N	T	#

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1	5	10	15	20	25	30
EU-A803	421	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A804	422	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A805	423	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A806	424	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A807	425	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A808	426	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A809	427	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A810	428	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A811	429	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A812	430	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A813	431	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A814	432	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A815	433	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A816	434	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A817	435	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A818	436	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A819	437	H Alb	Q G T	F T S D Y	K Y L D E*	A	#
EU-A820	438	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A821	439	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A822	440	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A823	441	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A824	442	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A825	443	H G	Q G T	F T S D Y	K Y L D E*	A	#
EU-A826	444	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A827	445	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A828	446	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A829	447	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A830	448	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A831	449	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A832	450	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A833	451	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A834	452	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A835	453	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A836	454	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#
EU-A837	455	H αMePto	Q G T	F T S D Y	K Y L D E*	A	#

SEQ. ID. NO.	1		5				10				15			20			25	30													
EU-A838	456	H	Alb	Q	G	T	αMeF	T	S	D	Blp	Lys(C8)	#																		
EU-A839	457	H	Alb	Q	G	T	αMeF	T	S	D	Blp	Lys(C12)	#																		
EU-A840	458	H	Alb	Q	G	T	αMeF	T	S	D	Blp	Lys(C14)	#																		
EU-A841	459	H	Alb	Q	G	T	αMeF	T	S	D	Blp	Lys(C16)	#																		
EU-A842	450	H	Alb	Q	G	T	αMeF	T	S	D	Blp	Lys(C20)	#																		
EU-A843	451	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C8)	#																		
EU-A844	452	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C12)	#																		
EU-A845	453	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C14)	#																		
EU-A846	454	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C16)	#																		
EU-A847	455	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C18)	#																		
EU-A848	456	H	Alb	Q	G	T	αMeFF	T	S	D	Blp	Lys(C20)	#																		
EU-A849	457	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C8)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A850	458	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C12)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A851	459	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C14)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A852	460	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C16)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A853	461	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C18)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A854	462	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C20)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A855	463	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C8)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A856	464	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A857	465	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C14)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A858	466	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A859	467	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A860	468	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A861	469	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C8)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A862	470	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A863	471	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C14)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A864	472	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A865	473	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A866	474	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A867	475	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C8)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A868	476	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A869	477	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C14)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A870	478	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C16)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A871	479	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C18)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A872	480	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C20)	A	A	R	E	F	I	A	W	L	L	N	T	#

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID.	1	5	10	15	20	25	30																								
NO.																															
EU-A873	481	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C8)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A874	482	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A875	483	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C14)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A876	484	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A877	485	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A878	486	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A879	487	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C8)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A880	488	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C12)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A881	489	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C14)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A882	490	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C16)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A883	491	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C18)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A884	492	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Lys(C20)	A	A	R	E	F	I	A	W	L	L	N	T	#
EU-A885	493	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C8)	W	L	L	N	T	#
EU-A886	494	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C12)	W	L	L	N	T	#
EU-A887	495	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C14)	W	L	L	N	T	#
EU-A888	496	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C16)	W	L	L	N	T	#
EU-A889	497	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C18)	W	L	L	N	T	#
EU-A890	498	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	Q	A	A	R	E	F	I	Lys(C20)	W	L	L	N	T	#
EU-A891	499	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C8)	D	F	V	Q	W	L	L	N	T	#
EU-A892	500	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C12)	D	F	V	Q	W	L	L	N	T	#
EU-A893	501	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C14)	D	F	V	Q	W	L	L	N	T	#
EU-A894	502	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C16)	D	F	V	Q	W	L	L	N	T	#
EU-A895	503	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#
EU-A896	504	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	N	T	#
EU-A897	505	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	N	T	#
EU-A898	506	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C8)	D	F	V	Q	W	L	L	N	T	#
EU-A899	507	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C14)	D	F	V	Q	W	L	L	N	T	#
EU-A900	508	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C16)	D	F	V	Q	W	L	L	N	T	#
EU-A901	509	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	N	T	#
EU-A902	510	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C8)	W	L	L	N	T	#
EU-A903	511	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C12)	W	L	L	N	T	#
EU-A904	512	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C14)	W	L	L	N	T	#
EU-A905	513	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C16)	W	L	L	N	T	#
EU-A906	514	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C18)	W	L	L	N	T	#
EU-A907	515	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	A	R	R	A	Q	D	F	V	Lys(C20)	W	L	L	N	T	#

Seq. ID.	1	5	10	15	20	25	30																										
NO.																																	
EU-A908	516	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A909	517	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C8)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A910	518	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C12)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A911	519	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C14)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A912	520	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C16)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A913	521	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C18)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A914	522	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C20)	A	A	K	E	F	I	A	W	L	L	N	T	#	
EU-A915	523	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C8)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A916	524	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C12)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A917	525	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C14)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A918	526	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C16)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A919	527	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C18)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A920	528	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Lys(C20)	A	A	R	E	F	I	A	W	L	L	N	T	#	
EU-A921	529	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C18)	D	F	V	A	Q	W	L	L	N	T	#
EU-A922	530	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C8)	D	F	V	A	Q	W	L	L	N	T	#
EU-A923	531	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C14)	D	F	V	A	Q	W	L	L	N	T	#
EU-A924	532	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C16)	D	F	V	A	Q	W	L	L	N	T	#
EU-A925	533	H	Aib	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C20)	D	F	V	A	Q	W	L	L	N	T	#
EU-A926	534	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C8)	D	F	V	A	Q	W	L	L	N	T	#
EU-A927	535	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C12)	D	F	V	A	Q	W	L	L	N	T	#
EU-A928	536	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C14)	D	F	V	A	Q	W	L	L	N	T	#
EU-A929	537	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C16)	D	F	V	A	Q	W	L	L	N	T	#
EU-A930	538	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C18)	D	F	V	A	Q	W	L	L	N	T	#
EU-A931	539	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Lys(C20)	D	F	V	A	Q	W	L	L	N	T	#
EU-A932	540	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C8)	W	L	L	N	T	#	
EU-A933	541	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C12)	W	L	L	N	T	#	
EU-A934	542	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C14)	W	L	L	N	T	#	
EU-A935	543	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C16)	W	L	L	N	T	#	
EU-A936	544	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C18)	W	L	L	N	T	#	
EU-A937	545	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	Q	A	A	R	E	F	I	Lys(C20)	W	L	L	N	T	#	
EU-A938	546	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	A	A	Q	D	F	V	Lys(C8)	W	L	L	N	T	#	
EU-A939	547	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Q	D	F	V	Lys(C12)	W	L	L	N	T	#	
EU-A940	548	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Q	D	F	V	Lys(C14)	W	L	L	N	T	#	
EU-A941	549	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Q	D	F	V	Lys(C16)	W	L	L	N	T	#	
EU-A942	550	H	G	H	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Aib	R	R	A	Q	D	F	V	Lys(C18)	W	L	L	N	T	#	

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1		5		10			15			20				25		30														
EU-A943	551	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	R	A	Q	D	F	Y	Lys(C20)	W	L	L	N	T	#	
EU-A944	552	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C8)	W	L	L	Q	T	#	
EU-A945	553	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C12)	W	L	L	Q	T	#	
EU-A946	554	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C14)	W	L	L	Q	T	#	
EU-A947	555	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C16)	W	L	L	Q	T	#	
EU-A948	556	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C18)	W	L	L	Q	T	#	
EU-A949	557	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	R	E	F	I	Lys(C20)	W	L	L	Q	T	#	
EU-A950	558	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C8)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A951	559	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C12)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A952	560	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C14)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A953	561	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C16)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A954	562	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A955	563	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C20)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A956	564	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C8)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A957	565	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C12)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A958	566	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C14)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A959	567	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C16)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A960	568	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A961	569	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C20)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A962	570	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C8)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A963	571	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C12)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A964	572	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C14)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A965	573	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C16)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A966	574	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C18)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A967	575	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(C20)	A	A	K	E	F	I	A	W	L	L	Q	T	#
EU-A968	576	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C8)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A969	577	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C12)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A970	578	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C14)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A971	579	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C16)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A972	580	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C18)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A973	581	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	Alb	Lys(C20)	A	A	R	E	F	I	A	W	L	L	Q	T	#
EU-A974	582	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C8)	D	F	Y	Q	W	L	L	Q	T	#	
EU-A975	583	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C12)	D	F	V	Q	W	L	L	Q	T	#	
EU-A976	584	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C14)	D	F	V	Q	W	L	L	Q	T	#	
EU-A977	585	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	A	Lys(C16)	D	F	V	Q	W	L	L	Q	T	#	

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1	5	10	15	20	25	30																								
EU-A978	586	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	Q	T	#
EU-A979	587	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	Q	T	#
EU-A980	588	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C8)	D	F	V	Q	W	L	L	Q	T	#
EU-A981	589	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C12)	D	F	V	Q	W	L	L	Q	T	#
EU-A982	590	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C14)	D	F	V	Q	W	L	L	Q	T	#
EU-A983	591	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C16)	D	F	V	Q	W	L	L	Q	T	#
EU-A984	592	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C18)	D	F	V	Q	W	L	L	Q	T	#
EU-A985	593	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	R	R	A	Lys(C20)	D	F	V	Q	W	L	L	Q	T	#
EU-A986	594	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C8)	W	L	M	Q	T	#
EU-A987	595	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C12)	W	L	M	Q	T	#
EU-A988	596	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C14)	W	L	M	Q	T	#
EU-A989	597	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C16)	W	L	M	Q	T	#
EU-A990	598	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C18)	W	L	M	Q	T	#
EU-A991	599	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C20)	W	L	M	Q	T	#
EU-A992	600	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C8)	W	L	L	Q	T	#
EU-A993	601	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C12)	W	L	L	Q	T	#
EU-A994	602	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C14)	W	L	L	Q	T	#
EU-A995	603	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C16)	W	L	L	Q	T	#
EU-A996	604	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C18)	W	L	L	Q	T	#
EU-A997	605	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C20)	W	L	L	Q	T	#
EU-A998	606	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M8)	W	L	L	Q	T	#
EU-A999	607	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M12)	W	L	L	Q	T	#
EU-A1000	608	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M14)	W	L	L	Q	T	#
EU-A1001	609	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M16)	W	L	L	Q	T	#
EU-A1002	610	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M18)	W	L	L	Q	T	#
EU-A1003	611	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(M20)	W	L	L	Q	T	#
EU-A1004	612	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M8)	W	L	L	Q	T	#
EU-A1005	613	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M12)	W	L	L	Q	T	#
EU-A1006	614	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M14)	W	L	L	Q	T	#
EU-A1007	615	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M16)	W	L	L	Q	T	#
EU-A1008	616	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M18)	W	L	L	Q	T	#
EU-A1009	617	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Q	A	A	R	E	F	I	Lys(M20)	W	L	L	Q	T	#
EU-A1010	618	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(M8)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A1011	619	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(M12)	A	A	K	E	F	I	A	W	L	L	N	T	#
EU-A1012	620	H	G	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E	Lys(M14)	A	A	K	E	F	I	A	W	L	L	N	T	#

