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(71) Applicant(s)
Sanofi

(72) Inventor(s)
Haack, Torsten;Wagner, Michael;Henkel, Bernd;Stengelin, Siegfried;Evers, Andreas;Lorenz, Martin;Lorenz, Katrin

(74) Agent / Attorney
Watermark Intellectual Property Pty Ltd, L 1 109 Burwood Rd, Hawthorn, VIC, 3122, AU

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(71) Applicant: **SANOFI** [FR/FR]; 54 rue La Boétie, F-75008 Paris (FR).

(72) Inventors: **HAACK, Torsten**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **WAGNER, Michael**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **HENKEL, Bernd**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **STENGELIN, Siegfried**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **EVERS, Andreas**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **LORENZ, Martin**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **LORENZ, Katrin**; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

(74) Agents: **WEISS, Wolfgang** et al.; Weickmann & Weickmann, Richard-Strauss-Str. 80, 81679 München (DE).

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(54) Title: DUAL GLP1/GIP OR TRIGONAL GLP1/GIP/GLUCAGON AGONISTS

(57) Abstract: The present invention relates to exendin-4 derivatives 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.

Dual GLP1/GIP or trigonal GLP1/GIP/Glucagon Agonists

Description

FIELD OF THE INVENTION

The present invention relates to exendin-4 peptide analogues which activate the glucagon-like peptide 1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP) receptor and optionally the glucagon receptor (GCG) 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., 267:7402-05,1992). Exendin-4 is an activator of the glucagon-like peptide-1 (GLP-1) receptor, whereas it shows only very low activation of the GIP receptor and does not activate the glucagon receptor (see Table 1).

Table 1: Potencies of exendin-4 at human GLP-1, GIP and Glucagon receptors (indicated in pM) at increasing concentrations and measuring the formed cAMP as described in Methods.

SEQ ID NO:	peptide	EC50 hGLP-1 R [pM]	EC50 hGIP R [pM]	EC50 hGlucagon R [pM]
1	exendin-4	0.4	12500.0	>10000000

Exendin-4 shares many of the glucoregulatory actions observed with GLP-1. Clinical and non-clinical studies have shown that exendin-4 has several beneficial antidiabetic properties including a glucose dependent

enhancement in insulin synthesis and secretion, glucose dependent suppression of glucagon secretion, slowing down gastric emptying, reduction of food intake and body weight, and an increase in beta-cell mass and markers of beta cell function (Gentilella R et al., Diabetes Obes Metab., 11:544-56, 2009; Norris SL et al., Diabet Med., 26:837-46, 2009; Bunck MC et al., Diabetes Care., 34:2041-7, 2011).

These effects are beneficial not only for diabetics but also for patients suffering from obesity. Patients with obesity have a higher risk of getting diabetes, hypertension, hyperlipidemia, cardiovascular and musculoskeletal diseases.

Relative to GLP-1 and GIP, exendin-4 is more resistant to cleavage by dipeptidyl peptidase-4 (DPP4) resulting in a longer half-life and duration of action in vivo (Eng J., Diabetes, 45 (Suppl 2):152A (abstract 554), 1996; Deacon CF, Horm Metab Res, 36: 761-5, 2004).

Exendin-4 was also shown to be much more stable towards degradation by neutral endopeptidase (NEP), when compared to GLP-1, glucagon or oxyntomodulin (Druce MR et al., Endocrinology, 150(4), 1712-1721, 2009).

Nevertheless, exendin-4 is chemically labile due to methionine oxdiation in position 14 (Hargrove DM et al., Regul. Pept., 141: 113-9, 2007) as well as deamidation and isomerization of asparagine in position 28 (WO 2004/035623).

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

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2

The amino acid sequence of GLP-1(7-36)-amide is shown as SEQ ID NO: 2:

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH_2

Liraglutide is a marketed chemically modified GLP-1 analogue in which, among other modifications, a fatty acid is linked to a lysine in position 20 leading to a prolonged duration of action (Drucker DJ et al, Nature Drug Disc. Rev. 9, 267-268, 2010; Buse, JB et al., Lancet, 374:39-47, 2009).

