Exendin-4 Peptide Analogues

Description

FIELD OF THE INVENTION

The present invention relates to exendin-4 peptide analogues and their medical use, for example in the treatment of disorders of the metabolic syndrome, including diabetes and obesity, as well as reduction of excess food intake.

BACKGROUND OF THE INVENTION

Exendin-4 is a 39 amino acid peptide which is produced by the salivary glands of the Gila monster (Heloderma suspectum) (Eng, J. et al., J. Biol. Chem., 265: 20259-62,1990; Ng,J. et al., J. Biol. Chem., 267:7402-05,1992). Like GLP-1, exendin-4 is an activator of the GLP-1 receptor. Unlike GLP-1, exendin-4 has a prolonged glucose-lowering action in vivo (Eng J., Diabetes, 45(Suppl 2):152A (abstract 554), 1996).

The amino acid sequence of exendin-4 is shown as SEQ ID NO: 1:

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH2

The amino acid sequence of GLP-1 is shown as SEQ ID NO: 2:

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

Its actions include stimulation of insulin synthesis and secretion, inhibition of glucagon secretion, and inhibition of food intake. GLP-1 has been shown to reduce hyperglycemia in diabetics.

There is also evidence that GLP-1 and exendin-4 may reduce food intake and promote weight loss (Buse J.B. et al., Lancet, 374:39-47,2009). This effect would be beneficial

not only for diabetics but also for patients suffering from obesity. Such patients with obesity have a higher risk of diabetes, hypertension, hyperlipidemia, cardiovascular disease, and musculoskeletal diseases.

Glucagon is a 29-amino acid peptide which is released into the bloodstream when circulating glucose is low. Glucagon has the amino acid sequence as shown in SEQ ID NO: 3:

HSQGTFTSDYSKYLDSRRAQDFVQWLMNT

During hypoglycemia, when blood glucose levels drop below normal, glucagon signals the liver to break down glycogen and release glucose, causing blood glucose levels to rise towards a normal level. Hypoglycemia is a common side effect of insulin therapy in patients with hyperglycemia (elevated blood glucose levels) due to diabetes. Thus, glucagon's most recognized role in glucose regulation is to counteract the action of insulin and maintain blood glucose levels.

Other peptides which bind and activate both the glucagon and the GLP-1 receptor (Hjort et al. Journal of Biological Chemistry, 269, 30121-30124, 1994) and suppress body weight gain and reduce food intake are described in WO 2011/075393, WO 2011/006497, WO 2011/152181, and WO 2011/152182, the contents of which are herein incorporated by reference.

The use of exendin-4 agonists has been proposed for the treatment of diabetes mellitus, reduce of gastric motility, delay of gastric emptying and the prevention of hyperglycemia (U.S. Patent No. 5,424,286, U.S. Patent No. 6,858,576, W098/05351). The use of exendin-4 agonists for reducing food intake is described in WO98/30231, the contents of which are herein incorporated by reference.

Exendin-4 analogues have been described in WO99/43708, W09/035540, the contents of which are herein incorporated by reference.

BRIEF SUMMARY OF THE INVENTION

The invention provides a peptidic compound having the formula (I):

R1 - Z - R2 (I)

wherein Z is a peptide moiety having the formula (II)

X0m-X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-X14-X15-X16-X17-X18-X19-X20-X21-Phe-Ile-Glu-Trp-Leu-Lys-X28-X29-Gly-Pro-Ser-Ser-Gly-X35-Pro-Pro-Pro-X39-X40n (II)

X0 is absent or represents an amino acid residue selected from Gly,
X1 represents an amino acid residue selected from His, D-His, and Des-amino-His,
X2 represents an amino acid residue selected from Gly, Ser or functionalized-Ser, e.g. Ser (OCH3), D-Ser or functionalized D-Ser, e.g. D-Ser (OCH3), Aib, Ala, or D-Ala, wherein Ser may be functionalized in that the H of the OH side chain group is substituted by C1-4 alkyl, e.g. methyl,
X3 represents an amino acid residue selected from Glu, Gln, His and α-amino-functionalized Gln, e.g. Gln (α-NHCH3), wherein Gln may be functionalized in that an H of the α-NH2 group is substituted by C1-4 alkyl, e.g. methyl,
X14 represents an amino acid residue selected from Met, Phe, Aib, Nle, or Cycloalkyl-Ala, e.g. Cyclohexyl (Chx)-Ala, Cyclopentyl (Cp)-Ala or Cyclobutyl (Cb)-Ala, wherein Ala may be functionalized in that one H of the CH3 side chain group is substituted by C3-8 cycloalkyl,
X15 represents an amino acid residue selected from Glu or Asp,
X16 represents an amino acid residue selected from Ser, Glu and Lys,
X17 represents an amino acid residue selected from Arg, Glu, Gln, Aib and Lys,
X18 represents an amino acid residue selected from Arg, Ala and Lys,
X19 represents an amino acid residue selected from Ala and Val,
X20 represents an amino acid residue selected from Gln, Arg, Lys, His and Aib,

X21 represents an amino acid residue selected from Asp, Leu and Glu,
X28 represents an amino acid residue selected from Asn, Arg, Lys, Aib, Ser, Glu and Ala,
X29 represents an amino acid residue selected from Gly, Ala, D-Ala or Thr, and
X35 represents an amino acid residue selected from Ala, Glu, Arg and Lys,
X39 represents an amino acid residue selected from Ser,
an amino acid residue having a side chain with an -NH2 group, particularly Lys, Orn, Dab or Dap, wherein the -NH2 side chain group is optionally functionalized and
an amino acid residue having a side chain with an -SH group, particularly Cys, wherein the -SH side chain group is optionally functionalized, and
X40 represents an amino acid residue selected from an amino acid residue having a side chain with an -NH2 group, particularly Lys, Orn, Dab or Dap, wherein the -NH2 side chain group is optionally functionalized and
an amino acid residue having a side chain with an -SH group, particularly Cys, wherein the -SH side chain group is optionally functionalized,
R1 represents the N-terminal group of the peptidic compound and is selected from NH2 or mono- or bisfunctionalized NH2,
R2 represents the C-terminal group of the peptidic compound and is selected from
(i) OH or functionalized OH and
(ii) NH2 or mono- or bisfunctionalized NH2,

m and n are in each case independently selected from 0 or 1
or a salt or solvate thereof
with the proviso that Exendin-4 (SEQ ID NO: 1) is not encompassed.

The compounds of the invention are typically GLP-1 and/or glucagon receptor agonists, preferably dual GLP-1 and glucagon receptor agonists as determined by the observation that they are capable of stimulating intracellular cAMP formation upon binding at least one of the receptors for GLP-1, as well as glucagon. The compounds may e.g. exhibit an EC50 value (determined by an in vitro cellular assay as described

in the Examples) for the GLP1 receptor, which is less than 5 nM, preferably less than 1 nM, more preferably less than 500 pM and even more preferably of less than 200 pM. Further, the compounds may exhibit an EC50 value (as determined according to the Examples) for the glucagon receptor which is less than 5 nM, preferably less than 1 nM, more preferably less than 500 pM and even more preferably less than 200 pM. Furthermore, the compounds may exhibit an EC50 value for the GLP1 receptor and an EC50 value for the glucagon receptor, which is less than 5 nM, preferably less than 1 nM, more preferably less than 500 pM, and even more preferably less than 200 pM.

Further, the compounds of the invention preferably have a high solubility at pH 4.5 and/or at pH 7.4 at 25ºC (determined as described in the Examples), preferably at least 0.5 mg/ml and more preferably at least 1.0 mg/ml.

Furthermore, the compounds of the invention preferably have a high stability when stored for 7 days at 25ºC (determined by chromatographic analyses as described in the Examples), preferably a remaining peptide amount of at least 80%, more preferably of at least 85%, even more preferably at least 90% and even more preferably of at least 95%.

Preferably, the compounds of the present invention comprise a peptide moiety Z (II) which is a linear sequence of 39-41 amino carboxylic acids, particularly α-amino carboxylic acids linked by peptide, i.e. carboxamide bonds.

The peptide moiety Z has variable positions X0, X1, X2, X3, X14, X15, X16, X17, X18, X19, X20, X21, X28, X29, X35, X39 and X40, which in each case independently represent an amino acid residue as described above, with the proviso that X0 and/or X40 may be absent. The amino acid residue at the variable positions is preferably an α-amino carboxylic acid residue having a side chain which may be non-functionalized or functionalized. The amino acid residues at non-variable positions are amino carboxylic acids, particularly L-amino carboxylic acids with a side chain corresponding to the indicated meaning in formula (II).

At least one amino acid residue at the variable positions differs from the corresponding amino acid residue in Exendin-4 (SEQ ID NO. 1). The difference may constitute the presence of a different side chain, e.g. Ser or functionalized Ser instead of Gly or the presence of a functionalized side chain instead of a non-functionalized side chain, e.g. N-functionalized Lys instead of Lys.

R1 represents the N-terminal group and is selected from NH2 or mono- or bisfunctionalized NH2. The term "mono- or bisfunctionalized NH2" for R1 means that at least one H of the NH2 group is substituted by a different moiety, e.g. an organic moiety of up to 20 or up to 30 carbon atoms and optionally comprising heteroatoms, such as halo (F, Cl, Br, or I), N, O, S and/or P, or an organic polymer, particularly a hydrophilic organic polymer. Preferred polymers are (poly)alkylene oxide-based polymers comprising up to 2000 alkylene oxide groups, particularly (poly)ethylene oxide-based polymers. Examples of functional groups for R1 are alkyl, formyl, (poly)alkoxyalkyl, -C(O)-alkyl or -C(O)-(poly)alkoxyalkyl, wherein each alkoxy or alkyl may comprise 1-12, preferably 1-8, and more preferably 1-5 C-atoms, and may be substituted by halo and/or OH, and wherein a (poly)alkoxyalkyl group may comprise up to 2000 alkylene oxide groups, particularly CH2-CH2-O groups. Specific examples of functional groups are methyl, ethyl, formyl, acetyl, trifluoroacetyl or benzoyl.

R2 represents the C-terminal group of the peptidic compound and is selected from OH or functionalized OH and NH2 or mono- or bisfunctionalized NH2. The terms "functionalized OH" and "mono- or bisfunctionalized NH2" for R2 mean that the H of the OH group is substituted by a different moiety, e.g. an organic moiety or that at least one H of the NH2 group is substituted by a different moiety, e.g. an organic moiety, e.g. an organic moiety of up to 30 or up to 40 carbon atoms and optionally comprising heteroatoms, such as halo (F, Cl, Br, or I), N, O, S and/or P, or an organic polymer, particularly a hydrophilic organic polymer. Preferred polymers are (poly)alkylene oxide-based polymers comprising up to 2000 alkylene oxide groups, particularly (poly)ethylene oxide-based polymers. Examples of functional groups for R2 are moieties of the formula R3-R4, wherein R3 is alkylene or (poly)alkoxy-alkylene, wherein each alkoxy or alkylene may comprise 1-12, preferably 1-8 and more

preferably 1-5 C-atoms and may be substituted by halo, and/or OH, wherein a (poly)alkoxy-alkylene may comprise up to 2000 alkylene oxide groups, particularly CH2-CH2-O groups, and R4 is H, NH2, NH(C1-4 alkyl), N(C1-C4 alkyl), N(C1-4 alkyl)2, OH, O(C1-4 alkyl), SH, S(C1-4 alkyl). Alternatively, an amino group may also be functionalized by OH or NH2. Specific examples of functional groups are 2-mercapto-ethyl, 2-tert-butyl sulfanyl-ethyl, 5-hydroxy-pentyl, 4-amino-butyl, 5-amino-pentyl, or 3-{2-[2-(5-amino-pentyloxy)-ethoxy]-ethoxy}-propyl.

In an embodiment, the N-terminal group R1 is NH2. In a further embodiment, the C-terminal group R2 is NH2. In still a further embodiment the N-terminal group R1 and the C-terminal group R2 are NH2.

In a further embodiment 1, 2 or 3 amino acids residues selected from X2, X3, X19 are amino acid residues which differ from corresponding amino acid residues in Exendin-4 (SEQ ID NO: 1).

In a still further embodiment, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues selected from X1, X2, X3, X14, X15, X16, X17, X18, X19, X20, X21, X28, X29, X35 and X39 are amino acid residues which differ from corresponding amino acid residues in Exendin-4 (SEQ ID NO: 1).

For example, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 amino acid residues selected from X1, X2, X3, X14, X15, X16, X17, X18, X19, X20, X21, X28, X29, X35 and X39 may be amino acid residues which differ from the corresponding amino acid residues in Exendin-4 (SEQ ID NO: 1).

In an embodiment of the invention X0 is absent. In a further embodiment, X40 is absent. In still a further embodiment, X0 is absent and X40 is present. In a still further embodiment, X0 is present and X40 is absent. In still a further embodiment, X0 is present and X40 is present.

If X40 is absent, X39 preferably represents Ser or an amino acid residue with a non-functionalized or functionalized -NH2 side chain group, such as Lys or functionalized Lys, Orn, functionalized Orn, Dab, functionalized Dab, Dap, or functionalized Dap, more preferably Lys or functionalized Lys and even more preferably functionalized Lys.

If X40 is present, X39 preferably represents Ser. If X40 is present, it preferably represents an amino acid residue with a non-functionalized or functionalized -NH2 side chain group or an amino acid residue with a functionalized -SH side chain group, such as Lys or functionalized Lys, Orn, functionalized Orn, Dab, functionalized Dab, Dap, functionalized Dap, or functionalized Cys, more preferably Lys or functionalized Lys and even more preferably functionalized Lys.