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID.	1	5	10	15		20	25	30
NO.								
EU-A1013 621	H	G	C	Lys(M16)	A	A	A	Lys(M16)
EU-A1014 622	H	G	G	Lys(M18)	A	A	A	Lys(M18)
EU-A1015 623	H	G	G	Lys(M20)	A	A	A	Lys(M20)
EU-A1016 624	H	G	G	Lys(M8)	A	A	A	Lys(M8)
EU-A1017 625	H	G	G	Lys(M12)	A	A	A	Lys(M12)
EU-A1018 626	H	G	G	Lys(M14)	A	A	A	Lys(M14)
EU-A1019 627	H	G	G	Lys(M16)	A	A	A	Lys(M16)
EU-A1020 628	H	G	G	Lys(M18)	A	A	A	Lys(M18)
EU-A1021 629	H	G	G	Lys(M20)	A	A	A	Lys(M20)
EU-A1022 630	H	Alb	Q	Q	A	A	A	Lys(M8)
EU-A1023 631	H	Alb	Q	E*	A	A	A	Lys(M12)
EU-A1024 632	H	Alb	Q	E*	A	A	A	Lys(M14)
EU-A1025 633	H	Alb	Q	E*	A	A	A	Lys(M16)
EU-A1026 634	H	Alb	Q	E*	A	A	A	Lys(M18)
EU-A1027 635	H	Alb	Q	E*	A	A	A	Lys(M20)
EU-A1028 636	H	G	Q	Q	A	A	A	Lys(M8)
EU-A1029 637	H	G	Q	Q	A	A	A	Lys(M12)
EU-A1030 638	H	G	Q	Q	A	A	A	Lys(M14)
EU-A1031 639	H	G	Q	Q	A	A	A	Lys(M16)
EU-A1032 640	H	G	Q	Q	A	A	A	Lys(M18)
EU-A1033 641	H	G	Q	Q	A	A	A	Lys(M20)
EU-A1034 642	H	G	Q	Lys(M8)	A	A	A	A
EU-A1035 643	H	G	Q	Lys(M12)	A	A	A	A
EU-A1036 644	H	G	Q	Lys(M14)	A	A	A	A
EU-A1037 645	H	G	Q	Lys(M16)	A	A	A	A
EU-A1038 646	H	G	Q	Lys(M18)	A	A	A	A
EU-A1039 647	H	G	Q	Lys(M20)	A	A	A	A
EU-A1040 648	H	G	Q	Lys(M8)	A	A	A	A
EU-A1041 649	H	G	Q	Lys(M12)	A	A	A	A
EU-A1042 650	H	G	Q	Lys(M14)	A	A	A	A
EU-A1043 651	H	G	Q	Lys(M16)	A	A	A	A
EU-A1044 652	H	G	Q	Lys(M18)	A	A	A	A
EU-A1045 653	H	G	Q	Lys(M20)	A	A	A	A
EU-A1046 654	H	G	Q	Lys(M8)	A	A	A	A
EU-A1047 655	H	G	Q	Lys(M12)	A	A	A	A
EU-A1048 656	H	G	Q	Lys(M14)	A	A	A	A
EU-A1049 657	H	G	Q	Lys(M16)	A	A	A	A
EU-A1050 658	H	G	Q	Lys(M18)	A	A	A	A
EU-A1051 659	H	G	Q	Lys(M20)	A	A	A	A
EU-A1052 660	H	G	Q	Lys(M8)	A	A	A	A
EU-A1053 661	H	G	Q	Lys(M12)	A	A	A	A
EU-A1054 662	H	G	Q	Lys(M14)	A	A	A	A
EU-A1055 663	H	G	Q	Lys(M16)	A	A	A	A
EU-A1056 664	H	G	Q	Lys(M18)	A	A	A	A
EU-A1057 665	H	G	Q	Lys(M20)	A	A	A	A
EU-A1058 666	H	G	Q	Lys(M8)	A	A	A	A
EU-A1059 667	H	G	Q	Lys(M12)	A	A	A	A
EU-A1060 668	H	G	Q	Lys(M14)	A	A	A	A
EU-A1061 669	H	G	Q	Lys(M16)	A	A	A	A
EU-A1062 670	H	G	Q	Lys(M18)	A	A	A	A
EU-A1063 671	H	G	Q	Lys(M20)	A	A	A	A
EU-A1064 672	H	G	Q	Lys(M8)	A	A	A	A
EU-A1065 673	H	G	Q	Lys(M12)	A	A	A	A
EU-A1066 674	H	G	Q	Lys(M14)	A	A	A	A
EU-A1067 675	H	G	Q	Lys(M16)	A	A	A	A
EU-A1068 676	H	G	Q	Lys(M18)	A	A	A	A
EU-A1069 677	H	G	Q	Lys(M20)	A	A	A	A
EU-A1070 678	H	G	Q	Lys(M8)	A	A	A	A
EU-A1071 679	H	G	Q	Lys(M12)	A	A	A	A
EU-A1072 680	H	G	Q	Lys(M14)	A	A	A	A
EU-A1073 681	H	G	Q	Lys(M16)	A	A	A	A
EU-A1074 682	H	G	Q	Lys(M18)	A	A	A	A
EU-A1075 683	H	G	Q	Lys(M20)	A	A	A	A
EU-A1076 684	H	G	Q	Lys(M8)	A	A	A	A
EU-A1077 685	H	G	Q	Lys(M12)	A	A	A	A
EU-A1078 686	H	G	Q	Lys(M14)	A	A	A	A
EU-A1079 687	H	G	Q	Lys(M16)	A	A	A	A
EU-A1080 688	H	G	Q	Lys(M18)	A	A	A	A
EU-A1081 689	H	G	Q	Lys(M20)	A	A	A	A
EU-A1082 690	H	G	Q	Lys(M8)	A	A	A	A
EU-A1083 691	H	G	Q	Lys(M12)	A	A	A	A
EU-A1084 692	H	G	Q	Lys(M14)	A	A	A	A
EU-A1085 693	H	G	Q	Lys(M16)	A	A	A	A
EU-A1086 694	H	G	Q	Lys(M18)	A	A	A	A
EU-A1087 695	H	G	Q	Lys(M20)	A	A	A	A
EU-A1088 696	H	G	Q	Lys(M8)	A	A	A	A
EU-A1089 697	H	G	Q	Lys(M12)	A	A	A	A
EU-A1090 698	H	G	Q	Lys(M14)	A	A	A	A
EU-A1091 699	H	G	Q	Lys(M16)	A	A	A	A
EU-A1092 700	H	G	Q	Lys(M18)	A	A	A	A
EU-A1093 701	H	G	Q	Lys(M20)	A	A	A	A
EU-A1094 702	H	G	Q	Lys(M8)	A	A	A	A
EU-A1095 703	H	G	Q	Lys(M12)	A	A	A	A
EU-A1096 704	H	G	Q	Lys(M14)	A	A	A	A
EU-A1097 705	H	G	Q	Lys(M16)	A	A	A	A
EU-A1098 706	H	G	Q	Lys(M18)	A	A	A	A
EU-A1099 707	H	G	Q	Lys(M20)	A	A	A	A
EU-A1100 708	H	G	Q	Lys(M8)	A	A	A	A
EU-A1101 709	H	G	Q	Lys(M12)	A	A	A	A
EU-A1102 710	H	G	Q	Lys(M14)	A	A	A	A
EU-A1103 711	H	G	Q	Lys(M16)	A	A	A	A
EU-A1104 712	H	G	Q	Lys(M18)	A	A	A	A
EU-A1105 713	H	G	Q	Lys(M20)	A	A	A	A
EU-A1106 714	H	G	Q	Lys(M8)	A	A	A	A
EU-A1107 715	H	G	Q	Lys(M12)	A	A	A	A
EU-A1108 716	H	G	Q	Lys(M14)	A	A	A	A
EU-A1109 717	H	G	Q	Lys(M16)	A	A	A	A
EU-A1110 718	H	G	Q	Lys(M18)	A	A	A	A
EU-A1111 719	H	G	Q	Lys(M20)	A	A	A	A
EU-A1112 720	H	G	Q	Lys(M8)	A	A	A	A
EU-A1113 721	H	G	Q	Lys(M12)	A	A	A	A
EU-A1114 722	H	G	Q	Lys(M14)	A	A	A	A
EU-A1115 723	H	G	Q	Lys(M16)	A	A	A	A
EU-A1116 724	H	G	Q	Lys(M18)	A	A	A	A
EU-A1117 725	H	G	Q	Lys(M20)	A	A	A	A
EU-A1118 726	H	G	Q	Lys(M8)	A	A	A	A
EU-A1119 727	H	G	Q	Lys(M12)	A	A	A	A
EU-A1120 728	H	G	Q	Lys(M14)	A	A	A	A
EU-A1121 729	H	G	Q	Lys(M16)	A	A	A	A
EU-A1122 730	H	G	Q	Lys(M18)	A	A	A	A
EU-A1123 731	H	G	Q	Lys(M20)	A	A	A	A
EU-A1124 732	H	G	Q	Lys(M8)	A	A	A	A
EU-A1125 733	H	G	Q	Lys(M12)	A	A	A	A
EU-A1126 734	H	G	Q	Lys(M14)	A	A	A	A
EU-A1127 735	H	G	Q	Lys(M16)	A	A	A	A
EU-A1128 736	H	G	Q	Lys(M18)	A	A	A	A
EU-A1129 737	H	G	Q	Lys(M20)	A	A	A	A
EU-A1130 738	H	G	Q	Lys(M8)	A	A	A	A
EU-A1131 739	H	G	Q	Lys(M12)	A	A	A	A
EU-A1132 740	H	G	Q	Lys(M14)	A	A	A	A
EU-A1133 741	H	G	Q	Lys(M16)	A	A	A	A
EU-A1134 742	H	G	Q	Lys(M18)	A	A	A	A
EU-A1135 743	H	G	Q	Lys(M20)	A	A	A	A
EU-A1136 744	H	G	Q	Lys(M8)	A	A	A	A
EU-A1137 745	H	G	Q	Lys(M12)	A	A	A	A
EU-A1138 746	H	G	Q	Lys(M14)	A	A	A	A
EU-A1139 747	H	G	Q	Lys(M16)	A	A	A	A
EU-A1140 748	H	G	Q	Lys(M18)	A	A	A	A
EU-A1141 749	H	G	Q	Lys(M20)	A	A	A	A
EU-A1142 750	H	G	Q	Lys(M8)	A	A	A	A
EU-A1143 751	H	G	Q	Lys(M12)	A	A	A	A
EU-A1144 752	H	G	Q	Lys(M14)	A	A	A	A
EU-A1145 753	H	G	Q	Lys(M16)	A	A	A	A
EU-A1146 754	H	G	Q	Lys(M18)	A	A	A	A
EU-A1147 755	H	G	Q	Lys(M20)	A	A	A	A
EU-A1148 756	H	G	Q	Lys(M8)	A	A	A	A
EU-A1149 757	H	G	Q	Lys(M12)	A	A	A	A
EU-A1150 758	H	G	Q	Lys(M14)	A	A	A	A
EU-A1151 759	H	G	Q	Lys(M16)	A	A	A	A
EU-A1152 760	H	G	Q	Lys(M18)	A	A	A	A
EU-A1153 761	H	G	Q	Lys(M20)	A	A	A	A
EU-A1154 762	H	G	Q	Lys(M8)	A	A	A	A
EU-A1155 763	H	G	Q	Lys(M12)	A	A	A	A
EU-A1156 764	H	G	Q	Lys(M14)	A	A	A	A
EU-A1157 765	H	G	Q	Lys(M16)	A	A	A	A
EU-A1158 766	H	G	Q	Lys(M18)	A	A	A	A
EU-A1159 767	H	G	Q	Lys(M20)	A	A	A	A
EU-A1160 768	H	G	Q	Lys(M8)	A	A	A	A
EU-A1161 769	H	G	Q	Lys(M12)	A	A	A	A
EU-A1162 770	H	G	Q	Lys(M14)	A	A	A	A
EU-A1163 771	H	G	Q	Lys(M16)	A	A	A	A
EU-A1164 772	H	G	Q	Lys(M18)	A	A	A	A
EU-A1165 773	H	G	Q	Lys(M20)	A	A	A	A
EU-A1166 774	H	G	Q	Lys(M8)	A	A	A	A
EU-A1167 775	H	G	Q	Lys(M12)	A	A	A	A
EU-A1168 776	H	G	Q	Lys(M14)	A	A	A	A
EU-A1169 777	H	G	Q	Lys(M16)	A	A	A	A
EU-A1170 778	H	G	Q	Lys(M18)	A	A	A	A
EU-A1171 779	H	G	Q	Lys(M20)	A	A	A	A
EU-A1172 780	H	G	Q	Lys(M8)	A	A	A	A
EU-A1173 781	H	G	Q	Lys(M12)	A	A	A	A
EU-A1174 782	H	G	Q	Lys(M14)	A	A	A	A
EU-A1175 783	H	G	Q	Lys(M16)	A	A	A	A
EU-A1176 784	H	G	Q	Lys(M18)	A	A	A	A
EU-A1177 785	H	G	Q	Lys(M20)	A	A	A	A
EU-A1178 786	H	G	Q	Lys(M8)	A	A	A	A
EU-A1179 787	H	G	Q	Lys(M12)	A	A	A	A
EU-A1180 788	H	G	Q	Lys(M14)	A	A	A	A
EU-A1181 789	H	G	Q	Lys(M16)	A	A	A	A
EU-A1182 790	H	G	Q	Lys(M18)	A	A	A	A
EU-A1183 791	H	G	Q	Lys(M20)	A	A	A	A
EU-A1184 792	H	G	Q	Lys(M8)	A	A	A	A
EU-A1185 793	H	G	Q	Lys(M12)	A	A	A	A
EU-A1186 794	H	G	Q	Lys(M14)	A	A	A	A
EU-A1187 795	H	G	Q	Lys(M16)	A	A	A	A
EU-A1188 796	H	G	Q	Lys(M18)	A	A	A	A
EU-A1189 797	H	G	Q	Lys(M20)	A	A	A	A
EU-A1190 798	H	G	Q	Lys(M8)	A	A	A	A
EU-A1191 799	H	G	Q	Lys(M12)	A	A	A	A
EU-A1192 800	H	G	Q	Lys(M14)	A	A	A	A
EU-A1193 801	H	G	Q	Lys(M16)	A	A	A	A
EU-A1194 802	H	G	Q	Lys(M18)	A	A	A	A
EU-A1195 803	H	G	Q	Lys(M20)	A	A	A	A
EU-A1196 804	H	G	Q	Lys(M8)	A	A	A	A
EU-A1197 805	H	G	Q	Lys(M12)	A	A	A	A
EU-A1198 806	H	G	Q	Lys(M14)	A	A	A	A
EU-A1199 807	H	G	Q	Lys(M16)	A	A	A	A
EU-A1200 808	H	G	Q	Lys(M18)	A	A	A	A
EU-A1201 809	H	G	Q	Lys(M20)	A	A	A	A
EU-A1202 810	H	G	Q	Lys(M8)	A	A	A	A
EU-A1203 811	H	G	Q	Lys(M12)	A	A	A	A
EU-A1204 812	H	G	Q	Lys(M14)</				