The amino acid sequence of Liraglutide is shown as SEQ ID NO: 3:

HAEGTFTSDVSSYLEGQAAK((S)-4-Carboxy-4-hexadecanoylamino-butyryl-) EFIAWLVRGRG-OH

GIP (glucose-dependent insulinotropic polypeptide) is a 42 amino acid peptide that is released from intestinal K-cells following food intake. GIP and GLP-1 are the two gut enteroendocrine cell-derived hormones accounting for the incretin effect, which accounts for over 70% of the insulin response to an oral glucose challenge (Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology 2007; 132: 2131–2157).

GIP's amino acid sequence is shown as SEQ ID NO: 4:

YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-OH

Glucagon is a 29-amino acid peptide which is released into the bloodstream when circulating glucose is low. Glucagon's amino acid sequence is shown in SEQ ID NO: 5:

HSQGTFTSDYSKYLDSRRAQDFVQWLMNT-OH

During hypoglycemia, when blood glucose levels drop below normal, glucagon signals the liver to break down glycogen and release glucose, causing an increase of blood glucose levels to reach a normal level.

Hypoglycemia is a common side effect of insulin treated patients with hyperglycemia (elevated blood glucose levels) due to diabetes. Thus, glucagon's most predominant role in glucose regulation is to counteract insulin action and maintain blood glucose levels.

Holst (Holst, J. J. Physiol. Rev. 2007, 87, 1409) and Meier (Meier, J. J. Nat. Rev. Endocrinol. 2012, 8, 728) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, improve glycemic control in patients with T2DM by reducing fasting and postprandial glucose (FPG and PPG). Peptides which bind and activate the GLP-1 receptor are described in patent applications WO 98/08871 A1, WO2008/081418 A1 and WO2008/023050 A1, the contents of which are herein incorporated by reference.

It has been described that dual activation of the GLP-1 and GIP receptors, e.g. by combining the actions of GLP-1 and GIP in one preparation, leads to a therapeutic principle with significantly better reduction of blood glucose levels, increased insulin secretion and reduced body weight in mice with T2DM and obesity compared to the marketed GLP-1 agonist Liraglutide (e.g. VA Gault et al., Clin Sci (Lond), 121, 107-117, 2011). Native GLP-1 and GIP were proven in humans following co-infusion to interact in an additive manner with a significantly increased insulinotropic effect compared to GLP-1 alone (MA Nauck et al., J. Clin. Endocrinol. Metab., 76, 912-917, 1993).

Designing hybrid molecules which combine agonism on the GLP-1 receptor, the GIP receptor and the glucagon receptor offers the therapeutic potential to achieve significantly better reduction of blood glucose levels, increased insulin secretion and an even more pronounced significant effect on body weight reduction compared to the marketed GLP-1 agonist Liraglutide (e.g. VA Gault et al., Clin Sci (Lond), 121, 107-117, 2011).

Compounds of this invention are exendin-4 derivatives, which show agonistic activity at the GLP-1 and the GIP receptor and optionally the glucagon

receptor and which have – among others - preferably the following modifications: Tyr at position 1 and Ile at position 12.

Surprisingly, it was found that the modification of the selective GLP-1R agonist Exendin-4 by Tyr in position 1 and Ile in position 12 results in a peptide with high dual activity at the GLP-1 and GIP receptors. This observation is surprising, since the same modification in other GLP-1 agonists, such as GLP-1 itself, does not result in high activity at the GIP receptor, as shown in Table 2.

Table 2: Potencies of exendin-4 and GLP-1 peptide analogues at GLP-1 and GIP receptors (indicated in pM) at increasing concentrations and measuring the formed cAMP as described in Methods.

SEQ ID NO:	peptide	EC50 hGIP R [pM]	EC50 hGLP-1 R [pM]
6	Tyr(1)Ile(12)-exendin-4	93.9	1.3
7	Tyr(1)Ile(12)-GLP1	3660.0	5.0

Peptides which bind and activate both the GIP and the GLP-1 receptor and optionally the glucagon receptor, and improve glycaemic control, suppress body weight gain and reduce food intake are described in patent applications WO 2011/119657 A1, WO 2012/138941 A1, WO 2010/011439 A2, WO 2010/148089 A1, WO 2011/094337 A1, WO 2012/088116 A2, the contents of which are herein incorporated by reference. These applications disclose that mixed agonists of the GLP-1 receptor, the GIP receptor and optionally the glucagon receptor can be designed as analogues of the native GIP or glucagon sequences.