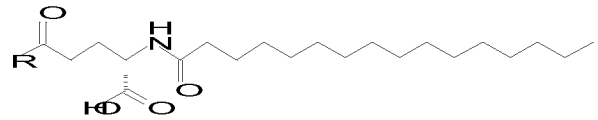
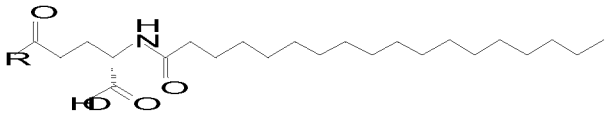
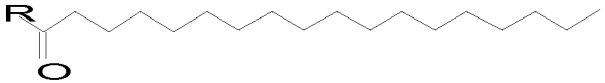
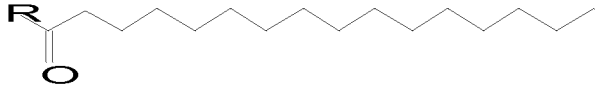
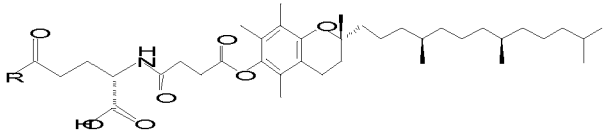
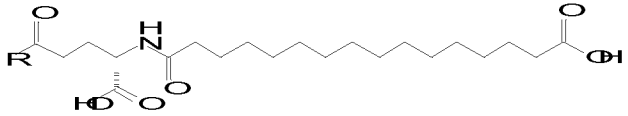
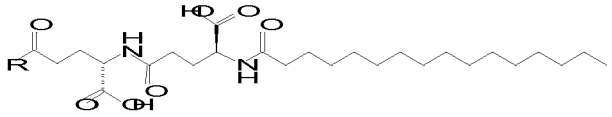
An amino acid residue with an -NH2 side chain group, e.g. Lys, Orn, Dab or Dap, may be functionalized in that at least one H atom of the -NH2 side chain group is replaced by -C(O)-R5, -S(O)2-R5 or R5, preferably by -C(O)-R5, wherein R5 may be (i) a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halo, N, O, S and/or P, and/or (ii) an organic polymer, particularly a hydrophilic organic polymer. Preferred groups R5 may be comprise a lipophilic moiety, e.g. an acyclic linear or branched C12-30 saturated or unsaturated hydrocarbon group, and/or a cyclic saturated, unsaturated or aromatic group, e.g. cyclohexyl, phenyl, biphenyl, chromanyl, phenanthrenyl or naphthyl, wherein the acyclic or cyclic group may be unsubstituted or substituted e.g. by halo, -OH and/or CO2H. The lipophilic moiety may be attached to the -NH2 side chain group by a linker, e.g. a linker comprising one or more, e.g. 2 amino acid linker groups such as γ-aminobutyric acid (γ-Abt), ε-aminohexanoic acid (ε-Ahx), γ-Glu and/or β-Ala. Specific examples of amino acid linker groups are (β-Ala)1-4, (γ-Glu)1-4, (ε-Ahx)1-4, or (γ-Abt)1-4. Still further preferred groups R5 may comprise a C1-4 acyl group, e.g. acetyl. Still further preferred groups R5 may comprise at least one amino acid residue, e.g. γ-Abt, ε-Ahx, γ-Glu and/or β-Ala. Preferred polymers are (poly)alkylene oxide-based polymers, particularly (poly)ethylene oxide-based polymers, e.g. polymers comprising a (CH2-CH2-O)q-R6 group, wherein q is 1-2000 and R6 is H or C1-4 alkyl. Examples are (poly)ethylenglycols having an average weight-based molecular mass from about 1000

up to about 100,000 Da, e.g. about 2000, about 5000, about 20,000, about 40,000 or about 80,000 Da.

An amino acid residue with an -SH side chain, e.g. Cys may be functionalized in that the H atom of the -SH side chain group is replaced by -Y-R7, wherein Y is a bond or a thiol linker group, e.g. a maleimide or acetamide group or thiol and R7 represents a group as defined for R5 above. Preferably R7 is an organic polymer, particularly a (poly)ethyleneoxide-based polymer as defined above.

Specific preferred examples for -C(O)-R5 groups are listed in the following Table 1. Further preferred are stereoisomers, particularly enantiomers of these groups, either S- or R-enantiomers. The term "R" in Table 1 is intended to mean the attachment site of -C(O)-R5 at the peptide back bone, i.e. particularly the ε-amino group of Lys.

Table 1

CHEMISTRY	IUPAC name	alternative name
	(S)-4-Carboxy-4-hexadecanoylamino-butyryl-	γ-Glu(N-α-hexadecanoyl)
	(S)-4-Carboxy-4-octadecanoylamino-butyryl-	γ-Glu(N-α-octadecanoyl)
	octadecanoyl-	N-α-octadecanoyl
	Hexadecanoyl-	N-α-hexadecanoyl
	(S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-	γ-Glu(N-α-tocopheryl-succinyl)
	(S)-4-Carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl-	γ-Glu(N-α-(ω-carboxypentadecanoyl))
	(S)-4-Carboxy-4-((S)-4-carboxy-4-hexadecanoylamino-butyrylamino)-butyryl-	γ-Glu(N-α-(γ-Glu(N-α-hexadecanoyl)))

	(S)-4-Carboxy-4-octadecanoylamino-butyryl-	
	3-(3-Hexadecanoylamino-propionyla-mino)-propionyl-	β-Ala(N-α-(β-Ala(N-α-hexadecanoyl)))
	3-Hexadecanoylamino-propionyl-	β-Ala(N-α-hexadecanoyl)
	6-[(4,4-Diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl-	
	(S)-4-Carboxy-4-[(R)-4-((3R,5S,7R,8R,9R,10S,12S,13R,14R,17R)-3,7,12-trihydroxy-8,10,13-trimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoylamino]-butyryl-	γ-Glu(N-α-cholyl)
	(S)-4-Carboxy-4-[(R)-4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoylamino]-butyryl-	γ-Glu(N-α-lithocholyl)

	(S)-4-Carboxy-4-((9S,10R)-9,10,16-trihydroxy-hexadecanoylamino)-butyryl-	γ-Glu(N-α-aleuritolyl)
	(S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-	γ-Glu(N-α-tocopheryl-succinyl)
	(S)-4-Carboxy-4-((9Z,12Z)-octadeca-9,12-dienoylamino)-butyryl-	γ-Glu(N-α-linoleoyl)
	(S)-4-Carboxy-4-(4-dodecyloxy-benzoylamino)-butyryl-	γ-Glu(N-α-(4-dodecyclobenzoyl))
	(S)-4-Carboxy-4-henicosanoylamino-butyryl-	γ-Glu(N-α-heneicosanoyl)
	(S)-4-Carboxy-4-docosanoylamino-butyryl-	γ-Glu(N-α-behenoyl)
	(S)-4-Carboxy-4-((Z)-nonadec-10-enoylamino)-butyryl-	γ-Glu(N-α-(cis-1-nonadecanoyl))

	(S)-4-Carboxy-4-(4-decyloxy-benzoylamino)-butyryl-	γ-Glu(N-α-(4-n-decycloxybenzoyl))
	(S)-4-Carboxy-4-[(4'-octyloxy-biphenyl-4-carbonyl)-amino]-butyryl-	γ-Glu(N-α-(4'-octyloxy-biphenyl-4-carbonyl))
	(S)-4-Carboxy-4-(12-phenyl-dodecanoylamino)-butyryl-	γ-Glu(N-α-(12-phenyl-dodecanoyl))
	acetyl	acetyl
	4-Hexadecanoylamino-butyryl-	γ-aminobutyroyl(N-γ-hexadecanoyl)
	(S)-4-Carboxy-4-isobutyrylamino-butyryl-	γ-Glu(N-α-propionyl)

	(S)-4-Carboxy-4-tetradecanoylamino-butyryl-	γ-Glu(N-α-tetradecanoyl)
	tetradecanoyl-	N-α-tetradecanoyl
	11-Carboxy-undecanoyl-	N-α-(ω-carboxydodecanoyl)
	11-Benzyloxycarbonyl-undecanoyl	
	(S)-4-Carboxy-4-((S)-4-carboxy-4-tetradecanoylamino-butyrylamino)-butyryl-	γ-Glu(N-α-(γ-Glu(N-α-tetradecanoyl)))
	(S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-	γ-Glu(N-α-(γ-Glu(N-α-octadecanoyl)))

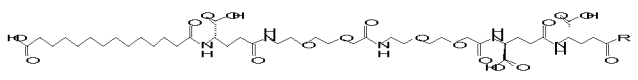
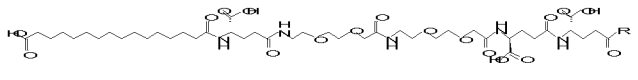
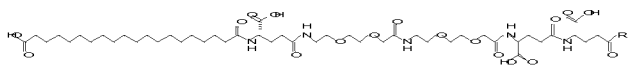
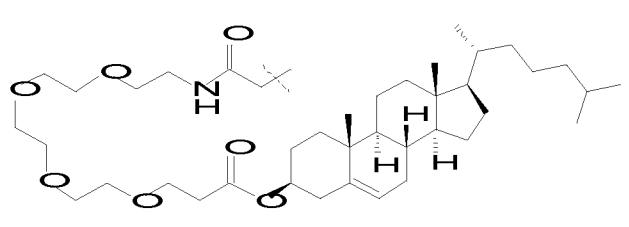
	3-Aminopropionyl-	β-Ala
	3-(3-Amino-propionylamino)-propionyl-	β-Ala-β-Ala
	3-[3-(3-Amino-propionylamino)-propionylamino]-propionyl	β-Ala-β-Ala-β-Ala
	3-{3-[3-(3-Amino-propionylamino)-propionylamino]-propionylamino}-propionyl-	β-Ala-β-Ala-β-Ala-β-Ala
	3-(3-{3-[(R)-2,5,7,8-Tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-propionylamino)-propionyl-	β-Ala-β-Ala(N-α-tocopheryl-succinyl)))
	6-Amino-hexanoyl-	ε-Ahx
	6-(6-Amino-hexanoylamino)-hexanoyl-	ε-Ahx-ε-Ahx

	(2S,3R,4S,5R)-5-Carboxy-2,3,4,5-tetrahydroxy-pentanoyl
	8-Amino-octanoyl
	3-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-propionyl
	3-[2-(2-{2-[2 [2-(2-{2-[2-(2-{2-[2-(2-Methoxy-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]propionyl-
	8-Hexadecanoylamino-octanoyl-
	6-[Hydroxy-(naphthalen-2-yloxy)-phosphoryloxy]-hexanoyl-
	6-[Hydroxy-(5-phenyl-pentyloxy)-phosphoryloxy]-hexanoyl-

7-[4-(1-Carboxy-ethyl)-phenylcarbamoyl]-heptanoyl-	
4-(Naphthalene-2-sulfonylamino)-4-oxo-butyryl-	
4-(Biphenyl-4-sulfonylamino)-4-oxo-butyryl-	
(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl-	
(S)-4-Carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl	

	(S)-4-Carboxy-2-{(S)-4-carboxy-2-[2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl
	(S)-4-Carboxy-2-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl
	(S)-4-Carboxy-4-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl
	(S)-4-Carboxy-2-{(S)-4-carboxy-2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl
	(S)-4-Carboxy-2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl
	2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy)-acetyl-

	2-(2-{2-[(S)-4-Carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetyl
	(S)-4-Carboxy-4-((S)-4-carboxy-4-{(S)-4-carboxy-4-[(S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)-butyrylamino]-butyrylamino}-butyrylamino)-butyryl
	2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-1H-tetrazol-5-yl-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl
	2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-carboxy-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-butyrylamino}-butyryl
	(S)-4-Carboxy-4-((S)-4-carboxy-4-{2-[2-(2-{2-[2-(2-{(S)-4-carboxy-4-[10-(4-carboxy-phenoxy)-decanoylamino]-butyrylamino}-ethoxy)-ethoxy]-acetylamino}-ethoxy)-ethoxy]-acetylamino}-butyryl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(7-carboxy-heptanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(11-carboxy-undecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl

	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(13-carboxy-tridecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(15-carboxy-pentadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{2-[(S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl
	2-(2-[2-{2-(2-[2-{(3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-1,5-dimethyl-hexyl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yloxycarbonyl}-ethoxy]-ethoxy)-ethoxy}-ethoxy]-ethylcarbamoyl)-methyl

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In a further embodiment, X14 represents Met or Nle, preferably Met.

In a still further embodiment, X3 represents Gln, X16 represents Ser, X17 represents Arg, X18 represents Arg, X19 represents Ala, X20 represents Gln and/or X21 represents Asp or Glu.

In a still further embodiment, X2 represents Ser, D-Ser or Aib, preferably D-Ser or Aib and more preferably D-Ser.

In a still further embodiment, (i) X2 represents D-Ser or Aib and X40 is functionalized Lys, (ii) X2 represents Ser, D-Ser or Aib, X39 is functionalized Lys and X40 is absent, (iii) X2 represents Ser, D-Ser or Aib and X40 is absent, or (iv) X2 represents Ser, D-Ser or Aib and X40 is functionalized Cys.

Lys is preferably functionalized, e.g. with a group -C(O)R5 as described above. Cys is preferably functionalized, e.g. with a group -Y-R7, wherein Y is a thiol linker and R7 is preferably a (poly)alkoxy group, e.g. an (CH2-CH2-O)q-R6 group, wherein q is 1-2000 and R6 is H or C1-4 alkyl.

In a still further embodiment X15 represents Glu, and/or X16 represents Lys or Ser, and/or X19 represents Ala, and/or X20 represents Lys or Gln, and/or X21 represents Leu or Glu.

In a still further embodiment, 1, 2, 3, 4, 5 or 6, particularly 5 or 6 amino acid residues selected from X15, X16, X17, X18, X19, X20 and X21 are amino acid residues which differ from the corresponding amino acid residues in Exendin-4 (SEQ ID NO: 1). This embodiment may particularly be combined with the above indicated specific amino acid residues at positions X15, X16, X17, X18, X19, X20 and/or X21.

A still further embodiment refers to a group of compounds, wherein

X2 = D-Ser;

X3 = Gln;
X14 = Met;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Arg, particularly Gln;
X21 = Asp or Leu;
X28 = Asn, Ala, Ser, Lys, Aib or Arg;
X29 = Gly or D-Ala;
X35 = Ala; and
(i) X39 = Ser and
X40 = Lys, Orn, Dab or Dap which are functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl,
(ii) X39 = Lys which is functionalized at its amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl, and
X40 = absent.

In a still preferred embodiment refers to a group of compounds,
wherein
X2 = D-Ser or Aib;
X3 = Gln;
X14 = Met;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg;
X18 = Arg;
X19 = Ala;

X20 = Gln or Lys;
X21 = Asp;
X28 = Asn, Ser, Lys or Aib;
X29 = Gly, Thr, Ala or D-Ala;
X35 = Ala and
(i) X39 = Ser and
X40 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl, or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl, and
X40 is absent.

A still further preferred embodiment relates to a group of compounds, wherein

X2 = D-Ser;
X3 = Gln;
X14 = Nle, Chx-Ala, Cp-Ala or Cb-Ala;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Lys;
X21 = Asp, Glu or Leu;
X28 =Ala or Ser;
X29 = Gly;
X35 = Ala;
(i) X39 = Ser and

X40 = Lys, Orn, Dab or Dap which are functionalized at the amino side chain group, particularly by (S)-4-Carboxy-4-hexadecanoylamino-butyryl, (S)-4-Carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl,
or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-Carboxy-4-hexadecanoylamino-butyryl,(S)-4-Carboxy-4-hexadecanoylamino-butyryl, (S)-4-Carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl and
X40 = absent.