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1	5	10	15	20	25	30
EU-A1048	656 H αMePro	Q G T	αMeF T S D	EBip Lys(C14) #			
EU-A1049	657 H αMePro	Q G T	αMeF T S D	EBip Lys(C16) #			
EU-A1050	658 H αMePro	Q G T	αMeF T S D	EBip Lys(C18) #			
EU-A1051	659 H αMePro	Q G T	αMeF T S D	EBip Lys(C20) #			
EU-A1052	660 H αMePro	Q G T	αMeF T S D	EBip Lys(C8) #			
EU-A1053	661 H αMePro	Q G T	αMeF T S D	EBip Lys(C12) #			
EU-A1054	662 H αMePro	Q G T	αMeF T S D	EBip Lys(C14) #			
EU-A1055	663 H αMePro	Q G T	αMeF T S D	EBip Lys(C16) #			
EU-A1056	664 H αMePro	Q G T	αMeF T S D	EBip Lys(C18) #			
EU-A1057	665 H αMePro	Q G T	αMeF T S D	EBip Lys(C20) #			
EU-A1058	666 H Alb	Q G T	αMeF T S D	EBip Lys(C8) #			
EU-A1059	667 H Alb	Q G T	αMeF T S D	EBip Lys(C12) #			
EU-A1060	668 H Alb	Q G T	αMeF T S D	EBip Lys(C14) #			
EU-A1061	669 H Alb	Q G T	αMeF T S D	EBip Lys(C16) #			
EU-A1062	670 H Alb	Q G T	αMeF T S D	EBip Lys(C18) #			
EU-A1063	671 H Alb	Q G T	αMeF T S D	EBip Lys(C20) #			
EU-A1064	672 H Alb	Q G T	αMeF T S D	EBip Lys(C8) #			
EU-A1065	673 H Alb	Q G T	αMeF T S D	EBip Lys(C12) #			
EU-A1066	674 H Alb	Q G T	αMeF T S D	EBip Lys(C14) #			
EU-A1067	675 H Alb	Q G T	αMeF T S D	EBip Lys(C16) #			
EU-A1068	676 H Alb	Q G T	αMeF T S D	EBip Lys(C18) #			
EU-A1069	677 H Alb	Q G T	αMeF T S D	EBip Lys(C20) #			
EU-A1070	678 H αMePro	Q G T	αMeF T S D	EBip Melys(C8) #			
EU-A1071	679 H αMePro	Q G T	αMeF T S D	EBip Melys(C12) #			
EU-A1072	680 H αMePro	Q G T	αMeF T S D	EBip Melys(C14) #			
EU-A1073	681 H αMePro	Q G T	αMeF T S D	EBip Melys(C16) #			
EU-A1074	682 H αMePro	Q G T	αMeF T S D	EBip Melys(C18) #			
EU-A1075	683 H αMePro	Q G T	αMeF T S D	EBip Melys(C20) #			
EU-A1076	684 H αMePro	Q G T	αMeF T S D	EBip Melys(C8) #			
EU-A1077	685 H αMePro	Q G T	αMeF T S D	EBip Melys(C12) #			
EU-A1078	686 H αMePro	Q G T	αMeF T S D	EBip Melys(C14) #			
EU-A1079	687 H αMePro	Q G T	αMeF T S D	EBip Melys(C16) #			
EU-A1080	688 H αMePro	Q G T	αMeF T S D	EBip Melys(C18) #			
EU-A1081	689 H αMePro	Q G T	αMeF T S D	EBip Melys(C20) #			
EU-A1082	690 H Alb	Q G T	αMeF T S D	EBip Melys(C8) #			

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID. NO.	1				5				10			15		20		25	30
EU-A1083	691	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Meys(C12)	#				
EU-A1084	692	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Meys(C14)	#				
EU-A1085	693	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Meys(C16)	#				
EU-A1086	694	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Meys(C18)	#				
EU-A1087	695	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Meys(C20)	#				
EU-A1088	696	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C8)	#				
EU-A1089	697	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C12)	#				
EU-A1090	698	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C14)	#				
EU-A1091	699	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C16)	#				
EU-A1092	700	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C18)	#				
EU-A1093	701	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Meys(C20)	#				
EU-A1094	702	H	αMePro	Q	G	T	αMeF	T	S	D	EBip	Me8	#				
EU-A1095	703	H	αMePro	Q	G	T	αMeF	T	S	D	EBip	Me12	#				
EU-A1096	704	H	αMePro	Q	G	T	αMeF	T	S	D	EBip	Me14	#				
EU-A1097	705	H	αMePro	Q	G	T	αMeF	T	S	D	EBip	Me16	#				
EU-A1098	706	H	αMePro	Q	G	T	αMeF	T	S	D	EBip	Me18	#				
EU-A1099	707	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me20	#				
EU-A1100	708	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me8	#				
EU-A1101	709	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me12	#				
EU-A1102	710	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me14	#				
EU-A1103	711	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me16	#				
EU-A1104	712	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me18	#				
EU-A1105	713	H	αMePro	Q	G	T	αMeFF	T	S	D	EBip	Me20	#				
EU-A1106	714	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Me8	#				
EU-A1107	715	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Me12	#				
EU-A1108	716	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Me14	#				
EU-A1109	717	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Me16	#				
EU-A1110	718	H	Alb	Q	G	T	αMeF	T	S	D	EBip	Me18	#				
EU-A1111	719	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me20	#				
EU-A1112	720	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me8	#				
EU-A1113	721	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me12	#				
EU-A1114	722	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me14	#				
EU-A1115	723	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me16	#				
EU-A1116	724	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me18	#				
EU-A1117	725	H	Alb	Q	G	T	αMeFF	T	S	D	EBip	Me20	#				

FIG. 3 (Continued)
Table 3 (Continued)

SEQ. ID.	1		5				10		15	20	25	30
NO.												
EU-A1118	726	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C8)	#	
EU-A1119	727	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C12)	#	
EU-A1120	728	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C14)	#	
EU-A1121	729	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C16)	#	
EU-A1122	730	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C18)	#	
EU-A1123	731	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Melys(C20)	#	
EU-A1124	732	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C8)	#	
EU-A1125	733	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C12)	#	
EU-A1126	734	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C14)	#	
EU-A1127	735	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C16)	#	
EU-A1128	736	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C18)	#	
EU-A1129	737	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Melys(C20)	#	
EU-A1130	738	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C8)	#	
EU-A1131	739	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C12)	#	
EU-A1132	740	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C14)	#	
EU-A1133	741	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C16)	#	
EU-A1134	742	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C18)	#	
EU-A1135	743	H	Alb	Q	G	T	aMeF	T S D	Blo	Melys(C20)	#	
EU-A1136	744	H	Alb	Q	G	T	aMeFF	T S D	Blo	Melys(C8)	#	
EU-A1137	745	H	Alb	Q	G	T	aMeFF	T S D	Blo	Melys(C12)	#	
EU-A1138	746	H	Alb	Q	G	T	aMeFF	T S D	Blo	Melys(C14)	#	
EU-A1139	747	I	Alb	Q	G	T	aMeTT	T S D	Blo	Melys(C16)	#	
EU-A1140	748	H	Alb	Q	G	T	aMeFF	T S D	Blo	Melys(C18)	#	
EU-A1141	749	H	Alb	Q	G	T	aMeFF	T S D	Blo	Melys(C20)	#	
EU-A1142	750	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me8	#	
EU-A1143	751	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me12	#	
EU-A1144	752	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me14	#	
EU-A1145	753	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me16	#	
EU-A1146	754	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me18	#	
EU-A1147	755	H	aMeP _{ro}	Q	G	T	aMeF	T S D	Blo	Me20	#	
EU-A1148	756	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Me8	#	
EU-A1149	757	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Me12	#	
EU-A1150	758	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Me14	#	
EU-A1151	759	H	aMeP _{ro}	Q	G	T	aMeFF	T S D	Blo	Me16	#	

FIG. 3 (Continued)
Table 3 (Continued)

	SEQ. ID. NO.	1				5			10			15			20			25		30													
	EU-A1152	760	H	αMePro	Q	G	T	αMeFF	T	S	D	Bip	Me18	#																			
	EU-A1153	761	H	αMePro	Q	G	T	αMeFF	T	S	D	Bip	Me20	#																			
	EU-A1154	762	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me8	#																			
	EU-A1155	763	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me12	#																			
	EU-A1156	764	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me14	#																			
	EU-A1157	765	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me16	#																			
	EU-A1158	766	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me18	#																			
	EU-A1159	767	H	Alb	Q	G	T	αMeF	T	S	D	Bip	Me20	#																			
	EU-A1160	768	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me8	#																			
	EU-A1161	769	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me12	#																			
	EU-A1162	770	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me14	#																			
	EU-A1163	771	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me16	#																			
	EU-A1164	772	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me18	#																			
	EU-A1165	773	H	Alb	Q	G	T	αMeFF	T	S	D	Bip	Me20	#																			
	EU-A1166	798	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(C9)	W	L	L	Q	T	#	
	EU-A1167	799	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(C10)	W	L	L	Q	T	#
	EU-A1168	800	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(C11)	W	L	L	Q	T	#
	EU-A1169	801	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*8)	W	L	L	Q	T	#
	EU-A1170	802	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*10)	W	L	L	Q	T	#
	EU-A1171	803	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*12)	W	L	L	Q	T	#
	EU-A1172	804	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*14)	W	L	L	Q	T	#
	EU-A1173	805	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*16)	W	L	L	Q	T	#
	EU-A1174	806	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	A	K*	E	F	I	Lys(Me*18)	W	L	L	Q	T	#

C with a numeral means 1-alkyl beta-D-glucuronoyl acyl group, while the numeral denotes the chain length.

MeLys = C-alpha-methyl-lysine, EtBip = 2'-ethyl-biphenylalanine; αMeF = C-α-methyl-Phe; αMeFF = C-α-methyl-2-fluoro-Phe

M is maltoside and Me is melibioside-based surfactant, while the numeral is the carbon chain length of the 1-alkyl substitution. Starred means alpha linked glycoside. For example Me* means alpha- melibioside.

Lys(C12) means N-epsilon-(1'-dodecyl beta-D-glucuronoyl)-L-lysine and other C numbers mean the corresponding 1'-alkyl glucuronide. The pair of amino acids E*, K* or K*, E* separated by 4 residues denotes a side chain lactam linkage formed between the side chain functional groups on these amino acids.

means amide C-terminus.

FIG. 4
Table 4

	SEQ ID NO	1				5				10				15				20				25			29	30					
EU-A1575	807	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Me10)	W	L	L	Q	T	OH
EU-A1576	808	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Me12)	W	L	L	Q	T	OH
EU-A1577	809	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Me14)	W	L	L	Q	T	OH
EU-A1578	810	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Me16)	W	L	L	Q	T	OH
EU-A1579	811	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Me18)	W	L	L	Q	T	OH
EU-A1580	812	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me10)	W	L	L	Q	T	OH
EU-A1581	813	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me12)	W	L	L	Q	T	OH
EU-A1582	814	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me14)	W	L	L	Q	T	OH
EU-A1583	815	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me16)	W	L	L	Q	T	OH
EU-A1584	816	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me18)	W	L	L	Q	T	OH
EU-A1585	817	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1586	818	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1587	819	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1588	820	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1589	821	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1590	822	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	OH
EU-A1591	823	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me12)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1592	824	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Me12)	A	A	K*	E	F	I	E	W	L	L	Q	T	OH
EU-A1593	825	H	Alb	Q	G	T	F	T	S	D	Lys(Me10)	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Q	W	L	L	Q	T	#

FIG. 4 (Continued)
Table 4 (Continued)

SEQ ID NO	1	5	10	15	20	25	29	30
826	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	Q	L Q T	#
827	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	Q	L Q T	#
828	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	Q	L Q T	#
829	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	Q	L Q T	#
830	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	E	L Q T	#
831	H Alb	Q G T F T S D	S K Y L D E* Q A A	W	E F I	E	L Q T	OH
832	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me10)		L Q T	#
833	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me12)		L Q T	#
834	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me14)		L Q T	#
835	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me16)		L Q T	#
836	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me18)		L Q T	#
837	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS2(Me10)		L Q T	#
838	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS2(Me12)		L Q T	#
839	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS2(Me14)		L Q T	#
840	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS2(Me16)		L Q T	#
841	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS2(Me18)		L Q T	#
842	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me10)		L Q T	OH
843	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me12)		L Q T	OH
844	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me14)		L Q T	OH
845	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me16)		L Q T	OH
846	H Alb	Q G T F T S D	Y S K Y L D E* Q A A	W	E F I LysS1(Me18)		L Q T	OH

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1			5				10			15			20			25		29	30
	EU-A1615	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS2(Mer10)	W L L Q T	OH		
	EU-A1616	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS2(Mer12)	W L L Q T	OH		
	EU-A1617	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS2(Mer14)	W L L Q T	OH		
	EU-A1618	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS2(Mer16)	W L L Q T	OH		
	EU-A1619	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS2(Mer18)	W L L Q T	OH		
	EU-A1620	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer12)	W L L Q T	OH		
	EU-A1621	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer10)	W L L Q T	OH		
	EU-A1622	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer14)	W L L Q T	OH		
	EU-A1623	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer16)	W L L Q T	OH		
	EU-A1624	H Alb	Q Alb	Q C T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer18)	W L L Q T	OH		
	EU-A1625	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer10)	W L L Q T	#		
	EU-A1626	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer12)	W L L Q T	#		
	EU-A1627	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer14)	W L L Q T	#		
	EU-A1628	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer16)	W L L Q T	#		
	EU-A1629	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer18)	W L L Q T	#		
	EU-A1630	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	LysS3(Mer18)	W L L Q T	#		
	EU-A1631	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	Lys(Z8)	W L L Q T	PEGa		
	EU-A1632	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	Lys(Z10)	W L L Q T	PEGa		
	EU-A1633	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	Lys(Z12)	W L L Q T	PEGa		
	EU-A1634	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	Lys(Z14)	W L L Q T	PEGa		
	EU-A1635	H Alb	Q Alb	Q G T F T S D	Y S K Y L D E*	Q A A									K*	E F I	Lys(Z16)	W L L Q T	PEGa		

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1								10					15					20					25			29	30			
	EUA-1636	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z18)	W	L	Q	T	PEGa	
	EUA-1637	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me6)	W	L	Q	T	PEGa	
	EUA-1638	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me10)	W	L	Q	T	PEGa	
	EUA-1639	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me12)	W	L	Q	T	PEGa	
	EUA-1640	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me14)	W	L	Q	T	PEGa	
	EUA-1641	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me16)	W	L	Q	T	PECa	
	EUA-1642	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Me18)	W	L	Q	T	PEGa	
	EUA-1643	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z8)	W	L	Q	T	PEGb	
	EUA-1644	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z10)	W	L	Q	T	PEGb	
	EUA-1645	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z12)	W	L	Q	T	PECb	
	EUA-1646	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z14)	W	L	Q	T	PEGb	
	EUA-1647	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z16)	W	L	Q	T	PEGb	
	EUA-1648	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			A	A	K*	E	F	I	Lys(Z18)	W	L	Q	T	PEGb	
	EUA-1649	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me6)	W	L	Q	T	PEGb
	EUA-1650	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me10)	W	L	Q	T	PEGb
	EUA-1651	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me12)	W	L	Q	T	PEGb
	EUA-1652	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me14)	W	L	Q	T	PEGb
	EUA-1653	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me16)	W	L	Q	T	PEGb
	EUA-1654	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			E	A	A	K*	E	F	I	Lys(Me18)	W	L	Q	T	PEGb
	EUA-1655	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			Q	A	A	K*	E	F	I	Lys(Z8)	W	L	Q	T	PEGc
	EUA-1656	H	Aib	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*			Q	A	A	K*	E	F	I	Lys(Z10)	W	L	Q	T	PEGc