Compounds of this invention are exendin-4 peptide analogues comprising leucine in position 10 and glutamine in position 13. Krstenansky et al. (Biochemistry, 25, 3833-3839, 1986) show the importance of residues 10 to 13 of glucagon for its receptor interactions and activation of adenylate

cyclase. In the exendin-4 peptide analogues of this invention, several of the underlying residues are different from said of glucagon. In particular, residues Tyr10 and Tyr13, are replaced by leucine in position 10 and glutamine, a non-aromatic polar amino acid, in position 13. This replacement, especially in combination with isoleucine in position 23 and glutamate in position 24 leads to exendin-4 derivatives with potentially improved biophysical properties as solubility or aggregation behavior in solution. The non-conservative replacement of an aromatic amino acid with a polar amino acid in position 13 of an exendin-4 analogue surprisingly leads to peptides with high activity on the GIP receptor and optionally on the glucagon receptor.

Furthermore, compounds of this invention are exendin-4 derivatives with fatty acid acylated residues in position 14. This fatty acid functionalization in position 14 results in an improved pharmacokinetic profile. Surprisingly, the fatty acid functionalization in position 14 also leads to peptides with a significantly higher GIPR activity, for example those shown in Example 5, Table 8.

Compounds of this invention are exendin-4 peptide analogues which contain alpha,alpha-dialkylated amino acids with a basic side-chain in position 20. Surprisingly, modification of the exendin-4 sequence with one of these amino acids leads to compounds with an improved biophysical profile, as solubility (in particular at low pH, especially at pH 4.5) or aggregation behaviour in solution, when the unnatural amino acid is incorporated at position 20. The resulting exendin-4 analogues thereby maintain their high activity at the GLP-1 receptor, the GIP receptor and optionally the glucagon receptor. The incorporation of these unnatural amino acids also increases enzymatic stability of the peptides, potentially resulting in improved pharmacokinetic properties.

BRIEF SUMMARY OF THE INVENTION

Provided herein are exendin-4 analogues which potently activate the GLP-1 and the GIP receptor and optionally the glucagon receptor. In these exendin-4 analogues – among other substitutions - methionine at position 14 is replaced by an amino acid carrying an $-NH_2$ group in the side-chain, which is further substituted with a lipophilic side-chain (e.g. a fatty acid optionally combined with a linker).

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

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

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

Tyr-Aib-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-X12-Gln-X14-X15-X16-X17-X18-X19-X20-X21-Phe-Ile-Glu-Trp-Leu-Lys-X28-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-X40 (II)

X3 represents an amino acid residue selected from Gln, Glu and His,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by $-C(O)-R^5$, $-C(O)O-R^5$, $-C(O)NH-R^5$, $-S(O)_2-R^5$ or R^5, preferably by $-C(O)-R^5$, wherein R^5 may be a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P,
X15 represents an amino acid residue selected from Asp and Glu,
X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,
X17 represents an amino acid residue selected from Arg, Lys, Ile, Glu, Gln, Leu, Aib, Tyr and Ala,

X18 represents an amino acid residue selected from Ala, Arg, Lys, Aib, Leu and Tyr,

X19 represents an amino acid residue selected from Ala, Val, Gln and Aib,

X20 represents an amino acid residue selected from Gln, Aib, Phe, Leu, Lys, His, Arg, Pip, (S)MeLys, (R)MeLys, (S)MeOrn and (R)MeOrn,

X21 represents an amino acid residue selected from Asp, Glu, Leu and Tyr,

X28 represents an amino acid residue selected from Asn, Ala, Arg, Lys, Aib and Ser,

X29 represents an amino acid residue selected from Gly, Thr, Aib, D-Ala and Ala,

X40 is absent or represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is optionally functionalized by $-C(O)-R^5$, $-C(O)O-R^5$, $-C(O)NH-R^5$, $-S(O)_2-R^5$ or R^5, preferably by $-C(O)-R^5$, wherein R^5 may be a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P,

R^1 represents NH_2,

R^2 represents OH or NH_2.

or a salt or solvate thereof.