A still further preferred embodiment relates to a group of compounds, wherein
X2 = Ser or D-Ser;
X3 = Gln;
X14 = Met;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;
X18 = Arg;
X19 = Ala;
X20 = Gln;
X21 = Asp;
X28 = Asn;
X29 = Gly;
X35 = Ala; and
(i) X39 = Ser and
X40 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl, or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl, and
X40 is absent.

A still further preferred embodiment relates to a group of compounds wherein

X2 = Ser or D-Ser;
X3 = Gln;
X14 = Met or Nle;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg or Glu;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln, Arg or Lys;
X21 = Asp, Glu or Leu;
X28 = Asn;
X29 = Gly;
X35 = Ala;
X39 = Ser and
X40 = absent.

A still further preferred embodiment relates to a group of compounds wherein

X2 = Aib or D-Ser;
X3 = Gln;
X14 = Met or Nle;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg, Lys or Gln;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Lys;
X21 = Asp;
X28 = Asn, Ala, Aib, Lys, Arg or Ser;

X29 = Gly, Ala, D-Ala or Thr;
X35 = Ala;
X39 = Ser and
X40 = absent or Lys.

Specific examples of peptidic compounds of formula (I) are the compounds of SEQ ID NO: 7-238 as well as salts and solvates thereof.

In certain embodiments, i.e. when the compound of formula (I) consists of genetically encoded amino acid residues, the invention further provides a nucleic acid (which may be DNA or RNA) encoding said compound, an expression vector comprising such a nucleic acid, and a host cell containing such a nucleic acid or expression vector.

In a further aspect, the present invention provides a composition comprising a compound of the invention in admixture with a carrier. In preferred embodiments, the composition is a pharmaceutically acceptable composition and the carrier is a pharmaceutically acceptable carrier. The compound of the invention may be in the form of a salt, e.g. a pharmaceutically acceptable salt or a solvate, e.g. a hydrate. In still a further aspect, the present invention provides a composition for use in a method of medical treatment, particularly in human medicine.

In certain embodiments, the nucleic acid or the expression vector may be used as therapeutic agents, e.g. in gene therapy.

The compounds of formula (I) are suitable for therapeutic application without an additionally therapeutically effective agent. In other embodiments, however, the compounds are used together with at least one additional therapeutically active agent, which may e.g. be a GLP1 compound and/or an insulinic compound and/or a gastrointestinal peptide.

The compounds of formula (I) are particularly suitable for the treatment or prevention of diseases or disorders caused by, associated with and/or accompanied by

disturbances in carbohydrate and/or lipid metabolism, e.g. for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity and metabolic syndrome. Further, the compounds of the invention are particularly for the treatment or prevention of degenerative diseases, particularly neurodegenerative diseases.

The compounds described find use, inter alia, in preventing weight gain or promoting weight loss. By "preventing" is meant inhibiting or reducing when compared to the absence of treatment, and is not necessarily meant to imply complete cessation of a disorder.

The compounds of the invention may cause a decrease in food intake and/or increase in energy expenditure, resulting in the observed effect on body weight.

Independently of their effect on body weight, the compounds of the invention may have a beneficial effect on circulating cholesterol levels, being capable of lowering circulating LDL levels and increasing HDL/LDL ratio.

Thus, the compounds of the invention can be used for direct or indirect therapy of any condition caused or characterised by excess body weight, such as the treatment and/or prevention of obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea. They may also be used for treatment and prevention of the metabolic syndrome, diabetes, hypertension, atherogenic dyslipidemia, atherosclerosis, arteriosclerosis, coronary heart disease, or stroke. Their effects in these conditions may be as a result of or associated with their effect on body weight, or may be independent thereof.

Preferred medical uses include delaying or preventing disease progression in type 2 diabetes, treating metabolic syndrome, treating obesity or preventing overweight, for decreasing food intake, increase energy expenditure, reducing body weight, delaying the progression from impaired glucose tolerance (IGT) to type 2 diabetes; delaying the progression from type 2 diabetes to insulin-requiring diabetes; regulating appetite;

inducing satiety; preventing weight regain after successful weight loss; treating a disease or state related to overweight or obesity; treating bulimia; treating binge eating; treating atherosclerosis, hypertension, type 2 diabetes, IGT, dyslipidemia, coronary heart disease, hepatic steatosis, treatment of beta-blocker poisoning, use for inhibition of the motility of the gastrointestinal tract, useful in connection with investigations of the gastrointestinal tract using techniques such as X-ray, CT- and NMR-scanning.

Further preferred medical uses include treatment or prevention of hypoglycemia, insulin induced hypoglycemia, reactive hypoglycemia, diabetic hypoglycemia, non-diabetic hypoglycemia, fasting, hypoglycemia, drug-induced hypoglycemia, gastric by-pass induced hypoglycemia, hypoglycemia in pregnancy, alcohol induced hypoglycemia, insulinoma and Von Girkes disease.

Further preferred medical uses include treatment or prevention of degenerative disorders, particularly neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ataxia, e.g spinocerebellar ataxia, Kennedy disease, myotonic dystrophy, Lewy body dementia, multi-systemic atrophy, amyotrophic lateral sclerosis, primary lateral sclerosis, spinal muscular atrophy, prion-associated diseases, e.g. Creutzfeldt-Jacob disease, multiple sclerosis, telangiectasia, Batten disease, corticobasal degeneration, Creutzfeldt-Jakob disease, subacute combined degeneration of spinal cord, Tabes dorsalis, Tay-Sachs disease, toxic encephalopathy, infantile Refsum disease, Refsum disease, neuroacanthocytosis, Niemann-Pick disease, Lyme disease, Machado-Joseph disease, Sandhoff disease, Shy-Drager syndrome, wobbly hedgehog syndrome, proteopathy, cerebral β-amyloid angiopathy, retinal ganglion cell degeneration in glaucoma, synucleinopathies, tauopathies, frontotemporal lobar degeneration (FTLD), dementia, cadasil syndrome, hereditary cerebral hemorrhage with amyloidosis, Alexander disease, seipinopathies, familial amyloidotic neuropathy, senile systemic amyloidosis, serpinopathies, AL (light chain) amyloidosis (primary systemic amyloidosis), AH (heavy chain) amyloidosis, AA (secondary) amyloidosis, aortic medial amyloidosis, ApoAI amyloidosis, ApoAII amyloidosis, ApoAIV amyloidosis, familial amyloidosis of the Finnish type (FAF), Lysozyme amyloidosis, Fibrinogen amyloidosis, Dialysis amyloidosis, Inclusion body

myositis/myopathy, Cataracts, Retinitis pigmentosa with rhodopsin mutations, medullary thyroid carcinoma, cardiac atrial amyloidosis, pituitary prolactinoma, Hereditary lattice corneal dystrophy, Cutaneous lichen amyloidosis, Mallory bodies, corneal lactoferrin amyloidosis, pulmonary alveolar proteinosis, odontogenic (Pindborg) tumor amyloid, cystic fibrosis, sickle cell disease or critical illness myopathy (CIM).

DESCRIPTION OF THE FIGURES

Figure 1. Effect of s.c. administration of compound SEQ ID NO: (7) on blood glucose in female diet-induced obese C57BL/6NCrl mice (9 months on high-fat diet). Data are mean+SEM. *p<0.05.

Figure 2. Effect of s.c. administration of compound SEQ ID NO: (7) on gastric emptying in female NMRI-mice. Data are mean+SEM.

Figure 3. Effect of s.c. administration of compound SEQ ID NO: (7) on intestinal motility in female NMRI-mice. Data are mean+SEM. *p<0.0001.

Figure 4. Effect of s.c. administration of compound SEQ ID NO: (7) on 22-hours feed intake in female NMRI-mice. Data are mean+SEM. *p<0.05.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The amino acid sequences of the present invention contain the conventional one letter and three letter codes for naturally occuring amino acids, as well as generally accepted three letter codes for other amino acids, such as Aib (α-aminoisobutyric acid), Orn (ornithin), Dab (2,4-diamino butyric acid), Dap (2,3-diamino propionic acid), Nle (norleucine), Abt (γ-aminobutyric acid) or Ahx (ε-aminohexanoic acid).

The term „native exendin-4“ refers to native exendin-4 having the sequence HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH2 (SEQ ID NO: (1)).

The invention provides peptidic compounds as defined above.

The peptidic compounds of the present invention comprise a linear backbone of amino carboxylic acids linked by peptide, i.e. carboxamide bonds. Preferably, the amino carboxylic acids are α-amino carboxylic acids and more preferably L-α-amino carboxylic acids, unless indicated otherwise. The peptidic compounds preferably comprise a backbone sequence of 39-41 amino carboxylic acids.

The peptidic compounds may be functionalized (covalently linked) with chemical moieties at their N-terminus, C-terminus and/or at least one side-chain. The N-terminus of the peptidic compound may be unmodified, i.e. an NH2 group or a mono- or bisfunctionalized NH2 group.

At the C-terminus, the peptidic compounds may be unmodified, i.e. have a OH group or be modified, e.g. with an NH2 group or a monofunctionalized or bisfunctionalized NH2 group.

The peptidic compounds of the present invention may have unmodified side-chains or carry at least one modification at one of the side chains.

For the avoidance of doubt, in the definitions provided herein, it is generally intended that the sequence of the peptidic moiety (II) differs from native exendin-4 at least at one of those positions which are stated to allow variation. Amino acids within the peptide moiety (II) can be considered to be numbered consecutively from 0 to 40 in the conventional N-terminal to C-terminal direction. Reference to a “position“ within peptidic moiety (II) should be constructed accordingly, as should reference to positions within native exendin-4 and other molecules.

Substitution of one or more of the naturally occurring amino acids at positions 39 and/or 40 with an amino acid having a reactive side chain, e.g. an NH2 or SH group which enables conjugation to a functional group. For example, the residues at positions 39 and/or 40 may be Lys, Orn, Dab, Dap or Cys.

The amino acid side chains may be conjugated with functional, e.g. lipophilic acyl groups. Thus, one or more selected amino acids of the peptides in the present invention may carry a covalent attachment at their side chains. In some cases those attachments may be lipophilic. These lipophilic side chain attachments have the potential to reduce in vivo clearance of the peptides thus increasing their in vivo half-lives.

The lipophilic attachment may consist of a lipophilic moiety which can be a branched or unbranched, aliphatic or unsaturated acyclic moiety and/or a cyclic moiety selected from one or several aliphatic or unsaturated homocycles or heterocycles, aromatic condensed or non-condensed homocycles or heterocycles, ether linkages, unsaturated bonds and substituents, e.g. hydroxy and/or carboxy groups. The lipophilic moiety may be attached to the peptide either directly (alkylation, reductive amination) or by an amide bond or a sulfonamide bond in case of amino acids carrying an amino group at their side chain, an ester bond in case of amino acids carrying a hydroxy group at their side chain or thioether or thioester linkages in case of amino acids carrying a thiol group at their side chain or it may be attached to a modified side-chain of an amino acid thus allowing the introduction of a lipophilic moiety by click-chemistry or Michael-addition.

Nonlimiting examples of lipophilic moieties that can be attached to amino acid side chains include fatty acids, e.g. C12-30 fatty acids such as palmitic acid, myristic acid, stearic acid and oleic acid, and/or cyclic groups as described above or derivatives thereof.

There might be one or several linkers between the amino acid of the peptide and the lipophilic attachment. Nonlimiting examples of those linkers are β-alanine, γ-glutamic acid, γ-aminobutyric acid and/or ε-aminohexanoic acid or dipeptides, such as β-Ala-β-Ala and/or γ-Glu-γ-Glu.

Thus, one nonlimiting example of a side chain attachment is palmitic acid which is covalently linked to the amino group of glutamic acid forming an amide bond. The γ-

carboxy group of this substituted glutamic acid can form an amide bond with the side chain amino group of a lysine within the peptide.

In a further aspect, the present invention provides a composition comprising a compound of the invention as described herein, or a salt or solvate thereof, in admixture with a carrier.

The invention also provides the use of a compound of the present invention for use as a medicament, particularly for the treatment of a condition as described below.

The invention also provides a composition wherein the composition is a pharmaceutically acceptable composition, and the carrier is a pharmaceutically acceptable carrier.

Peptide synthesis

The skilled person is aware of a variety of different methods to prepare peptides that are described in this invention. These methods include but are not limited to synthetic approaches and recombinant gene expression. Thus, one way of preparing these peptides is the synthesis in solution or on a solid support and subsequent isolation and purification. A different way of preparing the peptides is gene expression in a host cell in which a DNA sequence encoding the peptide has been introduced. Alternatively, the gene expression can be achieved without utilizing a cell system. The methods described above may also be combined in any way.

A preferred way to prepare the peptides of the present invention is solid phase synthesis on a suitable resin. Solid phase peptide synthesis is a well established methodology (see for example : Stewart and Young, Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, Ill., 1984; E. Atherton and R. C. Sheppard, Solid Phase Peptide Synthesis. A Practical Approach, Oxford-IRL Press, New York, 1989). Solid phase synthesis is initiated by attaching an N-terminally protected amino acid with its carboxy terminus to an inert solid support. This solid support can be any polymer that allows coupling of the initial amino acid such as e.g. a trityl resin, a

chlorotrityl resin, a Wang resin or a Rink resin in which the linkage of the carboxy group (or carboxamide for Rink resin) to the resin is sensitive to acid (when Fmoc strategy is used). The polymer support must be stable under the conditions used to deprotect the α-amino group during the peptide synthesis.

After the first amino acid has been coupled to the solid support, the α-amino protecting group of this amino acid is removed. The remaining protected amino acids are then coupled one after the other in the order represented by the peptide sequence using appropriate amide coupling reagents, for example BOP (benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium), HATU (O-(7-azabenztriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium) or DIC (N,N'-diisopropylcarbodiimide) / HOBt (1-hydroxybenzotriazol), wherein BOP, HBTU and HATU are used with tertiary amine bases. Alternatively, the liberated N-terminus can be functionalized with groups other than amino acids, for example carboxylic acids.

Usually, reactive side-chain groups of the amino acids are protected with suitable blocking groups. These protecting groups are removed after the desired peptides have been assembled. They are commonly removed while the desired product is being cleaved from the resin under the same conditions. Protecting groups and the procedures to introduce protecting groups can be found in Protective Groups in Organic Synthesis, 3d ed., Greene, T. W. and Wuts, P. G. M., Wiley & Sons (New York: 1999).