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10					15					20					25			29	30		
EU-A1657	889	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z12)	W	L	L	Q	T	PEGc
EU-A1658	890	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z14)	W	L	L	Q	T	PEGc
EU-A1659	891	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z16)	W	L	L	Q	T	PEGc
EU-A1660	892	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z18)	W	L	L	Q	T	PEGc
EU-A1661	893	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me6)	W	L	L	Q	T	PEGc
EU-A1662	894	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me10)	W	L	L	Q	T	PEGc
EU-A1663	895	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me12)	W	L	L	Q	T	PEGc
EU-A1664	896	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me14)	W	L	L	Q	T	PEGc
EU-A1665	897	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me16)	W	L	L	Q	T	PEGc
EU-A1666	898	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me18)	W	L	L	Q	T	PEGc
EU-A1667	899	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z8)	W	L	L	Q	T	PEGd
EU-A1668	900	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z10)	W	L	L	Q	T	PEGd
EU-A1669	901	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z12)	W	L	L	Q	T	PEGd
EU-A1670	902	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z14)	W	L	L	Q	T	PEGd
EU-A1671	903	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z16)	W	L	L	Q	T	PEGd
EU-A1672	904	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	K*	E	F	I	Lys(Z18)	W	L	L	Q	T	PEGd
EU-A1673	905	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me6)	W	L	L	Q	T	PEGd
EU-A1674	906	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me10)	W	L	L	Q	T	PEGd
EU-A1675	907	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me12)	W	L	L	Q	T	PEGd
EU-A1676	908	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me14)	W	L	L	Q	T	PEGd
EU-A1677	909	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	K*	E	F	I	Lys(Me16)	W	L	L	Q	T	PEGd

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10					15				20				25		29	30				
	EU-A1678	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Me18)	W	L	L	Q	T	PEGd
	EU-A1679	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z8)	W	L	L	Q	T	OH
	EU-A1680	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z10)	W	L	L	Q	T	OH
	EU-A1681	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z12)	W	L	L	Q	T	OH
	EU-A1682	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z14)	W	L	L	Q	T	OH
	EU-A1683	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z16)	W	L	L	Q	T	OH
	EU-A1684	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(Z18)	W	L	L	Q	T	OH
	EU-A1685	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z8)	W	L	L	Q	T	OH
	EU-A1686	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z10)	W	L	L	Q	T	OH
	EU-A1687	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z12)	W	L	L	Q	T	OH
	EU-A1688	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z14)	W	L	L	Q	T	OH
	EU-A1689	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z16)	W	L	L	Q	T	OH
	EU-A1690	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	E	A	A	E	F	I	Lys(Z18)	W	L	L	Q	T	OH
	EU-A1691	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z8)	W	L	L	Q	T	OH
	EU-A1692	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z10)	W	L	L	Q	T	OH
	EU-A1693	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z12)	W	L	L	Q	T	OH
	EU-A1694	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z14)	W	L	L	Q	T	OH
	EU-A1695	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z16)	W	L	L	Q	T	OH
	EU-A1696	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S1(Z18)	W	L	L	Q	T	OH
	EU-A1697	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S2(Z8)	W	L	L	Q	T	OH
	EU-A1698	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Q	A	A	E	F	I	Lys(S2(Z10)	W	L	L	Q	T	OH

FIG. 4 (Continued)
Table 4 (Continued)

SEQ ID NO	1	5	10	15	20	25	29	30
EU-A1699	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z12)	W L Q T	OH
EU-A1700	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z14)	W L Q T	OH
EU-A1701	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z16)	W L Q T	OH
EU-A1702	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z18)	W L Q T	OH
EU-A1703	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z8)	W L Q T	OH
EU-A1704	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS3(Z10)	W L Q T	OH
EU-A1705	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS3(Z12)	W L Q T	OH
EU-A1706	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS3(Z14)	W L Q T	OH
EU-A1707	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS3(Z16)	W L Q T	OH
EU-A1708	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS3(Z18)	W L Q T	OH
EU-A1709	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z8)	W L Q T	#
EU-A1710	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z10)	W L Q T	#
EU-A1711	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z12)	W L Q T	#
EU-A1712	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z14)	W L Q T	#
EU-A1713	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z16)	W L Q T	#
EU-A1714	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS1(Z18)	W L Q T	#
EU-A1715	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z8)	W L Q T	#
EU-A1716	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z10)	W L Q T	#
EU-A1717	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z12)	W L Q T	#
EU-A1718	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z14)	W L Q T	#
EU-A1719	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	LysS2(Z16)	W L Q T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1	5	10	15	20	25	29	30
EU-A1720	952	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys2(Z18)	W L L Q T	#
EU-A1721	953	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z8)	W L L Q T	#
EU-A1722	954	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z10)	W L L Q T	#
EU-A1723	955	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z12)	W L L Q T	#
EU-A1724	956	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z14)	W L L Q T	#
EU-A1725	957	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z16)	W L L Q T	#
EU-A1726	958	H Alb	Q G T F T S D	Y	S K Y L D E*	A A Q	Lys3(Z18)	W L L Q T	#
EU-A1727	959	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Me10)	Q	W L L Q T	#
EU-A1728	960	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Me12)	Q	W L L Q T	#
EU-A1729	961	I Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Me14)	Q	W L L Q T	#
EU-A1730	962	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Me16)	Q	W L L Q T	#
EU-A1731	963	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Me18)	Q	W L L Q T	#
EU-A1732	964	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Z10)	Q	W L L Q T	#
EU-A1733	965	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Z12)	Q	W L L Q T	#
EU-A1734	966	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Z14)	Q	W L L Q T	#
EU-A1735	967	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Z16)	Q	W L L Q T	#
EU-A1736	968	H Alb	Q G T F T S D	E*	S K Y K* D S	A A Lys(Z18)	Q	W L L Q T	#
EU-A1737	969	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A Lys(Me10)	Q	W L L Q T	#
EU-A1738	970	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A Lys(Me12)	Q	W L L Q T	#
EU-A1739	971	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A Lys(Me14)	Q	W L L Q T	#
EU-A1740	972	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A Lys(Me16)	Q	W L L Q T	#

FIG. 4 (Continued)
Table 4 (Continued)

SEQ ID NO	1	5	10	15	20	25	29	30
EU-A1741	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1742	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1743	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1744	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1745	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1746	H Alb	Q G T	Y S D	Y L D	A A Q	W	L Q T	#
EU-A1747	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1748	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1749	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1750	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1751	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1752	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1753	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1754	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1755	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1756	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1757	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1758	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1759	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1760	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#
EU-A1761	H Alb	Q G T	E* S D	Y K* D	A A Q	W	L Q T	#

FIG. 4 (Continued)
Table 4 (Continued)

SEQ ID NO	1	5	10	15	20	25	29	30
EU-A1762	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS1(Z16)	Q	E F I L Q T	#
EU-A1763	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS1(Z18)	Q	E F I L Q T	#
EU-A1764	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS2(Z14)	Q	E F I L Q T	#
EU-A1765	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS2(Z16)	Q	E F I L Q T	#
EU-A1766	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS2(Z18)	Q	E F I L Q T	#
EU-A1767	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS3(Z14)	Q	E F I L Q T	#
EU-A1768	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS3(Z16)	Q	E F I L Q T	#
EU-A1769	H Alb	Q G T F T S D	E*	S K Y K* D S	A A LysS3(Z18)	Q	E F I L Q T	#
EU-A1770	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Me10)	Q	E F I L Q T	#
EU-A1771	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Me12)	Q	E F I L Q T	#
EU-A1772	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Me14)	Q	E F I L Q T	#
EU-A1773	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Me16)	Q	E F I L Q T	#
EU-A1774	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Me18)	Q	E F I L Q T	#
EU-A1775	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS2(Me10)	Q	E F I L Q T	#
EU-A1776	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS2(Me12)	Q	E F I L Q T	#
EU-A1777	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS3(Me14)	Q	E F I L Q T	#
EU-A1778	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS3(Me16)	Q	E F I L Q T	#
EU-A1779	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS2(Me18)	Q	E F I L Q T	#
EU-A1780	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS2(Me14)	Q	E F I L Q T	#
EU-A1781	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS2(Me16)	Q	E F I L Q T	#
EU-A1782	H Alb	Q G T F T S D	Y	S E* Y L D K*	A A LysS1(Z10)	Q	E F I L Q T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10				15						20				25		29	30				
	EU-A1783	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS1(Z12)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1784	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS1(Z14)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1785	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS1(Z16)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1786	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS1(Z18)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1787	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS2(Z14)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1788	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS2(Z16)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1789	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS2(Z18)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1790	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS3(Z14)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1791	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS3(Z16)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1792	H	Alb	Q	G	T	F	T	S	D	Y	S	E*	Y	L	D	K*	Q	A	A	LysS3(Z18)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1793	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1794	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1795	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1796	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1797	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1798	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me14)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1799	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1800	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Me18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1801	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Me10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1802	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Me12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1803	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Me14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10				15				20					25			29	30				
	EU-A1804	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Met6)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1805	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Met8)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1806	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Met4)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1807	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Met6)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1808	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Met8)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1809	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1810	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1811	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1812	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met6)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1813	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met8)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1814	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met14)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1815	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met6)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1816	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Met8)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1817	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1818	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Z12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1819	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Z14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1820	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1821	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Z18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
	EU-A1822	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Z16)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1823	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS1(Z18)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
	EU-A1824	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1								10					15					20					25			29	30		
		Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#	
EU-A1825	1062	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1826	1063	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1827	1064	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1828	1065	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1829	1066	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z16)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1830	1067	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS2(Z18)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1831	1068	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z10)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1832	1069	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z12)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1833	1070	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z14)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1834	1071	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z16)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1835	1072	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z18)	A	A	K*	E	F	I	Q	W	L	L	Q	T	#
EU-A1836	1073	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z16)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1837	1074	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	LysS3(Z18)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1838	1075	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Met14)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1839	1076	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Met16)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1840	1077	H	Alb	Q	C	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Met18)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1841	1078	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Z14)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1842	1079	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Z16)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1843	1080	H	Alb	Q	G	T	F	T	S	D	Y	S	K	Y	L	D	E*	Lys(Z18)	A	A	K*	E	F	I	E	W	L	L	Q	T	#
EU-A1844	1081	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Met14)	E	F	I	E	W	L	L	Q	T	#
EU-A1845	1082	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Met16)	E	F	I	E	W	L	L	Q	T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10					15					20				25			29	30			
	EU-A1846	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Met8)	E	F	I	E	W	L	L	Q	T	#
	EU-A1847	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Z14)	E	F	I	E	W	L	L	Q	T	#
	EU-A1848	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Z16)	E	F	I	E	W	L	L	Q	T	#
	EU-A1849	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Q	A	A	Lys(Z18)	E	F	I	E	W	L	L	Q	T	#
	EU-A1850	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met4)	E	F	I	E	W	L	L	Q	T	#
	EU-A1851	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met6)	E	F	I	E	W	L	L	Q	T	#
	EU-A1852	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met8)	E	F	I	E	W	L	L	Q	T	#
	EU-A1853	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z14)	E	F	I	E	W	L	L	Q	T	#
	EU-A1854	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z16)	E	F	I	E	W	L	L	Q	T	#
	EU-A1855	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z18)	E	F	I	E	W	L	L	Q	T	#
	EU-A1856	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met4)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1857	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met6)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1858	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Met8)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1859	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z14)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1860	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z16)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1861	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	E	A	A	Lys(Z18)	E	F	I	Q	W	L	L	Q	T	#
	EU-A1862	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys(Z12)	A	A	Gln	E	F	I	Lys(Z12)	W	L	L	Q	T	#
	EU-A1863	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys(Z14)	A	A	Gln	E	F	I	Lys(Z14)	W	L	L	Q	T	#
	EU-A1864	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys(Z16)	A	A	Gln	E	F	I	Lys(Z16)	W	L	L	Q	T	#
	EU-A1865	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys(Z14CO ₂)	A	A	Gln	E	F	I	Q	W	L	L	Q	T	#
	EU-A1866	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys(Z16CO ₂)	A	A	Gln	E	F	I	Q	W	L	L	Q	T	#

FIG. 4 (Continued)
Table 4 (Continued)

	SEQ ID NO	1				5				10					15				20			25			29	30	
EU-A1867	1104	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Lys[Z18CO ₂]	A	A		W	L	L	Q	T	#
EU-A1868	1105	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Gln	A	A	Lys[Z14CO ₂]	W	L	L	Q	T	#
EU-A1869	1106	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Gln	A	A	Lys[Z16CO ₂]	W	L	L	Q	T	#
EU-A1870	1107	H	Alb	Q	G	T	F	T	S	D	E*	S	K	Y	K*	D	S	Gln	A	A	Lys[Z18CO ₂]	W	L	L	Q	T	#

The substitution on Lys in the peptide sequence is represented by a letter designation of the surfactant-derived X (Z means glucoside-derived; Me means melibioside-derived; M means maltoside-derived) with a number designating the alkyl substitution. Thus, for example, Lys(Me12) is Lys(N-epsilon linked 1-dodecyl beta-D-melibiosuronyl) and Lys(Z12) is Lys(N-epsilon linked 1-dodecyl beta-D-glucuronyl).

Z18CO₂ denotes 1-(17-carboxyheptadecyl) beta-D-glucuronyl.