The compounds of the invention are GLP-1 and GIP receptor agonists and optionally glucagon receptor agonists as determined by the observation that they are capable of stimulating intracellular cAMP formation. In vitro potency determination in cellular assays of agonists is quantified by determining the concentrations that cause 50% activation of maximal response (EC50) as described in Methods.

In certain embodiments, the invention therefore provides a peptidic

compound having the formula (I):

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

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

Tyr-Aib-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-X12-Gln-X14-X15-X16-X17-X18-X19-X20-X21-Phe-Ile-Glu-Trp-Leu-Lys-X28-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-X40 (II)

X3 represents an amino acid residue selected from Gln, Glu and His,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by $-C(O)-R^5$, $-C(O)O-R^5$, $-C(O)NH-R^5$, $-S(O)_2-R^5$ or R^5, preferably by $-C(O)-R^5$, wherein R^5 is a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P,
X15 represents an amino acid residue selected from Asp and Glu,
X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,
X17 represents an amino acid residue selected from Arg, Lys, Ile, Glu, Gln, Leu, Aib, Tyr and Ala,
X18 represents an amino acid residue selected from Ala, Arg, Lys, Aib, Leu and Tyr,
X19 represents an amino acid residue selected from Ala, Val, Gln and Aib,
X20 represents an amino acid residue selected from Gln, Aib, Phe, Leu, Lys, His, Arg, Pip, (S)MeLys, (R)MeLys, (S)MeOrn and (R)MeOrn,
X21 represents an amino acid residue selected from Asp, Glu, Leu and Tyr,
X28 represents an amino acid residue selected from Asn, Ala, Arg, Lys, Aib and Ser,

X29 represents an amino acid residue selected from Gly, Thr, Aib, D-Ala and Ala,

X40 is absent or represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is optionally functionalized by $-C(O)-R^5$, $-C(O)O-R^5$, $-C(O)NH-R^5$, $-S(O)_2-R^5$ or R^5, preferably by $-C(O)-R^5$, wherein R^5 may be a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P,

R^1 represents NH_2,

R^2 represents OH or NH_2.

or a salt or solvate thereof, wherein the peptidic compound has a relative activity of at least 0.04%, preferably at least 0.08%, more preferably at least 0.2% compared to that of natural GIP at the GIP receptor.

In addition, the peptidic compound, particularly with a lysine at position 14 which is further substituted with a lipophilic residue, exhibits a relative activity of at least 0.07%, preferably at least 0.1%, more preferably at least 0.14%, more preferably at least 0.35% and even more preferably at least 0.4% compared to that of GLP-1(7-36) at the GLP-1 receptor.

In addition, the peptidic compound, particularly with a lysine at position 14 which is further substituted with a lipophilic residue, exhibits a relative activity of at least 0.04% (i.e. EC_{50} < 1000 pM), more preferably 0.08% (i.e. EC_{50} < 500 pM) and even more preferably 0.2% (i.e. EC_{50} < 200 pM) compared to that of natural GIP at the GIP receptor (EC_{50} = 0.4 pM).

Optionally, in some embodiments, the peptidic compound, particularly with a lysine at position 14 which is further substituted with a lipophilic residue, exhibits a relative activity of at least 0.1%, preferably at least 0.2%, more

preferably at least 0.3%, more preferably at least 0.4% and even more preferably at least 0.5% compared to that of natural glucagon at the glucagon receptor.

The term "activity" as used herein preferably refers to the capability of a compound to activate the human GLP-1 receptor, the human GIP receptor and optionally the human glucagon receptor. More preferably the term "activity" as used herein refers to the capability of a compound to stimulate intracellular cAMP formation. The term "relative activity" as used herein is understood to refer to the capability of a compound to activate a receptor in a certain ratio as compared to another receptor agonist or as compared to another receptor. The activation of the receptors by the agonists (e.g. by measuring the cAMP level) is determined as described herein, e.g. as described in the examples.

According to one embodiment, the compounds of the invention have an EC_{50} for hGLP-1 receptor of 500 pM or less, preferably of 200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less.

According to one embodiment, the compounds of the invention have an EC_{50} for hGIP receptor of 500 pM or less, preferably of 200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less.

According to another embodiment, the compounds of the invention have optionally an EC_{50} for hGlucagon receptor of 500 pM or less, preferably of

200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less.