In some cases it might be desirable to have side-chain protecting groups that can selectively be removed while other side-chain protecting groups remain intact. In this case the liberated functionality can be selectively functionalized. For example, a lysine may be protected with an ivDde protecting group (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603) which is labile to a very nucleophilic base, for example 4% hydrazine in DMF (dimethyl formamide). Thus, if the N-terminal amino group and all side-chain functionalities are protected with acid labile protecting groups, the ivDde ([1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl) group can be selectively

removed using 4% hydrazine in DMF and can then be further modified, e.g. by acylation. The lysine can alternatively be coupled to a protected amino acid and the amino group of this amino acid can then be deprotected resulting in another free amino group which can be acylated or attached to further amino acids.

Finally the peptide is cleaved from the resin. This can be achieved by using King's cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The raw material can then be purified by chromatography if necessary.

Potency

As used herein, the term "potency" or "in vitro potency" is a measure for the ability of a compound to activate the receptors for GLP-1 or glucagon in a cell-based assay. Numerically, it is expressed as the "EC50 value", which is the effective concentration of a compound that induces a half maximal increase of response (e.g. formation of intracellular cAMP) in a dose-response experiment.

Therapeutic uses

The compounds of the invention are agonists for the receptors for GLP-1 and/or for glucagon (e.g. "dual agonists"), preferably for GLP-1 and glucagon and may provide an attractive option for targeting the metabolic syndrome by allowing simultaneous treatment of obesity and diabetes.

Metabolic syndrome is a combination of medical disorders that, when occurring together, increase the risk of developing type 2 diabetes, as well as atherosclerotic vascular disease, e.g. heart disease and stroke. Defining medical parameters for the metabolic syndrome include diabetes mellitus, impaired glucose tolerance, raised fasting glucose, insulin resistance, urinary albumin secretion, central obesity, hypertension, elevated triglycerides, elevated LDL cholesterol and reduced HDL cholesterol.

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health and life expectancy and due to its increasing prevalence in adults and children it has become one of the leading preventable causes of death in modern world. It increases the likelihood of various other diseases, including heart disease, type 2 diabetes, obstructive sleep apnoe, certain types of cancer, as well as osteoarthritis, and it is most commonly caused by a combination of excess food intake, reduced energy expenditure, as well as genetic susceptibility.

Diabetes mellitus, often simply called diabetes, is a group of metabolic diseases in which a person has a high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. The most common types of diabetes are: (1) type 1 diabetes, where the body fails to produce insulin; (2) type 2 diabetes, where the body fails to use insulin properly, combined with an increase in insulin deficiency over time, and (3) gestational diabetes, where women develop diabetes due to their pregnancy. All forms of diabetes increase the risk of long-term complications, which typically develop after many years. Most of these long-term complications are based on damage to blood vessels and can be divided into the two categories “macrovascular” disease, arising from atherosclerosis of larger blood vessels and “microvascular” disease, arising from damage of small blood vessels. Examples for macrovascular disease conditions are ischemic heart disease, myocardial infarction, stroke and peripheral vascular disease. Examples for microvascular diseases are diabetic retinopathy, diabetic nephropathy, as well as diabetic neuropathy.

The receptors for GLP-1 and glucagon are both members of the family B of G-protein coupled receptors. They are highly related to each other and share not only a significant level of sequence identity, but have also similar mechanisms of ligand recognition and intracellular signaling pathways.

Similarly, the peptides GLP-1 and glucagon are highly homologous to each other, with similar length and regions of high sequence identity. Both are produced from a

common precursor, preproglucagon, which is differentially processed in a tissue-specific manner to yield e.g. GLP-1 in intestinal endocrine cells and glucagon in alpha cells of pancreatic islets.

The incretin hormone GLP-1 is secreted by intestinal endocrine cells in response to food and enhances meal-stimulated insulin secretion. Evidence suggests that GLP-1 secretion is reduced in subjects with impaired glucose tolerance or type 2 diabetes, whereas responsiveness to GLP-1 is still preserved in these patients. Thus, targeting of the GLP-1 receptor with suitable agonists offers an attractive approach for treatment of metabolic disorders, including diabetes. The receptor for GLP-1 is distributed widely, being found mainly in pancreatic islets, brain, heart, kidney and the gastrointestinal tract. In the pancreas, GLP-1 acts in a strictly glucose-dependent manner by increasing secretion of insulin from beta cells. This glucose-dependency shows that activation of GLP-1 receptors is unlikely to cause hypoglycemia.

At the beta cell level, GLP-1 has been shown to promote glucose sensitivity, neogenesis, proliferation, transcription of proinsulin and hypertrophy, as well as antiapoptosis. Other relevant effects of GLP-1 beyond the pancreas include delayed gastric emptying, increased satiety, decreased food intake, reduction of body weight, as well as neuroprotective and cardioprotective effects. In patients with type 2 diabetes, such extrapancreatic effects could be particularly important considering the high rates of comorbidities like obesity and cardiovascular disease.

Glucagon is a 29-amino acid peptide hormone that is produced by pancreatic alpha cells and released into the bloodstream when circulating glucose is low. An important physiological role of glucagon is to stimulate glucose output in the liver, which is a process providing the mayor counterregulatory mechanism for insulin in maintaining glucose homeostasis in vivo.

Glucagon receptors are however also expressed in extrahepatic tissues such as kidney, heart, adipocytes, lymphoblasts, brain, retina, adrenal gland and gastrointestinal tract, suggesting a broader physiological role beyond glucose

homeostasis. Accordingly, recent studies have reported that glucagon has therapeutically positive effects on energy management, including stimulation of energy expenditure and thermogenesis, accompanied by reduction of food intake and body weight loss. Altogether, stimulation of glucagon receptors might be useful in the treatment of obesity and the metabolic syndrome.

Oxyntomodulin is a 37-amino acid peptide hormone consisting of glucagon with an eight amino acids encompassing C-terminal extension. Like GLP-1 and glucagon, it is preformed in preproglucagon and cleaved and secreted in a tissue-specific manner by endocrinal cells of the small bowel. Oxyntomodulin is known to stimulate both, the receptors for GLP-1 and glucagon and is therefore the prototype of a dual agonist.

As GLP-1 is known for its anti-diabetic effects, GLP-1 and glucagon are both known for their food intake-suppressing effects and glucagon is also a mediator of additional energy expenditure, it is conceivable that a combination of the activities of the two hormones in one molecule can yield a powerful medication for treatment of the metabolic syndrome and in particular its components diabetes and obesity.

Accordingly, the compounds of the invention may be used for treatment of glucose intolerance, insulin resistance, pre-diabetes, increased fasting glucose, type 2 diabetes, hypertension, dyslipidemia, atherosclerois, arteriosclerosis, coronary heart disease, peripheral artery disease, stroke or any combination of these individual disease components.

In addition, they may be used for control of appetite, feeding and calory intake, increase of energy expenditure, prevention of weight gain, promotion of weight loss, reduction of excess body weight and altogether treatment of obesity, including morbid obesity.

Further disease states and health conditions which could be treated with the compounds of the invention are obesity-linked inflammation, obesity-linked gallbladder disease and obesity-induced sleep apnea.

Although all these conditions could be associated directly or indirectly with obesity, the effects of the compounds of the invention may be mediated in whole or in part via an effect on body weight, or independent thereof.

Further, diseases to be treated are neurodegenerative diseases such as Alzheimer's disease or Parkinson's disease, or other degenerative diseases as described above.

Pharmaceutical compositions

The term "pharmaceutical composition" indicates a mixture containing ingredients that are compatible when mixed and which may be administered. A pharmaceutical composition may include one or more medicinal drugs. Additionally, the pharmaceutical composition may include carriers, solvents, adjuvants, emollients, expanders, stabilizers and other components, whether these are considered active or inactive ingredients. Guidance for the skilled in preparing pharmaceutical compositions may be found, for example, in Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A. R. Gennaro A. R., 2000, Lippencott Williams & Wilkins.

The exendin-4 peptide analogues of the present invention, or salts thereof, are administered in conjunction with an acceptable pharmaceutical carrier, diluent, or excipient as part of a pharmaceutical composition. A "pharmaceutically acceptable carrier" is a carrier which is physiologically acceptable while retaining the therapeutic properties of the substance with which it is administered. Standard acceptable pharmaceutical carriers and their formulations are known to one skilled in the art and described, for example, in Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A. R. Gennaro A. R., 2000, Lippencott Williams & Wilkins. One exemplary pharmaceutically acceptable carrier is physiological saline solution.

Acceptable pharmaceutical carriers or diluents include those used in formulations suitable for oral, rectal, nasal or parenteral (including subcutaneous, intramuscular,

intravenous, intradermal, and transdermal) administration. The compounds of the present invention will typically be administered parenterally.

The term “pharmaceutically acceptable salt” means salts of the compounds of the invention which are safe and effective for use in mammals. Pharmaceutically acceptable salts may include, but are not limited to, acid addition salts and basic salts. Examples of acid addition salts include chloride, sulfate, hydrogen sulfate, (hydrogen) phosphate, acetate, citrate, tosylate or mesylate salts. Examples of basic salts include salts with inorganic cations, e.g. alkaline or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts and salts with organic cations such as amine salts. Further examples of pharmaceutically acceptable salts are described in Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A. R. Gennaro A. R., 2000, Lippencott Williams & Wilkins or in Handbook of Pharmaceutical Salts, Properties, Selection and Use, e.d. P. H. Stahl, C. G. Wermuth, 2002, jointly published by Verlag Helvetica Chimica Acta, Zurich, Switzerland, and Wiley-VCH, Weinheim, Germany.

The term “solvate” means complexes of the compounds of the invention or salts thereof with solvent molecules, e.g. organic solvent molecules and/or water.

The term "therapeutically effective amount" of a compound refers to a nontoxic but sufficient amount of the compound to provide the desired effect. The amount of a compound of the formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

Pharmaceutical compositions of the invention are those suitable for parenteral (for example subcutaneous, intramuscular, intradermal or intravenous), oral, rectal, topical and peroral (for example sublingual) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the

condition to be treated and on the nature of the compound of formula I used in each case.

Suitable pharmaceutical compositions may be in the form of separate units, for example capsules, tablets and powders in vials or ampoules, each of which contains a defined amount of the compound; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. It may be provided in single dose injectable form, for example in the form of a pen. The compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact.

Combination therapy

The compounds of the present invention, dual agonists for the GLP-1 and glucagon receptors, can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2012, e.g. with all antidiabetics mentioned in the Rote Liste 2012, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2012, chapter 1, all lipid-lowering agents mentioned in the Rote Liste 2012, chapter 58, all antihypertensives and nephroprotectives, mentioned in the Rote Liste 2012, or all diuretics mentioned in the Rote Liste 2012, chapter 36.

The active ingredient combinations can be used especially for a synergistic improvement in action. They can be applied either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients are present in one pharmaceutical preparation. When the active ingredients are administered by separate administration of the active ingredients, this can be done simultaneously or successively.

Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2011.

Other active substances which are suitable for such combinations include in particular those which for example potentiate the therapeutic effect of one or more active substances with respect to one of the indications mentioned and/or which allow the dosage of one or more active substances to be reduced.

Therapeutic agents which are suitable for combinations include, for example, antidiabetic agents such as:

Insulin and Insulin derivatives, for example: Glargin / Lantus® (see www.lantus.com), Glulisin / Apidra®, Detemir / Levemir®, Lispro / Humalog® / Liprolog®, Degludec / DegludecPlus, Aspart, basal insulin and analogues (e.g.LY-2605541, LY2963016), PEGylated insulin Lispro, Humulin®, Linjeta, SuliXen®, NN1045, Insulin plus Symlin, fast-acting and short-acting insulins (e.g. Linjeta, PH20, NN1218, HinsBet), (APC-003)hydrogel, oral, inhalable, transdermal and sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza, Tregopil, TPM 02, Capsulin, Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, NN1953, VIAtab). Additionally included are also those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker.

GLP-1, GLP-1 analogues and GLP-1 receptor agonists, for example: Lixisenatide / AVE0010 / ZP10 / Lyxumia, Exenatide / Exendin-4 / Byetta / Bydureon / ITCA 650, Liraglutide / Victoza, Semaglutide, Taspoglutide, Albiglutide, Dulaglutide, rExendin-4, CJC-1134-PC, PB-1023, TTP-054, HM-11260C, CM-3, GLP-1 Eligen, ORMD-0901, NN-9924, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, MAR-701, ZP-2929, ZP-3022, CAM-2036, DA-15864, ARI-2651, ARI-2255, Exenatide-XTEN and Glucagon-Xten.

DPP-4 inhibitors, for example: Alogliptin / Nesina, Linagliptin / BI-1356 / Ondero / Trajenta / Tradjenta / Trayenta / Tradzenta, Saxagliptin / Onglyza, Sitagliptin / Januvia / Xelevia / Tesave / Janumet / Velmetia, Vildagliptin, Anagliptin, Gemigliptin, Tenegliptin, Melogliptin, Trelagliptin, DA-1229, MK-3102, KM-223.

SGLT2 inhibitors, for example: Canaglifozin, Dapaglifloxin, Remoglifoxin, Sergliflozin, Empagliflozin, Ipraglifloxin, Tofoglifloxin, Iuseoglifloxin, LX-4211, PF-04971729, RO-4998452, EGT-0001442, DSP-3235.

Biguanides (e.g. Metformin, Buformin, Phenformin), Thiazolidinediones (e.g. Pioglitazone, Rivoglitazone, Rosiglitazone, Troglitazone), dual PPAR agonists (e.g. Aleglitazar, Muraglitazar, Tesaglitazar), Sulfonylureas (e.g. Tolbutamide, Glibenclamide, Glimepiride/Amaryl, Glipizide), Meglitinides (e.g. Nateglinide, Repaglinide, Mitiglinide), Alpha-glucosidase inhibitors (e.g. Acarbose, Miglitol, Voglibose), Amylin and Amylin analogues (e.g. Pramlintide, Symlin).

GPR119 agonists (e.g. GSK-263A, PSN-821, MBX-2982, APD-597), GPR40 agonists (e.g. TAK-875, TUG-424, P-1736, JTT-851, GW9508).

Other suitable combination partners are: Cycloset, inhibitors of 11-beta-HSD (e.g. LY2523199, BMS770767, RG-4929, BMS816336, AZD-8329, HSD-016, BI-135585), activators of glucokinase (e.g. TTP-399, AMG-151, TAK-329), inhibitors of DGAT (e.g. LCQ-908), inhibitors of protein tyrosinephosphatase 1 (e.g. Trodusquemine), inhibitors of glucose-6-phosphatase, inhibitors of fructose-1,6-bisphosphatase, inhibitors of glycogen phosphorylase, inhibitors of phosphoenol pyruvate carboxykinase, inhibitors of glycogen synthase kinase, inhibitors of pyruvate dehydrokinase, alpha2-antagonists, CCR-2 antagonists.