OH is carboxyl and # is amide.

LysS1(Me12) is lysine with an epsilon linked spacer, for S1 that is alpha linked lysine with epsilon linked Me12.

S2 is a gamma-Glu linker like in liraglutide, S3 is a gamma-glu-gamma glu. PEGa is amino-dPEG4-OH, PEGb, dPEG8-OH.

PEGc is corresponding amido dPEG4-NH2 and PEGd is amido dPEG8-NH2.

The pair of amino acids E*, K* separated by 4 residues denotes a side chain lactam linkage formed between the side chain functional groups on these amino acids.

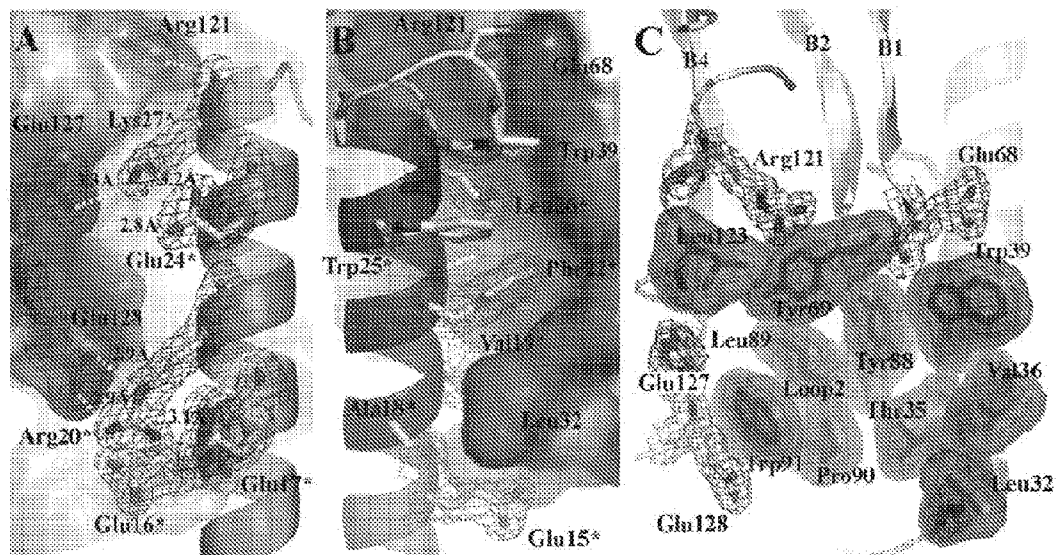


FIG. 5

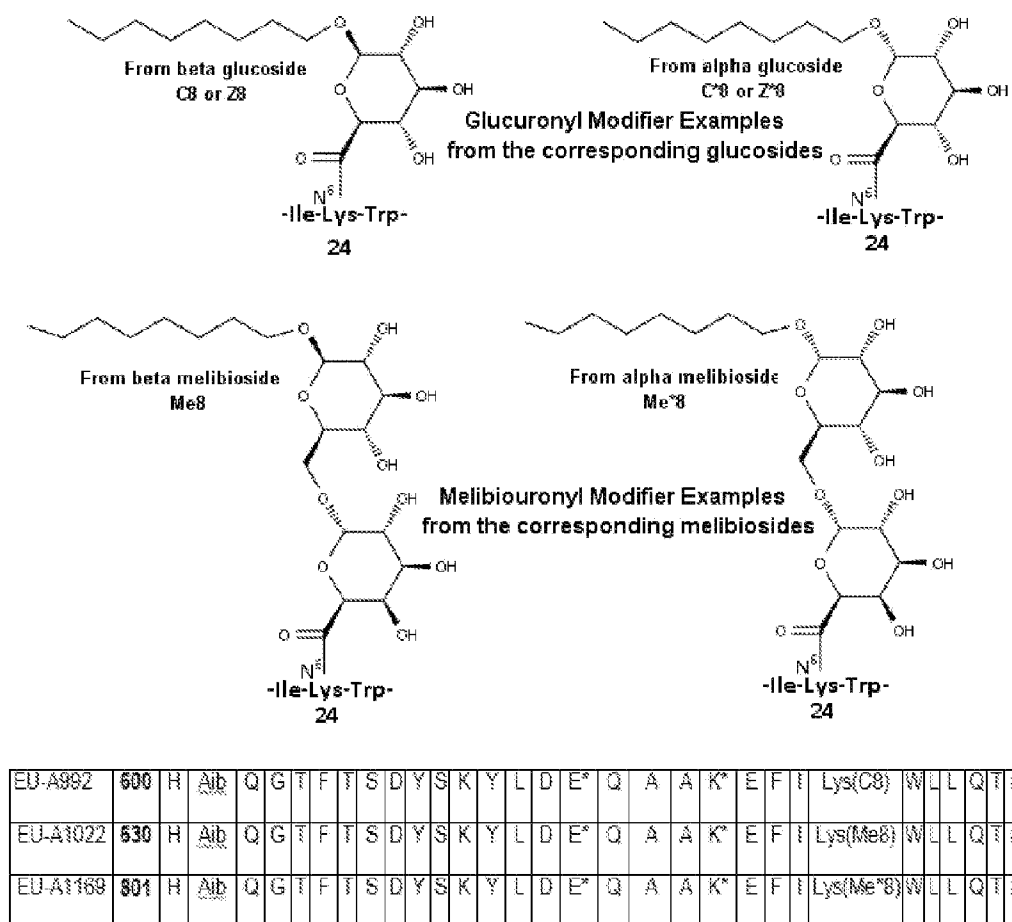


FIG. 6

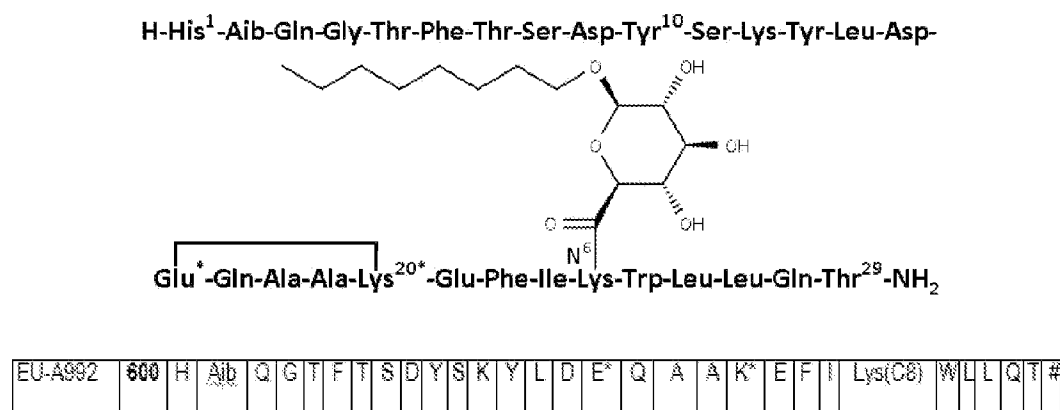
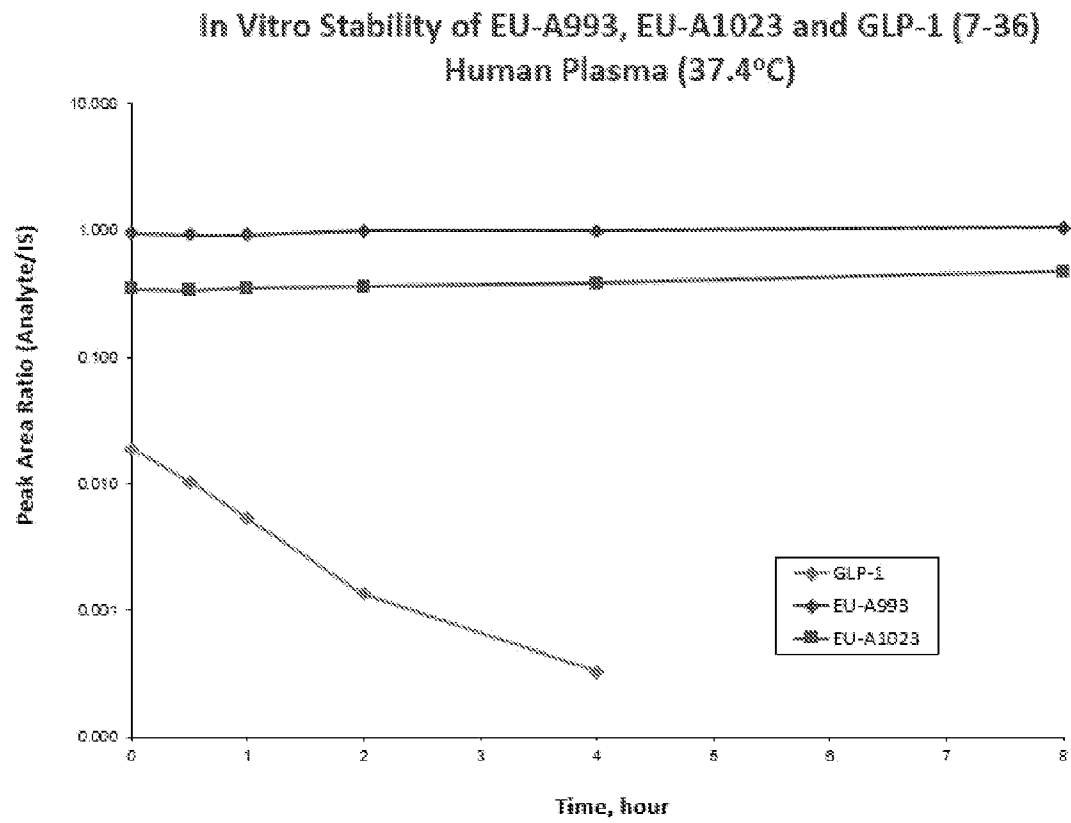


FIG. 7

**FIG. 8**

Blood Glucose Response - SC Injections 0, 7hr
EU-A992, -1167, -1168 in 0.2% BSA/saline pH 7.4
female db/db mice

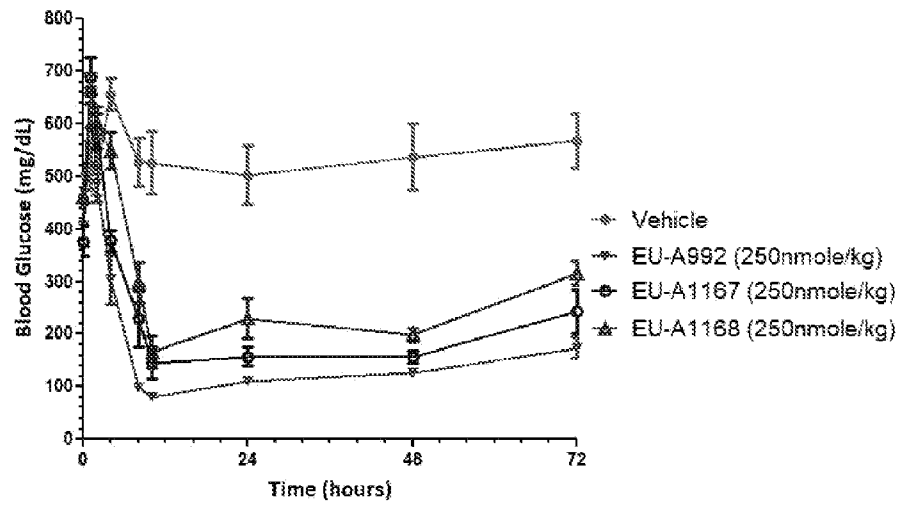


FIG. 9

% Day 0 Body Weight Change on Treatment
C57Bl/6J DIO mice JAX SP-M06

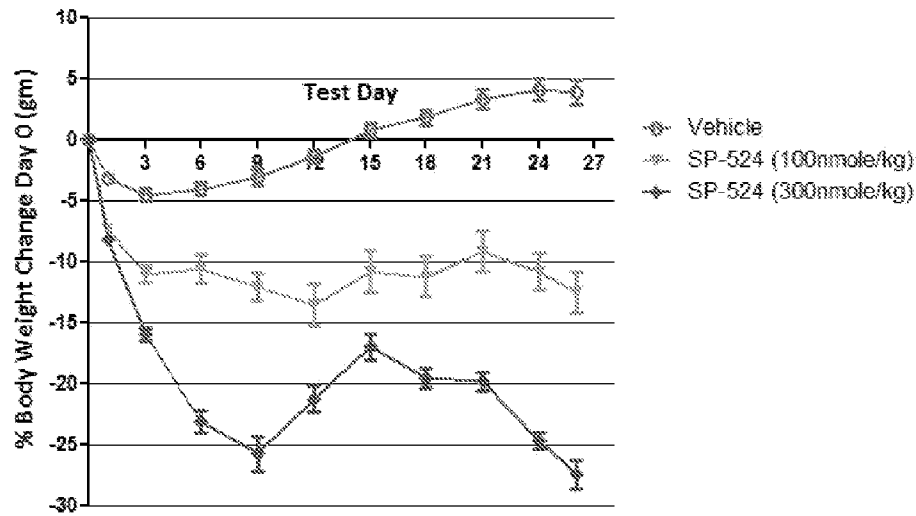


FIG. 10

Delta Fat Mass
C57Bl/6J DIO JAX SP-M06

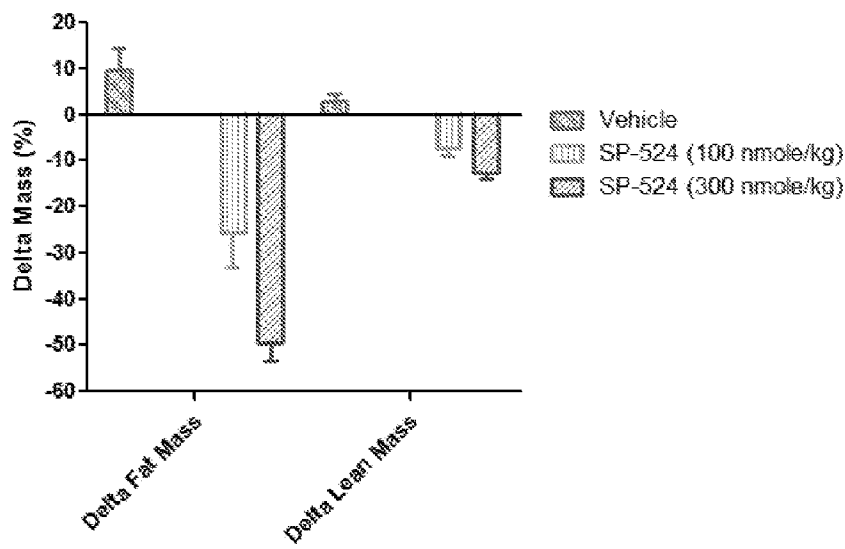
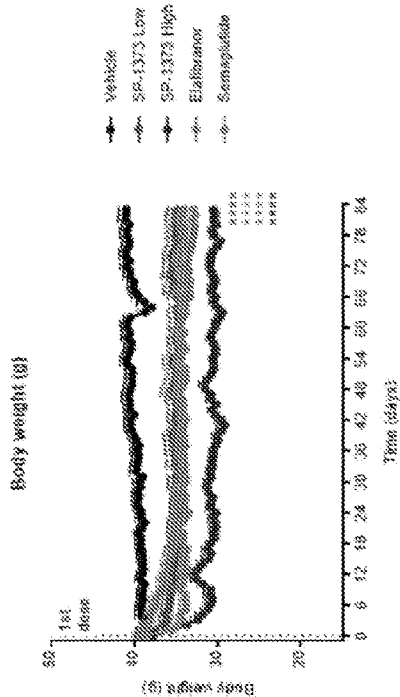