According to another embodiment, the compounds of the invention have an EC_{50} for hGLP-1 receptor of 500 pM or less, preferably of 200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less, and/or an EC_{50} for hGIP receptor of 500 pM or less, preferably of 200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less, and/or optionally an EC_{50} for hGlucagon receptor of 500 pM or less, preferably of 200 pM or less; more preferably of 150 pM or less, more preferably of 100 pM or less, more preferably of 90 pM or less, more preferably of 80 pM or less, more preferably of 70 pM or less, more preferably of 60 pM or less, more preferably of 50 pM or less, more preferably of 40 pM or less, more preferably of 30 pM or less, and more preferably of 20 pM or less.

In still another embodiment, the EC_{50} for both receptors, i.e. for the hGLP-1 receptor and for the hGIP receptor, is 500 pM or less, more preferably 200 pM or less, more preferably 150 pM or less, more preferably 100 pM or less, more preferably 90 pM or less, more preferably 80 pM or less, more preferably 70 pM or less, more preferably 60 pM or less, more preferably 50 pM or less, more preferably 40 pM or less, more preferably 30 pM or less,

more preferably 20 pM or less.

In still another embodiment, the EC_{50} for all three receptors, i.e. for the hGLP-1 receptor, for the hGIP receptor and for the hGlucagon receptor, is 500 pM or less, more preferably 200 pM or less, more preferably 150 pM or less, more preferably 100 pM or less, more preferably 90 pM or less, more preferably 80 pM or less, more preferably 70 pM or less, more preferably 60 pM or less, more preferably 50 pM or less, more preferably 40 pM or less, more preferably 30 pM or less, more preferably 20 pM or less.

The EC_{50} for hGLP-1 receptor, hGIP receptor and hGlucagon receptor may be determined as described in the Methods herein and as used to generate the results described in Example 5.

The compounds of the invention have the ability to reduce the intestinal passage, to increase the gastric content and/or to reduce the food intake of a patient. These activities of the compounds of the invention can be assessed in animal models known to the skilled person and also described herein in the Methods. The results of such experiments are described in Example 10. Preferred compounds of the invention may increase the gastric content of mice, preferably of female NMRI-mice, if administered as a single dose, preferably subcutaneous dose, of 0.02 mg/kg body weight by at least 25%, more preferably by at least 30%, more preferably by at least 40%, more preferably by at least 50%, more preferably by at least 60%, more preferably by at least 70%, more preferably by at least 80%.

Preferably, this result is measured 1 h after administration of the respective compound and 30 mins after administration of a bolus, and/or reduces intestinal passage of mice, preferably of female NMRI-mice, if administered as a single dose, preferably subcutaneous dose, of 0.02 mg/kg body weight at least by 45%; more preferably by at least 50%, more preferably by at least 55%, more preferably by at least 60%, and more preferably at least 65%;

and/or reduces food intake of mice, preferably of female NMRI-mice, over a period of 22 h, if administered as a single dose, preferably subcutaneous dose of 0.01 mg/kg body weight by at least 10%, more preferably 15%, and more preferably 20%.

The compounds of the invention have the ability to reduce blood glucose level, and/or to reduce HbA1c levels of a patient. These activities of the compounds of the invention can be assessed in animal models known to the skilled person and also described herein in the Methods. The results of such experiments are described in Examples 8 and 9.

Preferred compounds of the invention may reduce blood glucose level of mice, preferably in female leptin-receptor deficient diabetic db/db mice over a period of 24 h, if administered as a single dose, preferably subcutaneous dose, of 0.01 mg/kg body weight by at least 4 mmol/L; more preferably by at least 6 mmol/L, more preferably by at least 8 mmol/L. If the dose is increased to 0.1 mg/kg body weight a more pronounced reduction of blood glucose levels can be observed in mice over a period of 24 h, if administered as a single dose, preferably subcutaneous dose. Preferably the compounds of the invention lead to a reduction by at least 7 mmol/L; more preferably by at least 9 mmol/L, more preferably by at least 11 mmol/L. The compounds of the invention preferably reduce the increase of HbA1c levels of mice over a period of 4 weeks, if administered at a daily dose of 0.01 mg/kg to about the ignition value.