One or more lipid lowering agents are also suitable as combination partners, such as for example: HMG-CoA-reductase inhibitors (e.g. Simvastatin, Atorvastatin), fibrates (e.g. Bezafibrate, Fenofibrate), nicotinic acid and the derivatives thereof (e.g. Niacin), PPAR-(alpha, gamma or alpha/gamma) agonists or modulators (e.g. Aleglitazar), PPAR-delta agonists, ACAT inhibitors (e.g. Avasimibe), cholesterol absorption inhibitors (e.g. Ezetimibe), Bile acid-binding substances (e.g. Cholestyramine), ileal bile acid transport inhibitors, MTP inhibitors, or modulators of PCSK9.

HDL-raising compounds such as: CETP inhibitors (e.g. Torcetrapib, Anacetrapid, Dalcetrapid, Evacetrapid, JTT-302, DRL-17822, TA-8995) or ABC1 regulators.

Other suitable combination partners are one or more active substances for the treatment of obesity, such as for example: Sibutramine, Tesofensine, Orlistat, antagonists of the cannabinoid-1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists (e.g. Velneperit), beta-3-agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor (e.g. Lorcaserin), or the combinations of bupropione/naltrexone, bupropione/zonisamide, bupropione/phentermine or pramlintide/metreleptin.

Other suitable combination partners are:
Further gastrointestinal peptides such as Peptide YY 3-36 (PYY3-36) or analogues thereof, pancreatic polypeptide (PP) or analogues thereof.
Glucagon receptor agonists or antagonists, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, Xenin and analogues thereof.

Moreover, combinations with drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, such as e.g.: Angiotensin II receptor antagonists (e.g. telmisartan, candesartan, valsartan, losartan, eprosartan, irbesartan, olmesartan, tasosartan, azilsartan), ACE inhibitors, ECE inhibitors, diuretics, beta-blockers, calcium antagonists, centrally acting hypertensives, antagonists of the alpha-2-adrenergic receptor, inhibitors of neutral endopeptidase, thrombocyte aggregation inhibitors and others or combinations thereof are suitable.

In another aspect, this invention relates to the use of a compound according to the invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions which can be affected by binding to the receptors for GLP-1 and glucagon and by modulating their activity. This is preferably a disease in the context of the metabolic

syndrome, particularly one of the diseases or conditions listed above, most particularly diabetes or obesity or complications thereof.

The use of the compounds according to the invention, or a physiologically acceptable salt thereof, in combination with one or more active substances may take place simultaneously, separately or sequentially.

The use of the compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may take place simultaneously or at staggered times, but particularly within a short space of time. If they are administered simultaneously, the two active substances are given to the patient together; if they are used at staggered times, the two active substances are given to the patient within a period of less than or equal to 12 hours, but particularly less than or equal to 6 hours.

Consequently, in another aspect, this invention relates to a medicament which comprises a compound according to the invention or a physiologically acceptable salt of such a compound and at least one of the active substances described above as combination partners, optionally together with one or more inert carriers and/or diluents.

The compound according to the invention, or physiologically acceptable salt or solvate thereof, and the additional active substance to be combined therewith may both be present together in one formulation, for example a tablet or capsule, or separately in two identical or different formulations, for example as so-called kit-of-parts.

METHODS

General synthesis of peptidic compounds

Materials:

Different Rink-Amide resins (4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido-norleucylaminomethyl resin) were used for the synthesis of peptide amides with loadings in the range of 0.3-0.4 mmol/g. Suppliers were Merck Biosciences and Agilent Technologies. From the same suppliers 2-chloro-trityl-chloride polystyrene resins with loadings up to 1.4 mmol/g were purchased and used for the synthesis of peptide acids.

Fmoc protected natural amino acids were purchased from Protein Technologies Inc., Senn Chemicals, Merck Biosciences, Novabiochem or Iris Biotech. The following standard amino acids were used throughout the syntheses: Fmoc-L-Ala-OH, Fmoc-L-Asn(Trt)-OH, Fmoc-L-Asp(OtBu)-OH, Fmoc-L-Cys(Trt)-OH, Fmoc-L-Gln(Trt)-OH, Fmoc-L-Glu(OtBu)-OH, Fmoc-Gly-OH, Fmoc-L-His(Trt)-OH, Fmoc-L-Ile-OH, Fmoc-L-Leu-OH, Fmoc-L-Lys(Boc)-OH, Fmoc-L-Met-OH, Fmoc-L-Phe-OH, Fmoc-L-Pro-OH, Fmoc-L-Ser(tBu)-OH, Fmoc-L-Thr(tBu)-OH, Fmoc-L-Trp(Boc)-OH, Fmoc-L-Tyr(tBu)-OH, Fmoc-L-Val-OH.

In addition, the following special amino acids were purchased from the same suppliers as above: Fmoc-L-Lys(ivDde)-OH, Fmoc-Aib-OH, Fmoc-D-Ser(tBu)-OH, Fmoc-D-Ala-OH, Boc-L-His(Boc)-OH and Boc-L-His(Trt)-OH.

The solid phase peptide syntheses were performed on a Prelude Peptide Synthesizer (Protein Technologies Inc) using standard Fmoc chemistry and HBTU/DIPEA activation. DMF was used as the solvent. Deprotection : 20% piperidine/DMF for 2 x 2.5 min. Washes: 7 x DMF. Coupling 2:5:10 200 mM AA / 500 mM HBTU / 2M DIPEA in DMF 2 x for 20 min. Washes: 5 x DMF.

In cases where a Lys-side-chain was modified, Fmoc-L-Lys(ivDde)-OH was used in the corresponding position. After completion of the synthesis, the ivDde group was removed according to a literature procedure (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603). The following acylations were carried out by treating the resin with the N-hydroxy succinimide esters of the desired acid or using coupling reagents like HBTU/DIPEA or HOBt/DIC.

All the peptides that had been synthesized were cleaved from the resin with King's cleavage cocktail consisting of 82.5% TFA, 5% phenol, 5% water, 5% thioanisole, 2.5% EDT. The crude peptides were then precipitated in diethyl or diisopropyl ether, centrifuged, and lyophilized. Peptides were analyzed by analytical HPLC and checked by ESI mass spectrometry. Crude peptides were purified by a conventional preparative HPLC purification procedure.

Analytical HPLC was performed on an Agilent 1100 Series HPLC system with a Waters XBridge BEH130 3.5 µm C18 column (2.1 x 150 mm) at 40 °C with a gradient elution at a flow rate of 0.5 mL/min and monitored at 215 and 280 nm. The gradients were set up as 10% B to 90% B over 15 min and then 90% B for 1 min or as 15% B to 50% B over 12.5 min and then 50% B to 90% B over 3 min. Buffer A = 0.1 % formic acid in water and B = 0.1 % formic acid in acetonitrile.

General Preparative HPLC Purification Procedure:

The crude peptides were purified either on an Äkta Purifier System or on a Jasco semiprep HPLC System. Preparative RP-C18-HPLC columns of different sizes and with different flow rates were used depending on the amount of crude peptide to be purified. Acetonitrile + 0.1% TFA (B) and water + 0.1% TFA (A) were employed as eluents. Product-containing fractions were collected and lyophilized to obtain the purified product.

Solubility and Stability-Testing of exendin-4 analogues

Prior to the testing of solubility and stability of a peptide batch, its content was determined. Therefore, two parameters were investigated, its purity (HPLC-UV) and the amount of salt load of the batch (ion chromatgraphy). Since synthesized peptides contain primarily trifluoracetate anions, only anion chromatography was performed. The content was then calculated based on the assumption that peptide-related

impurities are detected at the same UV-absorption rate as the target peptide, as well as that cations are not present in the sample.

For solubility testing, the target concentration was 1.0 mg/mL pure compound. Therefore, solutions from solid samples were prepared in different buffer systems with a concentration of 1.0 mg/mL compound based on the previously determined content. HPLC-UV was performed after 2 h of gentle agitation from the supernatant, which was obtained by 20 min of centrifugation at 4000 rpm. The solubility was then determined by comparison with the UV peak areas obtained with a stock solution of the peptide at a concentration of 2 mg/mL in pure water or a variable amount of acetonitrile (optical control that all of the compound is solved). This analysis also served as t0 for the stability testing.

For stability testing, an aliquot of the supernatant obtained for solubility was stored for 7 days at 25°C. After that time course, the sample was centrifuged for 20 min at 4000 rpm and the supernatant was analysed with HPLC-UV.
For determination of the amount of the remaining peptide, the peak areas of the target compound at t0 and t7 were compared, resulting in “% remaining peptide”, following the equation

% remaining peptide = [(peak area peptide t7) x 100]/peak area peptide t0.

The amount of soluble degradation products was calculated from the comparison of the sum of the peak areas from all observed impurities reduced by the sum of peak areas observed at t0 (i.e. to determine the amount of newly formed peptide-related species). This value was given in percentual relation to the initial amount of peptide at t0, following the equation:

% soluble degradation products = {[(peak area sum of impurities t7) - (peak area sum of impurities t0)] x 100}/peak area peptide t0

The potential difference from the sum of "% remaining peptide" and "% soluble degradation products" to 100% reflects the amount of peptide which did not remain soluble upon stress conditions following the equation

% precipitate = 100-([% remaining peptide] + [% soluble degradation products])

This precipitate includes non-soluble degradation products, polymers and/or fibrils, which have been removed from analysis by centrifugation.

Anion Chromatography
Instrument: Dionex ICS-2000, pre/column: Ion Pac AG-18 2 x 50 mm (Dionex)/ AS18 2 x 250 mm (Dionex), eluent: aquous sodium hydroxide, flow: 0.38 mL/min, gradient: 0-6 min: 22 mM KOH, 6-12 min: 22-28 mM KOH, 12-15 min: 28-50 mM KOH, 15-20min: 22mM, suppressor: ASRS 300 2 mm, detection: conductivity.

HPLC-UV
Instrument: Agilent 1100, column: X-Bridge C18 3.5 µm 2,1 x 150 mm (Waters), eluent: A: H20 + 500 ppm TFA/ B: Methanol, flow: 0.55 mL/min, gradient: 0-5 min: 10 - 60% B; 5 - 15 min: 60 - 99% B; detection: 214 nm.

In vitro cellular assays for GLP-1 receptor and glucagon receptor efficacy

Agonism of compounds for the two receptors was determined by functional assays measuring cAMP response of HEK-293 cell lines stably expressing human GLP-1 or glucagon receptor.

cAMP content of cells was determined using a kit from Cisbio Corp. (cat. no. 62AM4PEC) based on HTRF (Homogenous Time Resolved Fluorescence). For preparation, cells were split into T175 culture flasks and grown overnight to near confluency in medium (DMEM / 10% FBS). Medium was then removed and cells washed with PBS lacking calcium and magnesium, followed by proteinase treatment with accutase (Sigma-Aldrich cat. no. A6964). Detached cells were washed and

resuspended in assay buffer (1 x HBSS; 20 mM HEPES, 0.1% BSA, 2 mM IBMX) and cellular density determined. They were then diluted to 400000 cells/ml and 25 µl-aliquots dispensed into the wells of 96-well plates. For measurement, 25 µl of test compound in assay buffer was added to the wells, followed by incubation for 30 minutes at room temperature. After addition of HTRF reagents diluted in lysis buffer (kit components), the plates were incubated for 1 hr, followed by measurement of the fluorescence ratio at 665 / 620 nm. In vitro potency of agonists was quantified by determining the concentrations that caused 50% activation of maximal response (EC50).

Single subcutaneous treatment of exendin-4 analogue on blood glucose in female diet-induced obese C57BL/6NCrl mice (9 months on high-fat diet)

Female C57BL/6NCrl mice were housed in groups (n = 8) and had ad-libitum access to high-fat diet and water. Initial blood samples were taken just before administration (s.c.) of vehicle (phosphate buffer solution) or the exendin-4 analogue (e.g. SEQ ID NO: (7)) (100 µg/kg in phosphate buffer) in fed DIO mice. The volume of administration was 5 mL/kg. The animals had access to high-fat diet and water during the experiment, food consumption was determined at all time points for blood sampling. Blood glucose levels were measured at t = 0.5 h, t = 1 h, t = 2 h, t = 4 h, t = 6 h, t = 8 h, and t = 24 h. Blood sampling was performed by tail incision without anaesthesia.

Statistical analyses were performed with Everstat 6.0 by repeated measures two-way ANOVA and Dunnetts post-hoc analyses. Differences were considered statistically significant at the $p < 0.05$ level.

Gastric emptying and intestinal passage in mice

Female NMRI-mice of a body weight between 20 and 30 g were used. Mice were adapted to housing conditions for at least one week.

Mice were overnight fasted, while water remained available all the time. On the study day, mice were weighed, single-caged and allowed access to 500 mg of feed for 30 min, while water was removed. At the end of the 30 min feeding period, remaining feed was removed and weighed. 60 min later, a coloured, non-caloric bolus was instilled via gavage into the stomach. The test product or its vehicle in the control group was administered subcutaneously, to reach Cmax when coloured bolus was administered. After another 30 min, the animals were sacrificed and the stomach and the small intestine prepared. The filled stomach was weighed, emptied, carefully cleaned and dried and reweighed. The calculated stomach content indicated the degree of gastric emptying. The small intestine was straightened without force and measured in length. Then the distance from the gastric beginning of the gut to the tip of the farthest travelled intestinal content bolus was measured. The intestinal passage was given as relation in percent of the latter distance and the total length of the small intestine.

Statistical analyses were performed with Everstat 6.0 by Student's T-Test. Differences were considered statistically significant at the $p < 0.05$ level.

Automated assessment of feed intake in mice

Female NMRI-mice of a body weight between 20 and 30 g were used. Mice were adapted to housing conditions for at least one week and for at least one day single-caged in the assessment equipment, when basal data were recorded simultaneously. On the study day, test product was administered subcutaneously close to the lights-off phase (12 h lights off) and assessment of feed consumption was directly started afterwards. Assessment included continued monitoring (every 30 min) over 22 hours. Repetition of this procedure over several days was possible. Restriction of assessment to 22 hours was for practical reason to allow for reweighing of animals, refilling of feed and water and drug administration between procedures. Results could be assessed as cumulated data over 22 hours or differentiated to 30 min intervals.

Statistical analyses were performed with Everstat 6.0 by two-way ANOVA on repeated measures and Dunnetts post-hoc analyses. Differences were considered statistically significant at the $p < 0.05$ level.

EXAMPLES

The invention is further illustrated by the following examples.

Example 1:

Synthesis of SEQ ID NO: (4)

H-His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

The solid phase synthesis was carried out on Rink-resin with a loading of 0.38 mmol/g, 75-150 µm from the company Agilent Technologies. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. The peptide was cleaved from the resin with King's cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (XBridge, BEH130, Prep C18, 5 µM) using an acetonitrile/water gradient (both buffers with 0.1% TFA).