FIG. 11

FIG. 12A

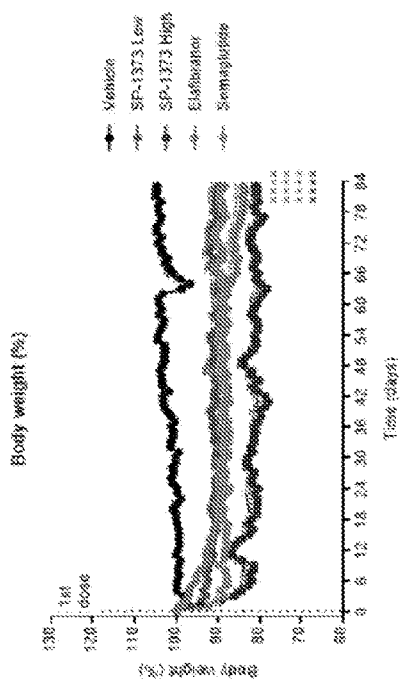


Absolute body weight recorded on a daily basis.
Data expressed as mean $\pm$ SEM (n = 11-12).

***p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 12B

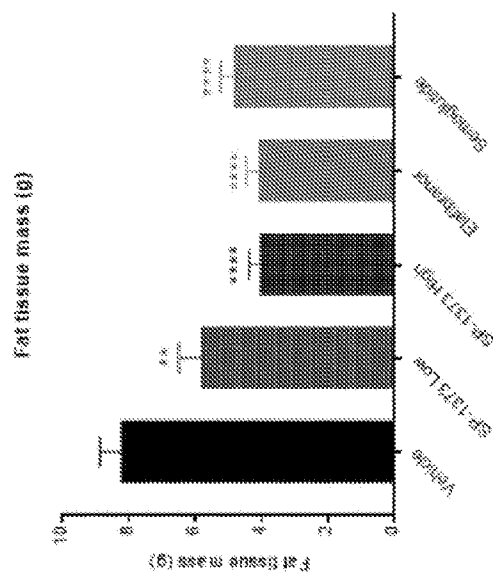


Relative body weight change from baseline (baseline day 0 = 100%).
Data expressed as mean $\pm$ SEM (n = 11-12).

***p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 13A



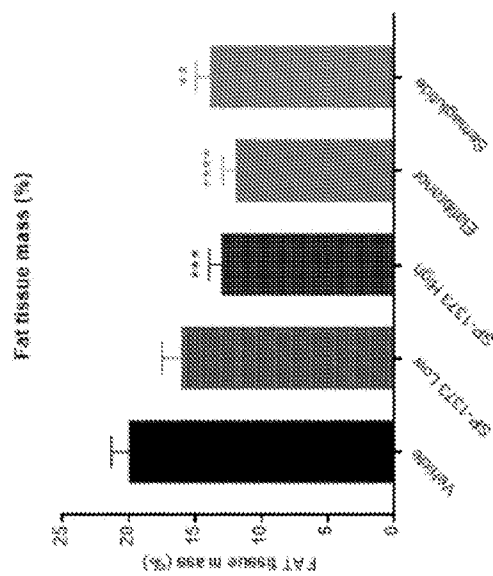
Absolute whole body fat tissue mass.

Data expressed as mean $\pm$ SEM (n = 11-12).

p<0.01, **p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 13B



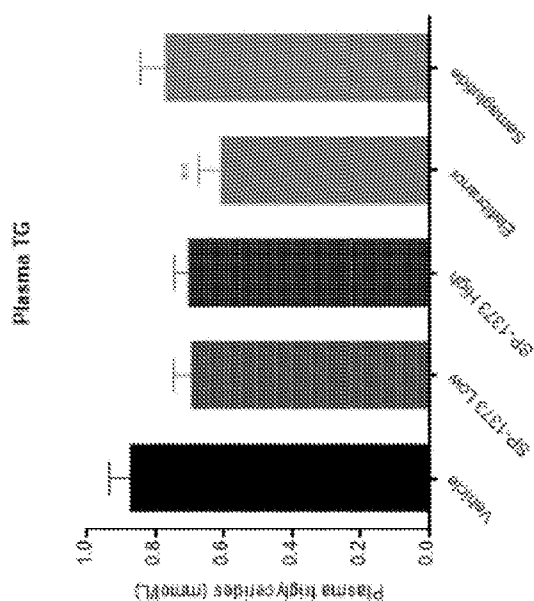
Whole body fat mass relative to body weight.

Data expressed as mean $\pm$ SEM (n = 11-12).

p<0.01, *p<0.001, ****p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 14A



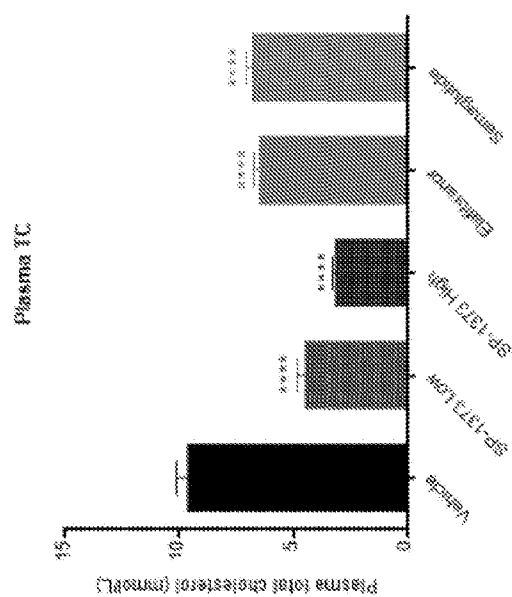
Plasma triglycerides (TG).

Data expressed as mean $\pm$ SEM (n = 11-12).

**p < 0.01 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 14B



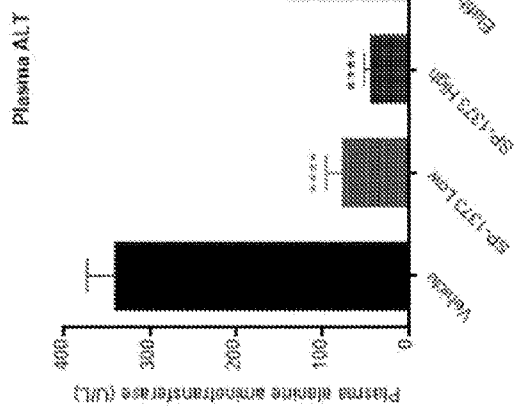
Plasma total cholesterol (TC).

Data expressed as mean $\pm$ SEM (n = 11-12).

****p < 0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 15A



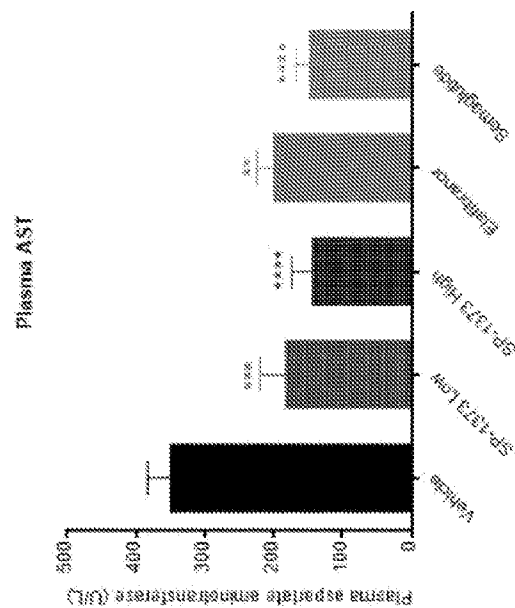
Plasma alanine transaminase (ALT).

Data expressed as mean $\pm$ SEM (n = 11-12).

****p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 15B

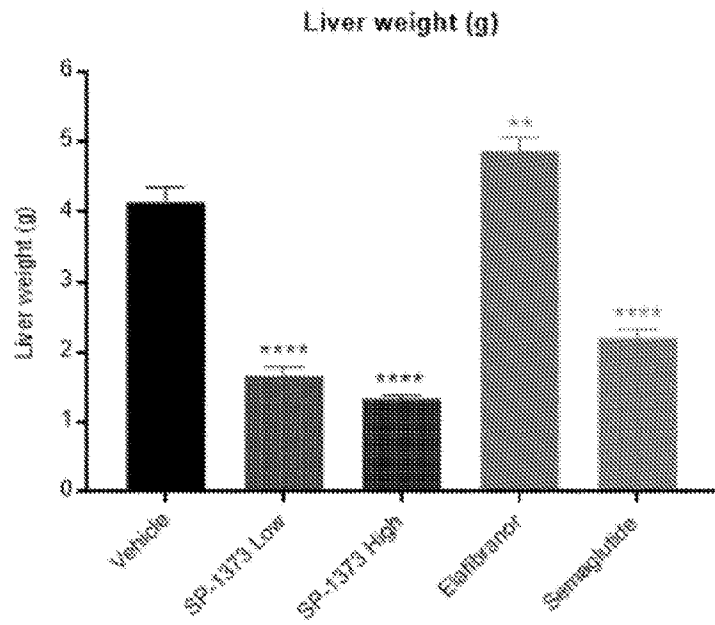


Plasma aspartate transaminase (AST).

Data expressed as mean $\pm$ SEM (n = 11-12).

p<0.01, *p<0.001, ****p<0.0001 vs. Vehicle.

One-way ANOVA with Dunnett's Multiple Comparison Test.

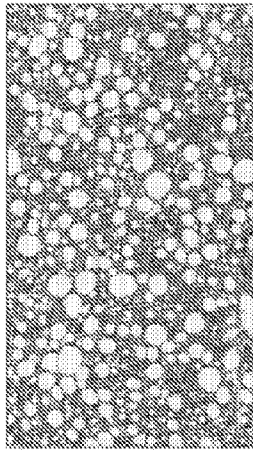


Liver weight.
Data expressed as mean + SEM (n=11-12).
P<0.01, **P<0.0001 vs. Vehicle. One-way ANOVA with
Dunnett's Multiple Comparison Test.