The compounds of the invention also have the ability to reduce body weight of a patient. These activities of the compounds of the invention can be assessed in animal models known to the skilled person and also described herein in the Methods and in Example 7.

Surprisingly, it was found that peptidic compounds of the formula (I), particularly those with a lysine (or close analogues) at position 14 which is

further substituted with a lipophilic residue, showed very potent GLP-1 and GIP receptor activation; additionally in combination with amino acids like Gln in position 3 also very potent glucagon receptor activation can be provided.

It is described in the literature (Murage EN et al., Bioorg. Med. Chem. 16 (2008), 10106-10112), that a GLP-1 analogue with an acetylated Lysine at Pos.14 showed significantly reduced potency compared to natural GLP-1.

Furthermore, oxidation (in vitro or in vivo) of methionine, present in the core structure of exendin-4, is not possible anymore for peptidic compounds of the formula (I).

Further, compounds of the invention preferably have a high solubility at acidic and/or physiological pH values, e.g., at pH 4.5 and/or at pH 7.4 at 25ºC, in another embodiment at least 0.5 mg/ml and in a particular embodiment at least 1.0 mg/ml.

Furthermore, according to one embodiment, compounds of the invention preferably have a high stability when stored in solution. Preferred assay conditions for determining the stability is storage for 7 days at 25ºC in solution at pH 4.5 or pH 7.4. The remaining amount of peptide is determined by chromatographic analyses as described in Methods and Examples. Preferably, after 7 days at 25ºC in solution at pH 4.5 or pH 7.4, the remaining peptide amount is at least 80%, more preferably at least 85%, even more preferably at least 90% and even more preferably at least 95%.

Preferably, the compounds of the present invention comprise a peptide moiety Z (formula II) which is a linear sequence of 39-40 amino carboxylic acids, particularly α-amino carboxylic acids linked by peptide, i.e. carboxamide, bonds.

In one embodiment position X14 represents an amino acid residue with a

functionalized -NH_2 side chain group, such as functionalized Lys, Orn, Dab, or Dap, more preferably functionalized Lys and X40 is absent or represents Lys.

An amino acid residue with an -NH_2 side chain group, e.g. Lys, Orn, Dab or Dap, may be functionalized in that at least one H atom of the -NH_2 side chain group is replaced by -C(O)-R^5, -C(O)O-R^5, -C(O)NH-R^5, -$S(O)_2$-R^5 or R^5, preferably by -C(O)-R^5, wherein R^5 is a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P.

In certain embodiments, R^5 may comprise a lipophilic moiety, e.g. an acyclic linear or branched saturated hydrocarbon group, wherein R^5 particularly comprises an acyclic linear or branched (C_4-C_{30}) saturated or unsaturated hydrocarbon group, and/or a cyclic saturated, unsaturated or aromatic group, particularly a mono-, bi-, or tricyclic group comprising 4 to 14 carbon atoms and 0, 1, or 2 heteroatoms selected from N, O, and S, e.g. cyclohexyl, phenyl, biphenyl, chromanyl, phenanthrenyl or naphthyl, wherein the acyclic or cyclic group may be unsubstituted or substituted e.g. by halogen, -OH and/or CO_2H.

More preferred groups R^5 may comprise a lipophilic moiety, e.g. an acyclic linear or branched (C_{12}-C_{22}) saturated or unsaturated hydrocarbon group. The lipophilic moiety may be attached to the -NH_2 side chain group by a linker in all stereoisomeric forms, e.g. a linker comprising one or more, e.g. 2, 3 or 4, amino acid linker groups such as γ-aminobutyric acid (GABA), ε-aminohexanoic acid (ε-Ahx), γ-Glu and/or β-Ala. In one embodiment the lipophilic moiety is attached to the -NH_2 side chain group by a linker. In another embodiment the lipophilic moiety is directly attached to the -NH_2 side chain group. Specific examples of amino acid linker groups are $(\beta\text{-Ala})_{1-4}$, $(\gamma\text{-Glu})_{1-4}$, $(\varepsilon\text{-Ahx})_{1-4}$, or $(GABA)_{1-4}$. Preferred amino acid linker groups are ß-Ala, γ-Glu, ß-Ala-ß-Ala and γ-Glu-γ-Glu.