Finally, the molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4188.5 g/mol; M.W. (found) = 4188.6 g/mol.

Example 2:

Synthesis of SEQ ID NO: (5)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

The solid phase synthesis was carried out on Novabiochem Rink-Amide resin (4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido-norleucylaminomethyl resin),

100-200 mesh, loading of 0.34 mmol/g. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. The peptide was cleaved from the resin with King's cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (Sunfire, Prep C18) using an acetonitrile/water gradient (both buffers with 0.1% TFA).

Finally, the molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4259.6 g/mol; M.W. (found) = 4259.0 g/mol.

Example 3:

Synthesis of SEQ ID NO: (6)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 2. In position 39 Fmoc-Lys(ivDde)-OH and in position 1 Boc-His(Boc)-OH were used in the solid phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin according to literature (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603). Hereafter Palm(γOSu)(αOtBu)Glu was coupled to the liberated amino-group. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4626.2 g/mol; M.W. (found) = 4626.2 g/mol.

Example 4:

Synthesis of SEQ ID NO: (7)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 2. In position 40 Fmoc-Lys(ivDde)-OH and in position 1 Boc-His(Boc)-OH were used in the solid phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin

according to literature (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603). Hereafter Palm(γOSu)(αOtBu)Glu was coupled to the liberated amino-group. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4713.3 g/mol; M.W. (found) = 4712.7 g/mol.

Example 5:

Synthesis of SEQ ID NO: (8)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH-CH2-CH2-SH.

The resin used for synthesis was purchased from Iris Biotech (1-amino-ethane-2-thiol (cysteamine)-Mmt Resin; 0.4 mmol/g; 200-400 mesh). Peptide synthesis with this resin, cleavage and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4277.8 g/mol; M.W. (found) = 4277.5 g/mol.

Example 6:

Synthesis of SEQ ID NO: (9)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1 . The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4217.6 g/mol; M.W. (found) = 4217.1 g/mol.

Example 7:

Synthesis of SEQ ID NO: (10)

H-His-Ser-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4218.6 g/mol; M.W. (found) = 4218.1 g/mol.

Example 8:

Synthesis of SEQ ID NO: (11)

H-His-Gly-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4187.6 g/mol; M.W. (found) = 4187.2 g/mol.

Example 9:

Synthesis of SEQ ID NO:(12)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4186.7 g/mol; M.W. (found) = 4186.6 g/mol.

Example 10:

Synthesis of SEQ ID NO: (13)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4271.8 g/mol; M.W. (found) = 4272.0 g/mol.

Example 11:
Synthesis of SEQ ID NO:(14)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4215.6 g/mol; M.W. (found) = 4215.5 g/mol.

Example 12:
Synthesis of SEQ ID NO: (15)
H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.
The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4273.7 g/mol; M.W. (found) = 4273.5 g/mol.

Example 13:
Synthesis of SEQ ID NO: (16)
H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4273.7 g/mol; M.W. (found) = 4273.6 g/mol.

Example 14:

Synthesis of SEQ ID NO: (17)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4246.6 g/mol; M.W. (found) = 4246.4 g/mol.

Example 15:

Synthesis of SEQ ID NO: (18)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Lys-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4159. 6 g/mol; M.W. (found) = 4159.1 g/mol.

Example 16:

Synthesis of SEQ ID NO:(19)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4258.7 g/mol; M.W. (found) = 4258.5 g/mol.

Example 17:

Synthesis of SEQ ID NO: (20)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(ω-carboxypentadecanoyl))))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4626.2 g/mol; M.W. (found) = 4626.2 g/mol.

Example 18:

Synthesis of SEQ ID NO: (21)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(hexadecanoyl))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4497.1 g/mol; M.W. (found) = 4497.1 g/mol.

Example 19:

Synthesis of SEQ ID NO: (22)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Ala-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4130.6 g/mol; M.W. (found) = 4130.0 g/mol.

Example 20:

Synthesis of SEQ ID NO: (23)

H-D-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. In position 1 Fmoc-D-His(Trt)-OH was used in the solid phase synthesis protocol. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4217.6 g/mol; M.W. (found) = 4217.5 g/mol.

Example 21:
Synthesis of SEQ ID NO: (24)
His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. In position 1 Des-amino His(Trt)-OH was used in the solid phase synthesis protocol. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4202.6 g/mol; M.W. (found) = 4202.5 g/mol.

Example 22:
Synthesis of SEQ ID NO: (25)
H-His-Ser-MeGln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. In position 3 N-methylated Gln was used in the solid phase synthesis, the protocol therefore was described in literature (E. Biron, J. Chatterjee, H. Kessler, J. Peptide Sci. 12, 2006, 213-219). The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4231.6 g/mol; M.W. (found) = 4231.5 g/mol.

Example 23:

Synthesis of SEQ ID NO: (26)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(hexadecanoyl))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4584.2 g/mol; M.W. (found) = 4583.5 g/mol.

Example 24:

Synthesis of SEQ ID NO: (27)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(ω-carboxypentadecanoyl))))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4743.3 g/mol; M.W. (found) = 4742.6 g/mol.

Example 25:

Synthesis of SEQ ID NO: (28)

H-His-Ser(Me)-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 1. In position 2 Fmoc-Ser(Me)-OH was used in the solid phase synthesis protocol. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4231.7 g/mol; M.W. (found) = 4231.4 g/mol.

Example 26:

Synthesis of SEQ ID NO: (29)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-His-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4226.6 g/mol; M.W. (found) = 4226.0 g/mol.

Example 27:
Synthesis of SEQ ID NO: (30)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4217.6 g/mol; M.W. (found) = 4217.0 g/mol.

Example 28:
Synthesis of SEQ ID NO: (31)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Arg-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4245.7 g/mol; M.W. (found) = 4245.2 g/mol.

Example 29:
Synthesis of SEQ ID NO: (32)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4259.7 g/mol; M.W. (found) = 4259.0 g/mol.

Example 30:

Synthesis of SEQ ID NO: (33)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Glu-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4289.7 g/mol; M.W. (found) = 4289.0 g/mol.

Example 31:

Synthesis of SEQ ID NO: (34)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Glu-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4231.7 g/mol; M.W. (found) = 4231.0 g/mol.

Example 32:

Synthesis of SEQ ID NO: (35)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4215. 7 g/mol; M.W. (found) = 4215.2 g/mol.

Example 33:

Synthesis of SEQ ID NO: (36)
H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH-CH2-CH2-S-tBu.

This peptide could be isolated via preparative HPLC from the crude product obtained in example 5. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4333.9 g/mol; M.W. (found) = 4333.6 g/mol.

Example 34:

Synthesis of SEQ ID NO: (37)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Glu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4231. 6 g/mol; M.W. (found) = 4231.0 g/mol.

Example 35:

Synthesis of SEQ ID NO: (38)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Aib-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4171.5 g/mol; M.W. (found) = 4171.0 g/mol.

Example 36:

Synthesis of SEQ ID NO: (39)

H-His-Ala-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4201. 6 g/mol; M.W. (found) = 4201.0 g/mol.

Example 37:

Synthesis of SEQ ID NO: (40)

H-His-D-Ala-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4201. 6 g/mol; M.W. (found) = 4201.0 g/mol.

Example 38:

Synthesis of SEQ ID NO: (41)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4174.6 g/mol; M.W. (found) = 4174.1 g/mol.

Example 39:
Synthesis of SEQ ID NO: (42)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4188.6 g/mol; M.W. (found) = 4188.4 g/mol.

Example 40:
Synthesis of SEQ ID NO: (43)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Phe-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4233.6 g/mol; M.W. (found) = 4233.1 g/mol.

Example 41:
Synthesis of SEQ ID NO: (44)
H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4215.7 g/mol; M.W. (found) = 4215.2 g/mol.

Example 42:

Synthesis of SEQ ID NO: (45)

H-His-Gly-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4185.6 g/mol; M.W. (found) = 4185.2 g/mol.

Example 43:

Synthesis of SEQ ID NO: (46)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4201.6 g/mol; M.W. (found) = 4201.0 g/mol.

Example 44:

Synthesis of SEQ ID NO: (47)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4173.6 g/mol; M.W. (found) = 4173.0 g/mol.

Example 45:

Synthesis of SEQ ID NO: (48)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Arg-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4242.7 g/mol; M.W. (found) = 4242.1 g/mol.

Example 46:

Synthesis of SEQ ID NO: (49)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Arg-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4300.8 g/mol; M.W. (found) = 4300.1 g/mol.

Example 47:

Synthesis of SEQ ID NO: (50)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH-(CH2)5-OH.

The resin used for synthesis was purchased from Iris Biotech (5-Amino-1-pentanol 2-chlorotrityl Resin; 0.6 mmol/g; 200-400 mesh). Peptide synthesis with this resin,

cleavage and purification was carried out as described in example 1. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4303.8 g/mol; M.W. (found) = 4303.5 g/mol.

Example 48:

Synthesis of SEQ ID NO: (51)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4626.2 g/mol; M.W. (found) = 4625.8 g/mol.

Example 49:

Synthesis of SEQ ID NO: (52)

H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4624.3 g/mol; M.W. (found) = 4623.5 g/mol.

Example 50:

Synthesis of SEQ ID NO: (53)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4187. 6 g/mol; M.W. (found) = 4187.0 g/mol.

Example 51:

Synthesis of SEQ ID NO: (54)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4187. 6g/mol; M.W. (found) = 4187.0 g/mol.

Example 52:

Synthesis of SEQ ID NO: (55)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4217.6 g/mol; M.W. (found) = 4217.0 g/mol.

Example 53:

Synthesis of SEQ ID NO: (56)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4159. 6 g/mol; M.W. (found) = 4159.2 g/mol.

Example 54:

Synthesis of SEQ ID NO: (57)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Arg-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4189. 5 g/mol; M.W. (found) = 4189.0 g/mol.

Example 55:

Synthesis of SEQ ID NO: (58)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Arg-Ala-Ala-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

The synthesis and purification was carried out as described in example 2. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4214. 7 g/mol; M.W. (found) = 4214.1 g/mol.

Example 56:

Synthesis of SEQ ID NO: (59)

H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 2. In position 40 Fmoc-Lys(ivDde)-OH and in position 1 Boc-His(Boc)-OH were used in the solid

phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin according to literature (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603). Hereafter Palm(γOSu)(αOtBu)Glu was coupled to the liberated amino-group. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4711.4 g/mol; M.W. (found) = 4710.6 g/mol.

Example 57:
Synthesis of SEQ ID NO: (60)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4670.3 g/mol; M.W. (found) = 4669.6 g/mol.

Example 58:
Synthesis of SEQ ID NO: (61)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4727.4 g/mol; M.W. (found) = 4726.6 g/mol.

Example 59:
Synthesis of SEQ ID NO: (62)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4725.4 g/mol; M.W. (found) = 4724.7 g/mol.

Example 60:

Synthesis of SEQ ID NO: (63)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4684.3 g/mol; M.W. (found) = 4683.7 g/mol.

Example 61:

Synthesis of SEQ ID NO: (64)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4741.4 g/mol; M.W. (found) = 4740.7 g/mol.

Example 62:

Synthesis of SEQ ID NO: (65)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4686.3 g/mol; M.W. (found) = 4685.7 g/mol.

Example 63:

Synthesis of SEQ ID NO: (66)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4727.4 g/mol; M.W. (found) = 4726.8 g/mol.

Example 64:

Synthesis of SEQ ID NO: (67)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4727.4 g/mol; M.W. (found) = 4726.8 g/mol.

Example 65:

Synthesis of SEQ ID NO: (68)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4727.4 g/mol; M.W. (found) = 4726.7 g/mol.

Example 66:

Synthesis of SEQ ID NO: (69)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4754.4 g/mol; M.W. (found) = 4753.8 g/mol.

Example 67:

Synthesis of SEQ ID NO: (70)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4755.4 g/mol; M.W. (found) = 4754.8 g/mol.

Example 68:

Synthesis of SEQ ID NO: (71)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4757.4 g/mol; M.W. (found) = 4757.0 g/mol.

Example 69:

Synthesis of SEQ ID NO: (72)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4684.3 g/mol; M.W. (found) = 4683.8 g/mol.

Example 70:

Synthesis of SEQ ID NO: (73)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4698.4 g/mol; M.W. (found) = 4697.9 g/mol.

Example 71:

Synthesis of SEQ ID NO: (74)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4771.4 g/mol; M.W. (found) = 4771.0 g/mol.

Example 72:

Synthesis of SEQ ID NO: (75)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4769.4 g/mol; M.W. (found) = 4769.0 g/mol.

Example 73:

Synthesis of SEQ ID NO: (76)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4783.5 g/mol; M.W. (found) = 4782.9 g/mol.

Example 74:

Synthesis of SEQ ID NO: (77)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4741.4 g/mol; M.W. (found) = 4740.9 g/mol.

Example 75:

Synthesis of SEQ ID NO: (78)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4700.3 g/mol; M.W. (found) = 4699.8 g/mol.

Example 76:

Synthesis of SEQ ID NO: (79)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Ala-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4597.3 g/mol; M.W. (found) = 4596.8 g/mol.

Example 77:

Synthesis of SEQ ID NO: (80)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4611.3 g/mol; M.W. (found) = 4610.5 g/mol.

Example 78:

Synthesis of SEQ ID NO: (81)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(hexadecanoyl))-NH2.

The synthesis and purification was carried out as described in example 3. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4482.2 g/mol; M.W. (found) = 4481.5 g/mol.

Example 79:

Synthesis of SEQ ID NO: (82)

H-Gly-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4.
The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4757.4 g/mol; M.W. (found) = 4756.6 g/mol.

Example 80:

Synthesis of SEQ ID NO: (83)

H-Ac-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4742.3 g/mol; M.W. (found) = 4741.4 g/mol.

Example 81:

Synthesis of SEQ ID NO: (84)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-octadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4728.4 g/mol; M.W. (found) = 4727.6 g/mol.

Example 82:

Synthesis of SEQ ID NO: (85)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(octadecanoyl))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4599.3 g/mol; M.W. (found) = 4598.5 g/mol.

Example 83:

Synthesis of SEQ ID NO: (86)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-tocopheryl-succinyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4974.7 g/mol; M.W. (found) = 4974.0 g/mol.

Example 84:

Synthesis of SEQ ID NO: (87)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4666.3 g/mol; M.W. (found) = 4665.5 g/mol.

Example 85:

Synthesis of SEQ ID NO: (88)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Orn(N-δ-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4686.3 g/mol; M.W. (found) = 4685.7 g/mol.

Example 86:

Synthesis of SEQ ID NO: (89)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Dab(N-γ-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4672.3 g/mol; M.W. (found) = 4671.5 g/mol.