FIG. 16

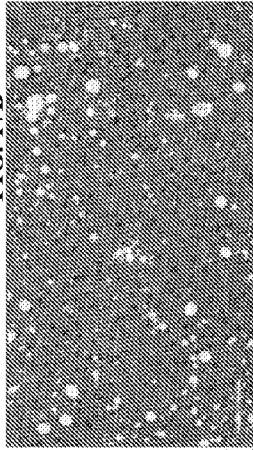
Vehicle #22416

FIG. 17A



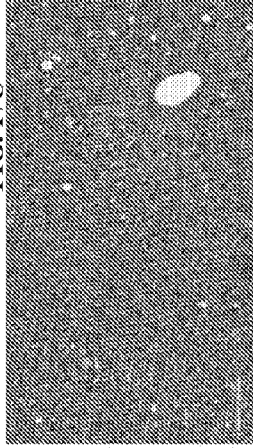
SP-1373 Low #32561

FIG. 17B



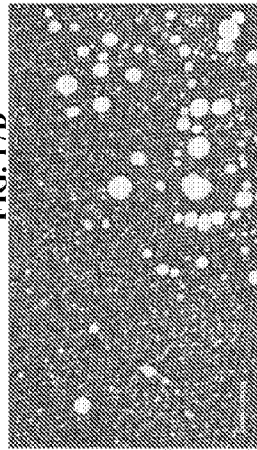
SP-1373 High #32567

FIG. 17C



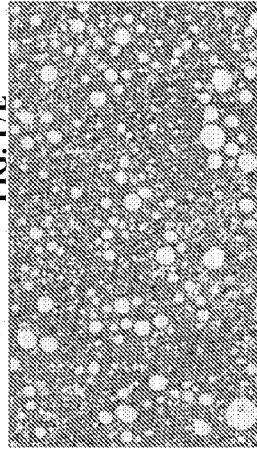
Elaitracor #32537

FIG. 17D



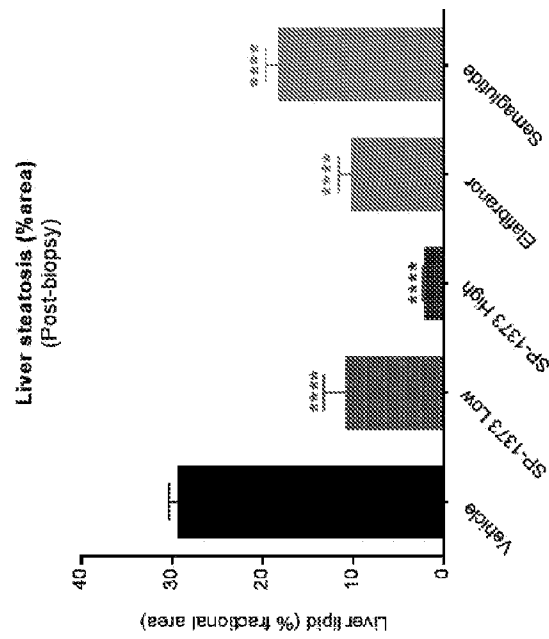
Semmelutide #32543

FIG. 17E



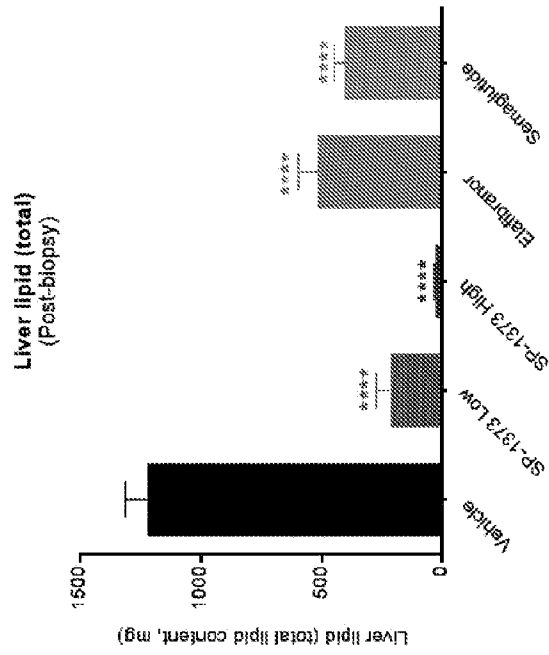
Representative images of liver morphology at the end of treatment period (magnification 20x, scale bar = 100 μ m).

FIG. 18A



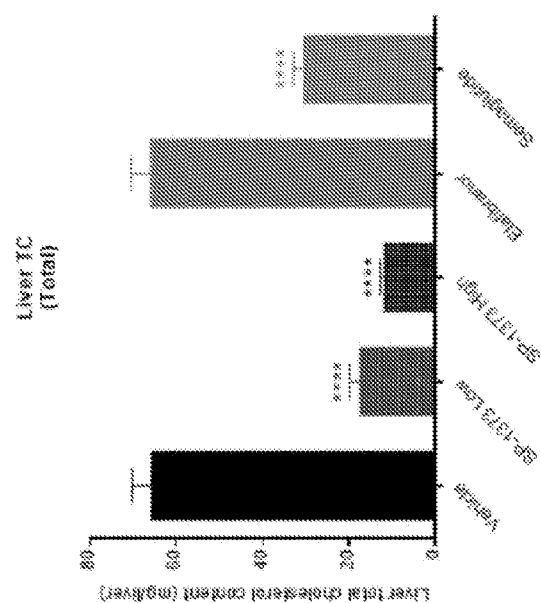
Terminal relative steatosis quantification as determined by morphometry. Data expressed as mean $\pm$ SEM (n = 11-12 per group). ****p < 0.0001 vs. Vehicle. One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 18B



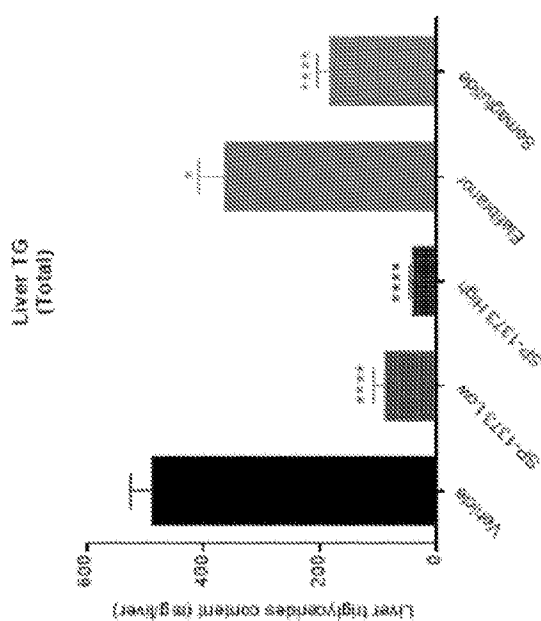
Terminal total liver steatosis quantification as determined by morphometry. Data expressed as mean $\pm$ SEM (n = 11-12 per group). ****p < 0.0001 vs. Vehicle. One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 19A

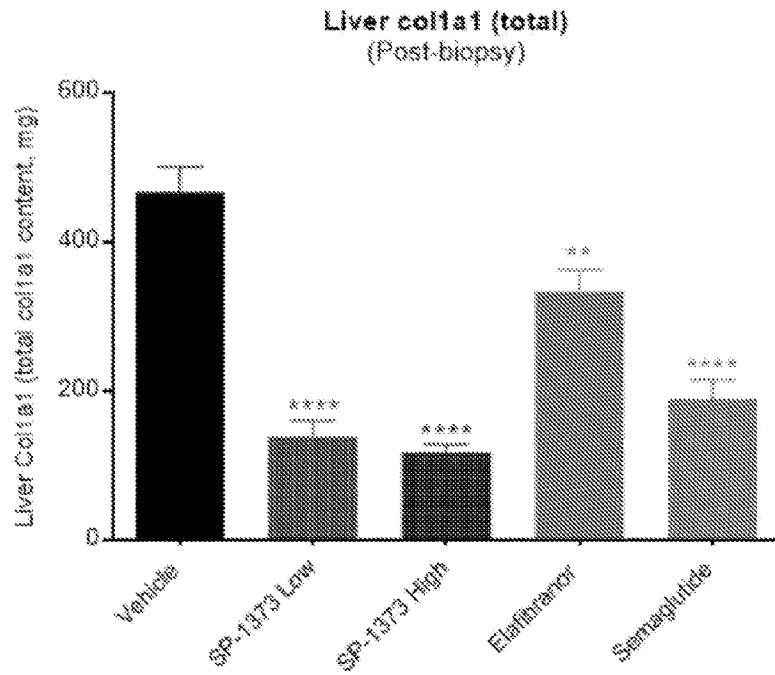


Total liver total cholesterol (TC).
 Data expressed as mean + SEM (n = 11-12).
 ***p<0.0001 vs. Vehicle, One-way ANOVA with Dunnett's
 Multiple Comparison Test.

FIG. 19B

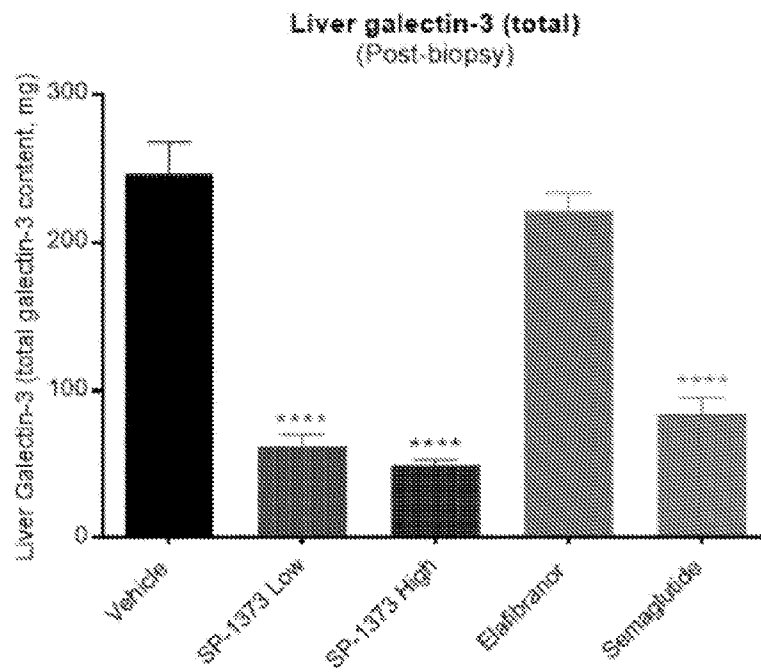


Total liver triglycerides (TG).
 Data expressed as mean + SEM (n = 11-12).
 *p<0.05, ***p<0.0001 vs. Vehicle, One-way ANOVA with
 Dunnett's Multiple Comparison Test.



Terminal total type I Collagen (Col1a1) quantification as determined by morphometry. Data expressed as mean $\pm$ SEM (n = 11-12 per group). **P < 0.01, ****P < 0.0001 vs. Vehicle. One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 20



Terminal total Galectin-3 (Gal-3) quantification as determined by morphometry. Data expressed as mean + SEM (n = 11-12 per group). ****P<0.0001 vs. Vehicle. One-way ANOVA with Dunnett's Multiple Comparison Test.

FIG. 21

FIG. 22A

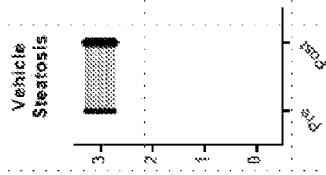


FIG. 22B

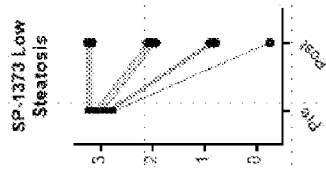


FIG. 22C

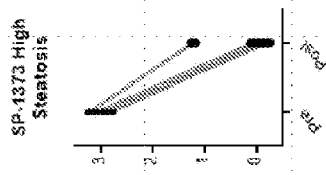


FIG. 22D

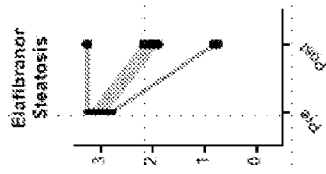


FIG. 22E

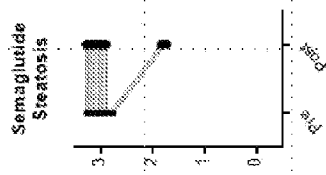


FIG. 23A

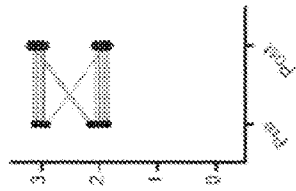
Vehicle
Inflammation

FIG. 23B

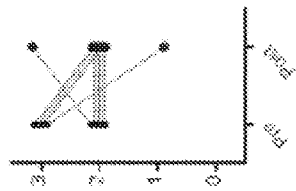
SP-1373 Low
Inflammation

FIG. 23C

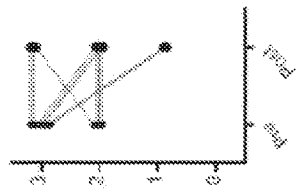
SP-1373 High
Inflammation

FIG. 23D

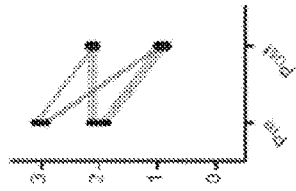
Elaftrator
Inflammation

FIG. 23E

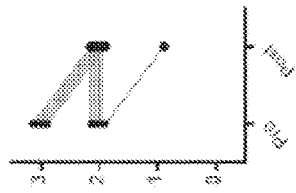
Semaglutide
Inflammation

FIG. 24A

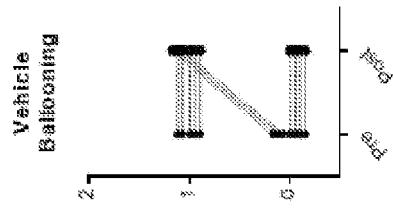


FIG. 24B

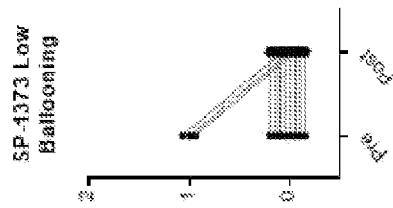


FIG. 24C

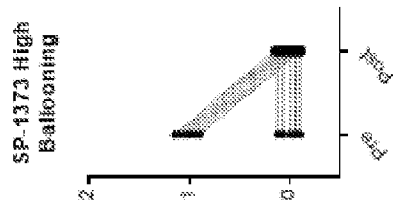


FIG. 24D

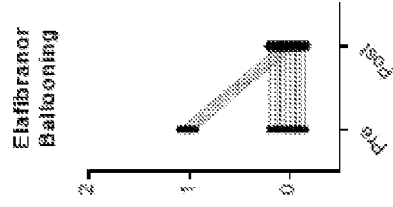


FIG. 24E

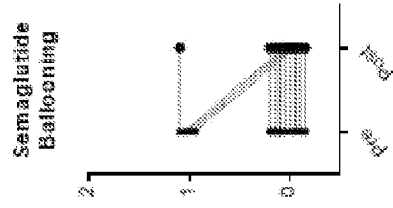


FIG. 25A

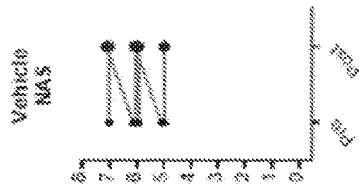


FIG. 25B

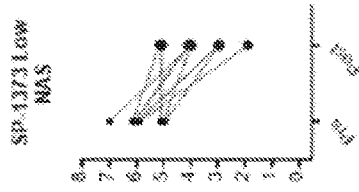


FIG. 25C

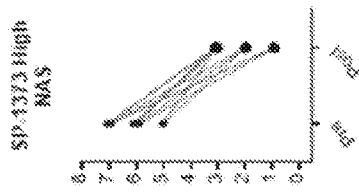


FIG. 25D

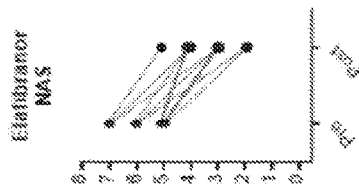


FIG. 25E

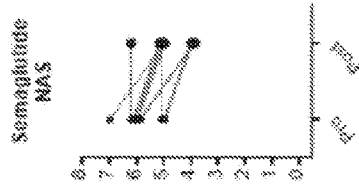


FIG. 26A

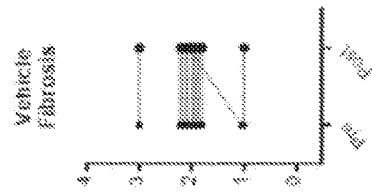


FIG. 26B

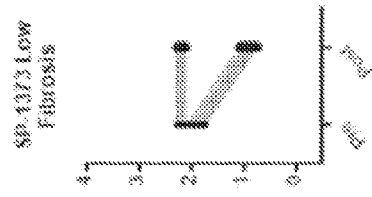


FIG. 26C

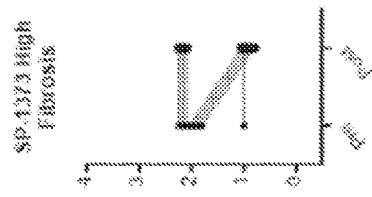


FIG. 26D

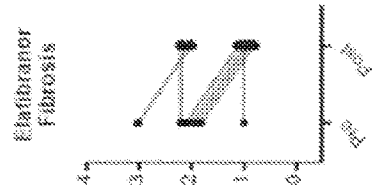


FIG. 26E

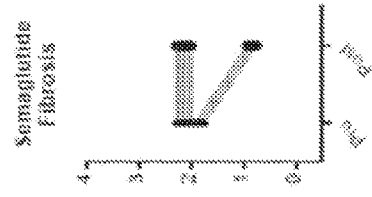


FIG. 27A

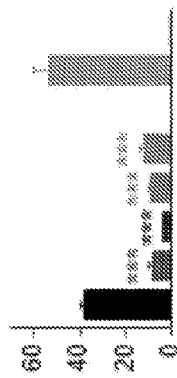
Collagen, type I, alpha 1
(COL1A1)

FIG. 27B

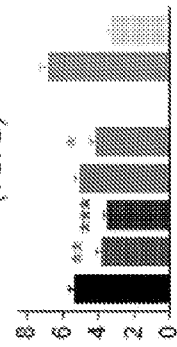
Transforming growth
factor, beta 1
(TCFB)

FIG. 27C

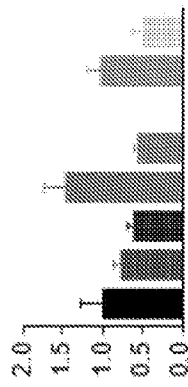
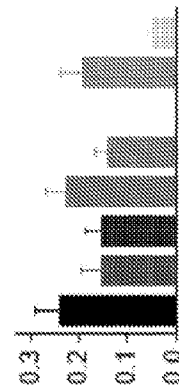
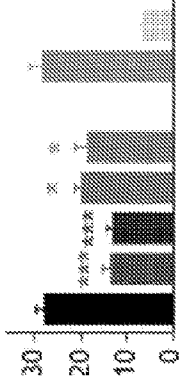
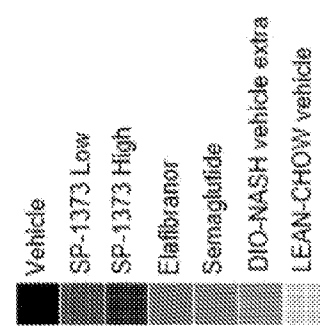
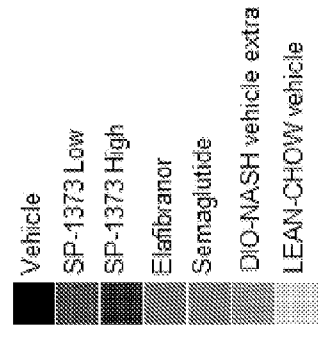
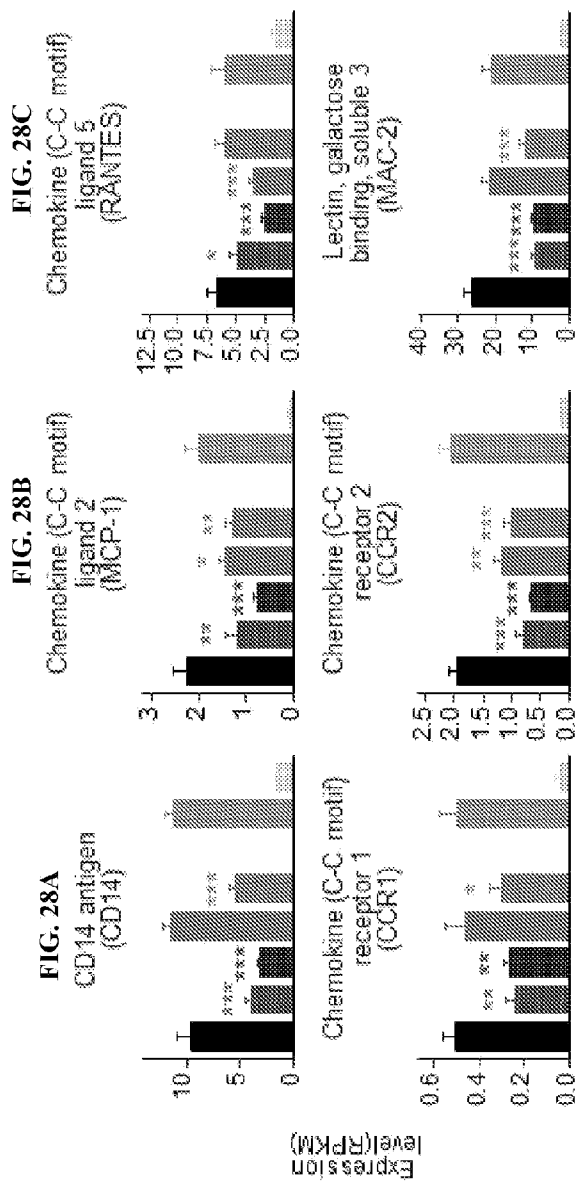
Interleukin 1 beta
(IL-1B)Expression
level (RPKM)Tumor necrosis factor
(TNFA)Chemokine (C-C motif)
ligand 2
(MCP-1)CD68 antigen
(CD68)

FIG. 27D

FIG. 27E

FIG. 27F





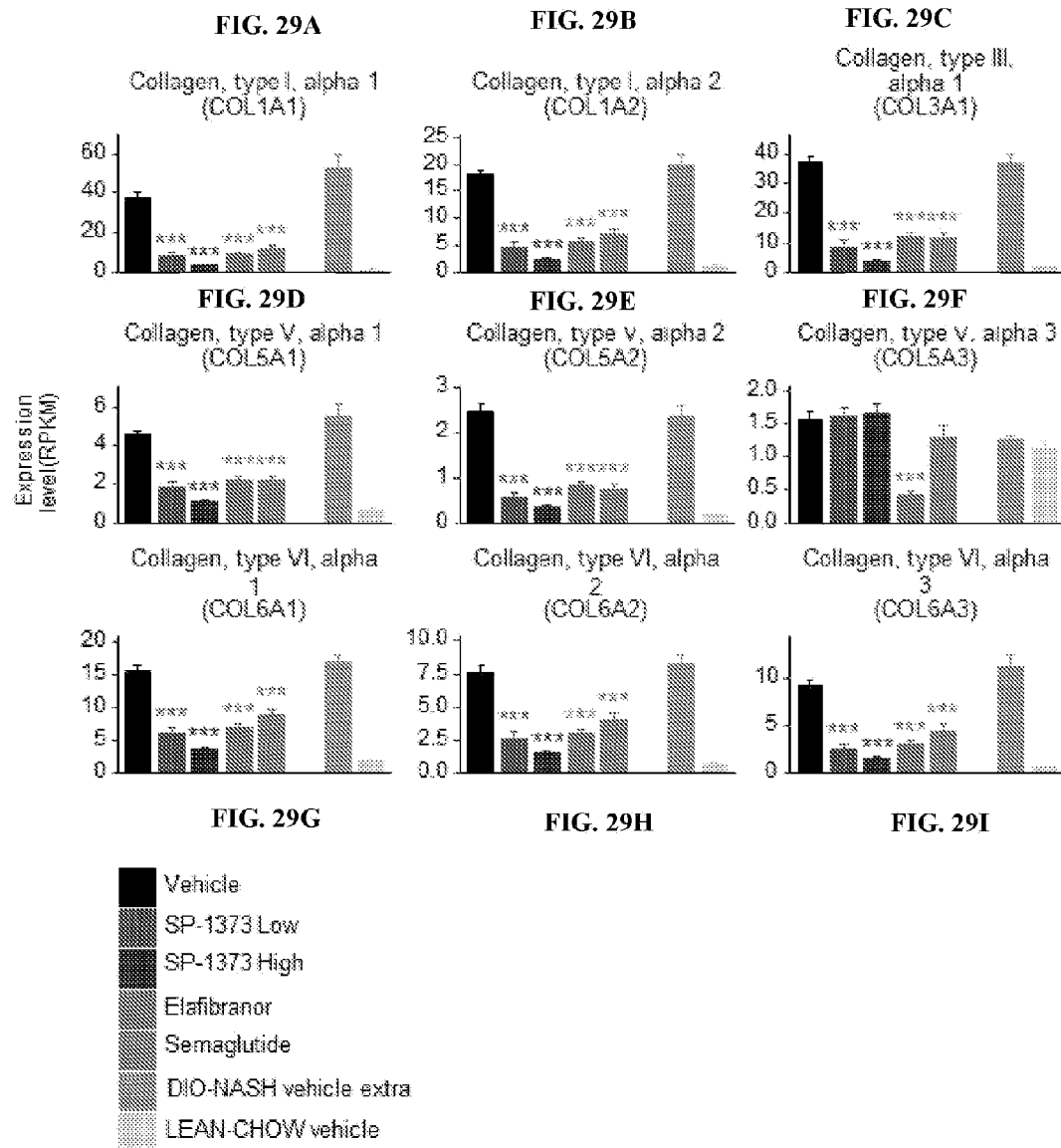


FIG. 30A

FIG. 30B

FIG. 30C

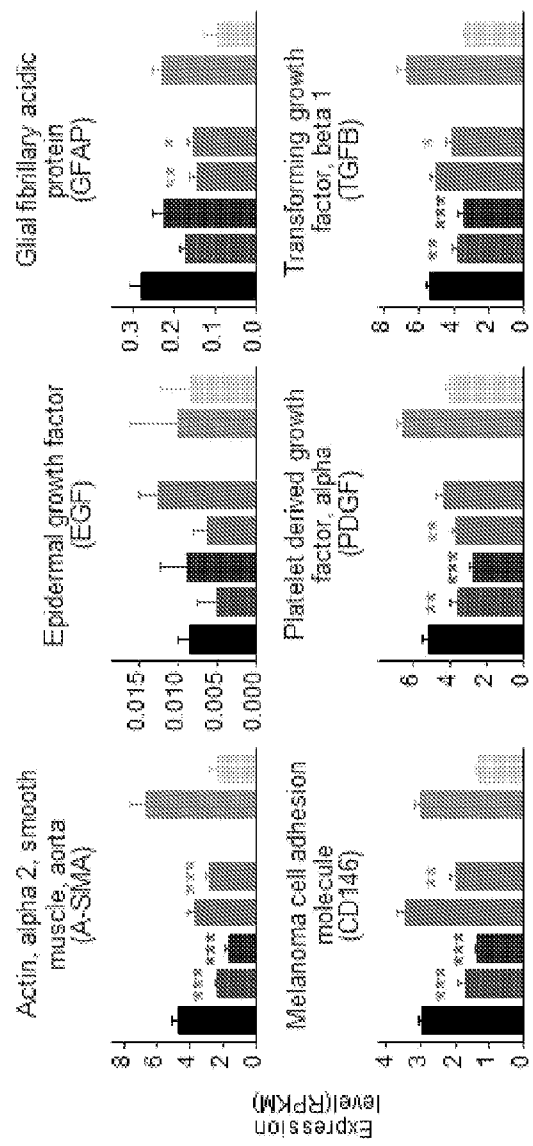


FIG. 30D

FIG. 30E

FIG. 30F

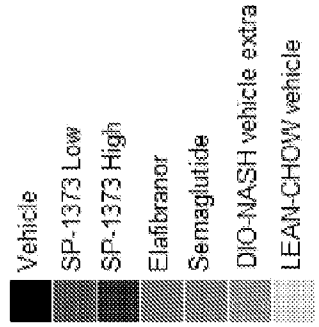
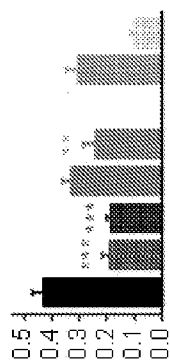
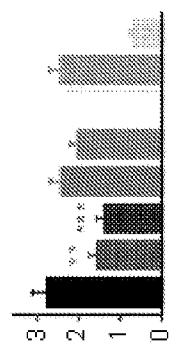


FIG. 31AAbsent in melanoma 2
(AIM2)**FIG. 31B**Caspase 1
(CASP1)**FIG. 31C**NLR family, pyrin domain
containing 3
(NLRP3)Interleukin 1 alpha
(IL-1A)**FIG. 31D****FIG. 31E**NLR family, CARD domain
containing 4
(IPAF)**FIG. 31F**NLR family, pyrin domain
containing 1B
(NLRP1B)