Example 87:

Synthesis of SEQ ID NO: (90)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Dap(N-β-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4658.2 g/mol; M.W. (found) = 4657.4 g/mol.

Example 88:

Synthesis of SEQ ID NO: (91)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4726.4 g/mol; M.W. (found) = 4725.7 g/mol.

Example 89:

Synthesis of SEQ ID NO: (92)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Glu-Gly-Gly-Pro-Ser-Ser-Gly-Arg-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4827.5 g/mol; M.W. (found) = 4826.8 g/mol.

Example 90:

Synthesis of SEQ ID NO: (93)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(γ-Glu(N-α-aleuritolyl))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4748.3 g/mol; M.W. (found) = 4747.6 g/mol.

Example 91:

Synthesis of SEQ ID NO: (94)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-α-aleuritolyl)-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4619.2 g/mol; M.W. (found) = 4618.6 g/mol.

Example 92:

Synthesis of SEQ ID NO: (95)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Chx-Ala-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4706.3 g/mol; M.W. (found) = 4705.6 g/mol.

Example 93:

Synthesis of SEQ ID NO: (96)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Cp-Ala-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4664.3 g/mol; M.W. (found) = 4663.6 g/mol.

Example 94:

Synthesis of SEQ ID NO: (97)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(γ-Glu(N-α-hexadecanoyl))))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4829.4 g/mol; M.W. (found) = 4828.9 g/mol.

Example 95:

Synthesis of SEQ ID NO: (98)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(β-Ala(N-α-(β-Ala(N-α-hexadecanoyl)))))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4713.4 g/mol; M.W. (found) = 4712.8 g/mol.

Example 96:

Synthesis of SEQ ID NO: (99)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-aminobutyroyl(N-γ-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4655.8 g/mol; M.W. (found) = 4656.3 g/mol.

Example 97:

Synthesis of SEQ ID NO: (100)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(β-Ala(N-α-(β-Ala(N-α-hexadecanoyl)))))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4626.3 g/mol; M.W. (found) = 4625.8 g/mol.

Example 98:

Synthesis of SEQ ID NO: (101)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(ß-Ala(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4555.2 g/mol; M.W. (found) = 4555.1 g/mol.

Example 99:

Synthesis of SEQ ID NO: (102)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Aib-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4657.3 g/mol; M.W. (found) = 4657.8 g/mol.

Example 100:

Synthesis of SEQ ID NO: (103)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4615.2 g/mol; M.W. (found) = 4614.5 g/mol.

Example 101:

Synthesis of SEQ ID NO: (104)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Glu-Gly-Gly-Pro-Ser-Ser-Gly-Lys-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4799.4 g/mol; M.W. (found) = 4799.0 g/mol.

Example 102:

Synthesis of SEQ ID NO: (105)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-acetyl)-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4374.8 g/mol; M.W. (found) = 4374.3 g/mol.

Example 103:

Synthesis of SEQ ID NO: (106)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-propionyl)))-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4532.0 g/mol; M.W. (found) = 4531.4 g/mol.

Example 104:

Synthesis of SEQ ID NO: (107)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(6-[(4,4-diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl)-NH2.

The synthesis and purification was carried out as described in example 4. The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4761.3 g/mol; M.W. (found) = 4760.6 g/mol.

Likewise, the following compounds were synthesized:

Example 105:
Synthesis of SEQ ID NO: (108)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4614.2 g/mol; M.W. (found) = 4613.2 g/mol.

Example 106:
Synthesis of SEQ ID NO: (109)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Glu-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4572.1 g/mol; M.W. (found) = 4571.2 g/mol.

Example 107:
Synthesis of SEQ ID NO: (110)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4614.2 g/mol; M.W. (found) = 4614.0 g/mol.

Example 108:

Synthesis of SEQ ID NO: (111)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Aib-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4528.1 g/mol; M.W. (found) = 4527.6 g/mol.

Example 109:

Synthesis of SEQ ID NO: (112)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Aib-Ala-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4526.2 g/mol; M.W. (found) = 4525.6 g/mol.

Example 110:

Synthesis of SEQ ID NO: (113)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Lys-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4612.3 g/mol; M.W. (found) = 4611.6 g/mol.

Example 111:

Synthesis of SEQ ID NO: (114)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Glu-Ala-Ala-Gln-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4570.2 g/mol; M.W. (found) = 4569.5 g/mol.

Example 112:
Synthesis of SEQ ID NO: (115)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Ala-Aib-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

The molecular mass of the purified peptide was confirmed by LC-MS. M.W. (calculated) = 4571.2 g/mol; M.W. (found) = 4569.5 g/mol.

In an analogous way, the following peptides can be synthesized:

Example 113:
SEQ ID NO: (116)
H-His-Ser-N-Me-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser- Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

Example 114:
SEQ ID NO: (117)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-octadecanoyl)))-NH2.

Example 115:

SEQ ID NO: (118)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-tocopheryl-succinyl)))-NH2.

Example 116:

SEQ ID NO: (119)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-aleuritolyl)))-NH2.

Example 117:

SEQ ID NO: (120)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Cb-Ala-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

Example 118:

SEQ ID NO: (121)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(γ-Glu(N-α-hexadecanoyl))))-NH2.

Example 119:

SEQ ID NO: (122)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

Example 120:

SEQ ID NO: (123)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Aib-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

Example 121:
SEQ ID NO: (124)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-aminobutyroyl(N-γ-hexadecanoyl))-NH2.

Example 122:
SEQ ID NO: (125)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-aminobutyroyl(N-γ-hexadecanoyl))-NH2.

Example 123:
SEQ ID NO: (126)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-cholyl)))-NH2.

Example 124:
SEQ ID NO: (127)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-lithocholyl)))-NH2.

Example 125:
SEQ ID NO: (128)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-linoleoyl)))-NH2.

Example 126:
SEQ ID NO: (129)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(4-dodecyclobenzoyl))))-NH2.
.

Example 127:
SEQ ID NO: (130)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-heneicosanoyl)))-NH2.

Example 128:
SEQ ID NO: (131)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-behenoyl)))-NH2.

Example 129:
SEQ ID NO: (132)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(cis-1-nonadecanoyl))))-NH2.

Example 130:
SEQ ID NO: (133)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(4-n-decycloxybenzoyl))))-NH2.

Example 131:
SEQ ID NO: (134)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(4'-octyloxy-biphenyl-4-carbonyl))))-NH2.

Example 132:
SEQ ID NO: (135)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Lys(N-ε-(γ-Glu(N-α-(12-phenyl-dodecanoyl))))-NH2.

Example 133:
SEQ ID NO: (136)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-cholyl)))-NH2.

Example 134:
SEQ ID NO: (137)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-lithocholyl)))-NH2.

Example 135:
SEQ ID NO: (138)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-linoleoyl)))-NH2.

Example 136:

SEQ ID NO: (139)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(4-dodecyclobenzoyl))))-NH2.

Example 137:

SEQ ID NO: (140)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-heneicosanoyl)))-NH2.

Example 138:

SEQ ID NO: (141)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-behenoyl)))-NH2.

Example 139:

SEQ ID NO: (142)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(cis-1-nonadecanoyl))))-NH2.

Example 140:

SEQ ID NO: (143)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(4-n-decycloxybenzoyl))))-NH2.

Example 141:

SEQ ID NO: (144)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(4'-octyloxy-biphenyl-4-carbonyl))))-NH2.

Example 142:

SEQ ID NO: (145)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-(12-phenyl-dodecanoyl))))-NH2.

Example 143:

SEQ ID NO: (146)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(β-Ala(N-α-hexadecanoyl)))-NH2.

Example 144:

SEQ ID NO: (147)

H-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Lys-Lys-Ala-Gln-Glu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

Example 145:

SEQ ID NO: (148)

H-Gly-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2.

Example 146:

SEQ ID NO: (149)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(PEG40kDa))-NH2.

PEG40kDa refers to a polyethylene glycol with a molecular mass of about 40 kDa.

Example 147:

SEQ ID NO: (150)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Cys(PEG40kDa)-NH2.

PEG40kDa refers to a polyethylene glycol with a molecular mass of about 40 kDa.

Example 148:

SEQ ID NO: (151)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Glu-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(γ-Glu(N-α-hexadecanoyl)))-NH2.

Example 149:

SEQ ID NO: (152)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys(N-ε-(hexadecanoyl))-NH2

Example 150:
SEQ ID NO: (153)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 151:
SEQ ID NO: (154)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 152:
SEQ ID NO: (155)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 153:
SEQ ID NO: (156)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 154:
SEQ ID NO: (157)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 155:
SEQ ID NO: (158)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 156:
SEQ ID NO: (159)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 157:
SEQ ID NO: (160)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 158:
SEQ ID NO: (161)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 159:
SEQ ID NO: (162)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 160:
SEQ ID NO: (163)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 161:
SEQ ID NO: (164)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 162:
SEQ ID NO: (165)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 163:
SEQ ID NO: (166)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 164:
SEQ ID NO: (167)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 165:
SEQ ID NO: (168)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 166:
SEQ ID NO: (169)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 167:
SEQ ID NO: (170)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 168:
SEQ ID NO: (171)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 169:
SEQ ID NO: (172)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 170:
SEQ ID NO: (173)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 171:
SEQ ID NO: (174)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 172:
SEQ ID NO: (175)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 173:
SEQ ID NO: (176)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 174:
SEQ ID NO: (177)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 175:
SEQ ID NO: (178)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 176:
SEQ ID NO: (179)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 177:
SEQ ID NO: (180)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 178:
SEQ ID NO: (181)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 179:
SEQ ID NO: (182)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 180:
SEQ ID NO: (183)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 181:
SEQ ID NO: (184)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 182:
SEQ ID NO: (185)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 183:
SEQ ID NO: (186)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 184:
SEQ ID NO: (187)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 185:
SEQ ID NO: (188)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 186:
SEQ ID NO: (189)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 187:
SEQ ID NO: (190)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 188:
SEQ ID NO: (191)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 189:
SEQ ID NO: (192)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 190:
SEQ ID NO: (193)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 191:

SEQ ID NO: (194)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 192:

SEQ ID NO: (195)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 193:

SEQ ID NO: (196)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 194:

SEQ ID NO: (197)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 195:

SEQ ID NO: (198)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 196:
SEQ ID NO: (199)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 197:
SEQ ID NO: (200)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 198:
SEQ ID NO: (201)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 199:
SEQ ID NO: (202)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 200:
SEQ ID NO: (203)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 201:
SEQ ID NO: (204)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 202:
SEQ ID NO: (205)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 203:
SEQ ID NO: (206)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 204:
SEQ ID NO: (207)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 205:
SEQ ID NO: (208)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH2

Example 206:
SEQ ID NO: (209)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 207:
SEQ ID NO: (210)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 208:
SEQ ID NO: (211)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 209:
SEQ ID NO: (212)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 210:
SEQ ID NO: (213)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 211:

SEQ ID NO: (214)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 212:

SEQ ID NO: (215)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 213:

SEQ ID NO: (216)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 214:

SEQ ID NO: (217)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 215:

SEQ ID NO: (218)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 216:
SEQ ID NO: (219)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Lys-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 217:
SEQ ID NO: (220)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Glu-Arg-Arg-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 218:
SEQ ID NO: (221)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 219:
SEQ ID NO: (222)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 220:
SEQ ID NO: (223)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Aib-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 221:
SEQ ID NO: (224)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Thr-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 222:
SEQ ID NO: (225)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 223:
SEQ ID NO: (226)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Arg-D-Ala-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 224:
SEQ ID NO: (227)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 225:
SEQ ID NO: (228)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ser-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 226:
SEQ ID NO: (229)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Gln-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 227:
SEQ ID NO: (230)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Gln-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 228:
SEQ ID NO: (231)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Gln-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 229:
SEQ ID NO: (232)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Gln-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 230:
SEQ ID NO: (233)

H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Arg-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 231:
SEQ ID NO: (234)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Arg-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 232:
SEQ ID NO: (235)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Lys-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 233:
SEQ ID NO: (236)
H-His-D-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Lys-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 234:
SEQ ID NO: (237)
H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Ser-Lys-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 235:
SEQ ID NO: (238)

H-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Nle-Glu-Ser-Lys-Ala-Ala-Gln-Asp-Phe-Ile-Glu-Trp-Leu-Lys-Ala-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2

Example 236: chemical stability and solubility

SEQ ID NO	stability		solubility [mg/ml]	
	pH4.5	pH7.4	pH4.5	pH7.4
(7)	99.4	86.7	>1	>1
(60)	99.0	97.8	>1	>1
(63)	99.9	87.7	>1	>1
(70)	99.1	90.9	>1	>1
(75)	98.3	84.9	>1	>1
(76)	98.9	88.6	0.952	>1
(77)	97.6	89.9	>1	>1
(78)	99.9	88.6	>1	>1
(79)	98.8	99.0	>1	0.666

Chemical stability of peptidic compounds was tested as described in Methods.

Example 237: In vitro data on GLP-1 and glucagon receptor

Potencies of peptidic compounds at the GLP-1 and glucagon receptors were determined by exposing cells expressing human glucagon receptor (hGlucagon R) and human GLP-1 receptor (hGLP-1 R) to the listed compounds at increasing concentrations and measuring the formed cAMP as described in Methods.

The results are shown in Table 1:

Table 1. EC50 values of exendin-4 peptide analogues at GLP-1 and Glucagon receptors (indicated in pM)

SEQ ID NO	EC50 hGLP-1R	EC50 hGlucagonR
(4)	17.4	565000.0
(9)	22.2	26.4
(10)	31.3	16700.0
(11)	25.4	2320.0
(12)	1.2	794.0
(13)	3.2	410.0
(14)	5.8	419.0
(5)	16.6	67.0
(15)	35.2	538.0
(16)	7.6	2130.0
(17)	24.1	3360.0
(18)	1.1	2570.0
(19)	17.0	52.0
(6)	3.1	1.9
(20)	7.7	1.8
(21)	78.2	547.0
(22)	0.8	127.0
(23)	723.0	374.0
(24)	264.0	168.0
(25)	170.0	171.0
(7)	5.2	6.2
(26)	9.7	3.3
(27)	202.0	2280.0
(28)	128.0	6480.0
(29)	28.0	149.0
(30)	50.5	1050.0
(31)	10.9	132.0
(32)	75.7	262.0
(33)	138.0	347.0
(34)	102.0	590.0
(35)	89.4	43.0
(8)	20.3	35.1
(36)	18.9	45.8
(37)	75.9	58.2
(50)	14.0	22.5
(38)	980.0	2810.0
(39)	4.6	683.0
(40)	8.1	1180.0
(41)	89.6	186.0
(42)	152.0	195.0
(43)	300.0	148.0
(44)	0.7	1120.0
(45)	0.8	103000.0
(46)	0.4	3520.0
(47)	0.8	1020.0
(48)	0.9	327.0
(49)	5.3	6880.0

(51)	5.8	6.3
(52)	4.1	24.1
(53)	0.2	317.0
(54)	0.6	2920.0
(55)	0.4	1020.0
(56)	1.8	2420.0
(57)	1.1	1080.0
(58)	0.9	413.0
(59)	2.9	40.9
(60)	3.5	4.8
(61)	4.2	30.4
(62)	6.3	130.0
(63)	9.9	58.0
(64)	21.9	67.0
(65)	15.0	5.7
(66)	13.0	16.2
(67)	21.5	7.7
(68)	12.3	7.8
(69)	7.6	5.9
(70)	5.0	17.2
(71)	5.6	1.9
(72)	5.2	2.9
(73)	4.4	21.2
(74)	39.6	35.5
(75)	4.6	64.1
(76)	4.8	74.1
(77)	3.0	37.2
(78)	4.2	18.1
(79)	3.7	195.0
(80)	10.8	38.1
(81)	19.7	29.3
(82)	2590.0	5520.0
(83)	369.0	375.0
(84)	3.9	13.8
(85)	6.4	9.0
(86)	28.1	21.8
(87)	5.7	19.1
(88)	5.1	18.2
(89)	5.9	19.8
(90)	4.9	33.6
(91)	6.7	121.0
(92)	6.0	38.0
(93)	188.0	1870.0
(95)	6.7	6.4
(96)	7.4	59.2
(97)	4.7	36.3
(98)	5.1	14.6
(100)	9.6	16.6

(102)	26.0	221.0
(103)	3.7	45.9
(104)	7.3	28.7
(105)	142.0	614.0
(106)	315.0	1320.0
(107)	9.0	5155.0
(108)	2.1	541.0
(109)	3.3	277.0
(110)	2.9	323.0
(111)	4.1	206.0
(112)	9.7	876.0
(113)	2.0	311.0
(114)	3.1	295.0
(115)	0.7	175.0
(124)	13.9	21.3
(125)	10.8	17.1

Example 238: Effect of single subcutaneous administration of SEQ ID NO: 7 on blood glucose in female diet-induced obese (DIO) C57BL/6NCrl mice (9 months on high-fat diet)

Treatment with SEQ ID NO: (7) significantly decreased blood glucose over 24 h in obese DIO mice compared to vehicle-treated control animals (Fig. 1).

Example 239: Effect of SEQ ID NO: 7 on gastric emptying and intestinal passage in female NMRI-mice

Female NMRI-mice, weighing on average 25 g, received 0.02 mg/kg of the test compound SEQ ID NO: (7) or phosphate buffered saline (vehicle control) subcutaneously, 30 min prior to the administration of the coloured bolus. 30 min later, the assessment of stomach contents (Fig. 2) and intestinal passage (Fig. 3) was done.

At the tested dose, SEQ ID NO: (7) reduced intestinal passage by 54% ($p<0.0001$, Student's T-Test).

Example 240: Effect of SEQ ID NO: 7 on 22-hours food intake in female NMRI-mice

Fed female NMRI-mice, weighing on average 27 g, were administered 0.01 or 0.1 mg/kg of SEQ ID NO: (7) or phosphate buffered saline (vehicle control) subcutaneously, directly prior to start of feeding monitoring. Lights-off phase (dark phase) started 4 hours later.

At the tested doses, SEQ ID NO: (7) demonstrated a dose-dependent reduction of feed intake, reaching 17% ($p=0.0027$) and 37% ($p<0.0001$, 2-W-ANOVA-RM, post hoc Dunnett's Test) at the end of the study, respectively (Fig. 4).

Claims

1. A peptidic compound having the formula (I):

$R^1 - Z - R^2$ (I)

wherein Z is a peptide moiety having the formula (II)

$X0_m$-X1-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-X14-X15-X16-X17-X18-X19-X20-X21-Phe-Ile-Glu-Trp-Leu-Lys-X28-X29-Gly-Pro-Ser-Ser-Gly-X35-Pro-Pro-Pro-X39-$X40_n$ (II)

X0 is absent or represents an amino acid residue selected from Gly,
X1 represents an amino acid residue selected from His, D-His, and Des-amino-His,
X2 represents an amino acid residue selected from Gly, Ser or functionalized-Ser, e.g. Ser (OCH_3), D-Ser or functionalized D-Ser, e.g. D-Ser (OCH_3) Aib, Ala, or D-Ala, wherein Ser may be functionalized in that the H of the OH side chain group is substituted by C_{1-4} alkyl, e.g. methyl,
X3 represents an amino acid residue selected from Glu, Gln, His and α-amino-functionalized Gln, e.g. Gln ($NHCH_3$), wherein Gln may be functionalized in that an H of the α-NH_2 group is substituted by C_{1-4} alkyl, e.g. methyl,
X14 represents an amino acid residue selected from Met, Phe, Aib, Nle, or Cycloalkyl-Ala, e.g. Cyclohexyl (Chx)-Ala, Cyclopentyl (Cp)-Ala or Cyclobutyl (Cb)-Ala, wherein Ala may be functionalized in that one of the CH_3 side-chain group is substituted by C_{3-8} cyclo alkyl,
X15 represents an amino acid residue selected from Glu or Asp,
X16 represents an amino acid residue selected from Ser, Glu and Lys,
X17 represents an amino acid residue selected from Arg, Glu, Gln, Aib and Lys,
X18 represents an amino acid residue selected from Arg, Ala and Lys,

X19 represents an amino acid residue selected from Ala and Val,
X20 represents an amino acid residue selected from Gln, Arg, Lys, His and Aib,
X21 represents an amino acid residue selected from Asp, Leu and Glu,
X28 represents an amino acid residue selected from Asn, Arg, Lys, Aib, Ser, Glu and Ala,
X29 represents an amino acid residue selected from Gly, Ala, D-Ala or Thr, and
X35 represents an amino acid residue selected from Ala, Glu, Arg and Lys,
X39 represents an amino acid residue selected from Ser,
an amino acid residue having a side chain with an $-NH_2$ group, particularly Lys, Orn, Dab or Dap, wherein the $-NH_2$ side chain group is optionally functionalized and
an amino acid residue having a side chain with an -SH group, particularly Cys, wherein the -SH side chain group is optionally functionalized, and
X40 represents an amino acid residue selected from an amino acid residue having a side chain with an $-NH_2$ group, particularly Lys, Orn, Dab or Dap, wherein the $-NH_2$ side chain group is optionally functionalized and
an amino acid residue having a side chain with an -SH group, particularly Cys, wherein the -SH side chain group is optionally functionalized,
R^1 represents the N-terminal group of the peptidic compound and is selected from NH_2 or mono- or bisfunctionalized NH_2,
R^2 represents the C-terminal group of the peptidic compound and is selected from
(i) OH or functionalized OH and
(ii) NH_2 or mono- or bisfunctionalized NH_2,

m and n are in each case independently selected from 0 or 1,
or a salt or solvate thereof
with the proviso that Exendin-4 (SEQ ID NO: 1) is not encompassed..

2. The compound of claim 1,

wherein

R^1 is NH_2,

R^2 is NH_2 or

R^1 and R^2 are NH_2.

3. The compound of claim 1 or 2,

wherein

X0 is absent.

4. The compound of any one of claims 1-3,

wherein

X40 is absent, particularly wherein X40 is absent and X39 represents Lys or functionalized Lys.

5. The compound of any one of claims 1-3,

wherein

X40 is present, particularly wherein X40 is present and X39 represents Ser, or X40 is present and represents Lys or functionalized Lys.

6. The compound of any one of claims 1-5,

wherein

the functionalized Lys is functionalized at its ε-amino group with

$-C(O)-R^5$, $S(O)_2-R^5$ or $-R^5$

wherein R^5 is

(i) a moiety comprising up to 100 carbon atoms and optionally heteroatoms selected from N, O, S and/or P, or

(ii) an organic polymer.

7. The compound of claim 6, wherein

$-C(O)-R^5$ is (S)-4-carboxy-4-hexadecanoyl-amino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, hexadecanoyl or octadecanoyl.

8. The compound of any one of claims 1-7, wherein

X14 represents Met or Nle, preferably Met.

9. The compound of any one of claims 1-8, wherein

X3 represents Gln,

X16 represents Ser,

X17 represents Arg,

X18 represents Arg,

X19 represents Ala,

X20 represents Gln and

X21 represents Asp or Glu.

10. The compound of any one of claims 1-9,

wherein

X2 represents Ser, D-Ser or Aib, preferably D-Ser or Aib and more preferably D-Ser.

11. The compound of any one of claims 1-10,

wherein

(i) X2 represents D-Ser or Aib and X40 is functionalized Lys,

(ii) X2 represents Ser, D-Ser or Aib, X39 is functionalized Lys and X40 is absent,

(iii) X2 represents Ser, D-Ser or Aib and X40 is absent, or

(iv) X2 represents Ser, D-Ser or Aib and X40 is functionalized Cys.

12. The compound of any one of claims 1-11,

wherein

X15 represents Glu.

13. The compound of any one of claims 1-12,

wherein

X16 represents Lys or Ser.

14. The compound of any one of claims 1-13,
wherein
X19 represents Ala.

15. The compound of any one of claims 1-14,
wherein
X20 represents Lys or Gln.

16. The compound of any one of claims 1-15,wherein
X21 represents Leu or Glu.

17. The compound of any one of claims 1-16, wherein
X15 represents Glu,
X16 represents Lys or Ser,
X19 represents Ala,
X20 represents Lys or Gln and
X21 represents Leu or Glu.

18. The compound of any one of claims 1-17,
wherein
1, 2, 3, 4, 5 or 6, particularly 5 or 6 amino acid residues selected from X15, X16, X17, X18, X19, X20 and X21 are amino acid residues which differ from the corresponding amino acid residues in Exendin-4 (SEQ ID NO: 1).

19. The compound of any one of claims 1-18, wherein
(a) X2 = D-Ser;
X3 = Gln;
X14 = Met;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;

X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Arg; particularly Gln;
X21 = Asp or Leu;
X28 = Asn, Ala, Ser, Lys, Aib or Arg;
X29 = Gly or D-Ala;
X35 = Ala; and
(i) X39 = Ser and
X40 = Lys, Orn, Dab or Dap which are functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-Carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, and
X40 = absent,

(b) X2 = D-Ser or Aib;
X3 = Gln;
X14 = Met;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg;
X18 = Arg;
X19 = Ala;
X20 = Gln or Lys;
X21 = Asp;
X28 = Asn, Ser, Lys or Aib;
X29 = Gly, Thr, Ala or D-Ala;
X35 = Ala;
X39 = Ser and

(i) X40 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, and
X40 is absent,

(c) X2 = D-Ser;
X3 = Gln;
X14 = Nle, Chx-Ala, Cp-Ala or Cb-Ala;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Lys;
X21 = Asp, Glu or Leu;
X28 =Ala or Ser;
X29 = Gly;
X35 = Ala and
(i) X39 = Ser and
X40 = Lys, Orn, Dab or Dap which are functionalized at the amino side chain group, particularly by (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl,
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-Carboxy-4-hexadecanoylamino-butyryl, (S)-4-Carboxy-4-octadecanoylamino-butyryl, octadecanoyl or hexadecanoyl and
X40 = absent,

(d) X2 = Ser or D-Ser;
X3 = Gln;

X14 = Met;
X15 = Asp or Glu;
X16 = Ser;
X17 = Arg;
X18 = Arg;
X19 = Ala;
X20 = Gln;
X21 = Asp;
X28 = Asn;
X29 = Gly;
X35 = Ala; and
(i) X39 = Ser and
X40 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-(hexadecanoylamino)-butyryl or (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, or
(ii) X39 = Lys which is functionalized at the amino side chain group, particularly by (S)-4-carboxy-4-hexadecanoylamino-butyryl, (S)-4-carboxy-4-octadecanoylamino-butyryl, octadecanoyl, or hexadecanoyl, and
X40 is absent,

(e) X2 = Ser or D-Ser;
X3 = Gln;
X14 = Met or Nle;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg or Glu;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln, Arg or Lys;
X21 = Asp, Glu or Leu;
X28 = Asn;
X29 = Gly;

X35 = Ala;
X39 = Ser and
X40 = absent, or

(f) X2 = Aib or D-Ser;
X3 = Gln;
X14 = Met or Nle;
X15 = Asp or Glu;
X16 = Ser, Glu or Lys;
X17 = Arg, Lys or Gln;
X18 = Arg or Ala;
X19 = Ala;
X20 = Gln or Lys;
X21 = Asp;
X28 = Asn, Ala, Aib, Lys, Arg or Ser;
X29 = Gly, Ala, D-Ala or Thr;
X35 = Ala;
X39 = Ser and
X40 = absent or Lys.

20. The compound of any one of claims 1-19, selected from the compounds of SEQ ID NO. 7-238, or a salt or solvate thereof.

21. The compound of any one of claims 1-20 for use in medicine, particularly in human medicine.

22. The compound for use according to claim 21 which is present as an active agent in a pharmaceutical composition together with at least one pharmaceutically acceptable carrier.

23. The compound for use according to claim 21 or 22 together with at least one additional therapeutically active agent, wherein the additional therapeutically

active agent particularly is a GLP-1 compound and/or an insulinic compound and/or a gastrointestinal peptide.

24. The compound for use according to any one of claims 21-23 for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, metabolic syndrome and neurodegenerative disorders, particularly for delaying or preventing disease progression in type 2 diabetes, treating metabolic syndrome, treating obesity or preventing overweight, for decreasing food intake, increase energy expenditure, reducing body weight, delaying the progression from impaired glucose tolerance (IGT) to type 2 diabetes; delaying the progression from type 2 diabetes to insulin-requiring diabetes;
regulating appetite; inducing satiety; preventing weight regain after successful weight loss; treating a disease or state related to overweight or obesity; treating bulimia; treating binge eating;
treating atherosclerosis, hypertension, type 2 diabetes, IGT, dyslipidemia, coronary heart disease, hepatic steatosis, treatment of beta-blocker poisoning, use for inhibition of the motility of the gastro-intestinal tract, useful in connection with investigations of the gastro-intestinal tract using techniques such as X-ray, CT- and NMR-scanning, or
. for the treatment or prevention of hypoglycemia, insulin induced hypoglycemia, reactive hypoglycemia, diabetic hypoglycemia, non-diabetic hypoglycemia, fasting,
hypoglycemia, drug-induced hypoglycemia, gastric by-pass induced hypoglycemia,
hypoglycemia in pregnancy, alcohol induced hypoglycemia, insulinomaand Von Girkes disease.