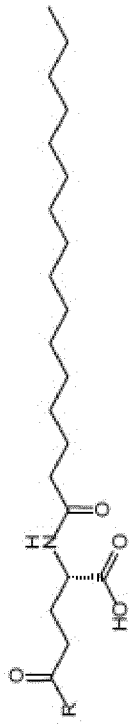
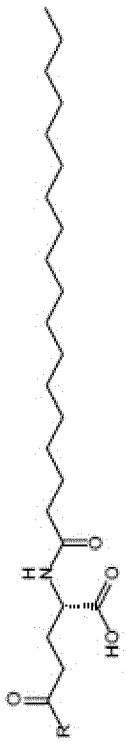
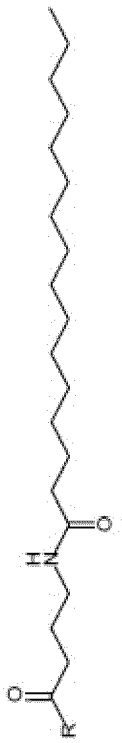
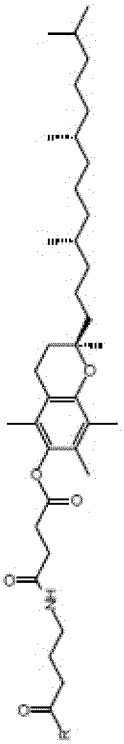
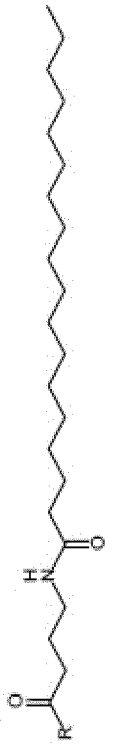
Specific preferred examples for -C(O)-R^5 groups are listed in the following Table 3, which are selected from the group consisting of (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, 4-Hexadecanoylamino-butyryl-, 4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-, 4-octadecanoylamino-butyryl-, 4-((Z)-octadec-9-enoylamino)-butyryl-, 6-[(4,4-Diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl-, Hexadecanoyl-, (S)-4-Carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl-, (S)-4-Carboxy-4-{3-[3-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-propionylamino]-propionylamino}-butyryl-, (S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-, (S)-4-Carboxy-4-((9Z,12Z)-octadeca-9,12-dienoylamino)-butyryl-, (S)-4-Carboxy-4-[6-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-hexanoylamino]-butyryl-, (S)-4-Carboxy-4-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-butyryl-, (S)-4-Carboxy-4-tetradecanoylamino-butyryl-, (S)-4-(11-Benzyloxycarbonyl-undecanoylamino)-4-carboxy-butyryl-, (S)-4-Carboxy-4-[11-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexylcarbamoyl)-undecanoylamino]-butyryl-, (S)-4-Carboxy-4-((Z)-octadec-9-enoylamino)-butyryl-, (S)-4-Carboxy-4-(4-dodecyloxy-benzoylamino)-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-, (S)-4-Carboxy-4-docosanoylamino-butyryl-, (S)-4-Carboxy-4-((Z)-nonadec-10-enoylamino)-butyryl-, (S)-4-Carboxy-4-(4-decyloxy-benzoylamino)-butyryl-, (S)-4-Carboxy-4-[(4'-octyloxy-biphenyl-4-carbonyl)-amino]-butyryl-, (S)-4-Carboxy-4-(12-phenyl-dodecanoylamino)-butyryl-, (S)-4-Carboxy-4-icosanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-hexadecanoylamino-butyrylamino)-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl-, 3-(3-Hexadecanoyl-amino-propionylamino)-propionyl-, 3-Hexadecanoylamino-propionyl-, (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-, (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-, (S)-4-Carboxy-4-((9S,10R)-9,10,16-trihydroxy-hexadecanoylamino)-butyryl-, Tetradecanoyl-, 11-Carboxy-undecanoyl-, 11-Benzyloxycarbonyl-undecanoyl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-tetradecanoylamino-butyrylamino)-butyryl-, 6-[Hydroxy-(naphthalene-2-yloxy)-phosphoryloxy]-hexanoyl-, 6-[Hydroxy-(5-phenyl-pentyloxy)-phosphoryloxy]-hexanoyl-, 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-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-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]-butyrylamino}-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}-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)-

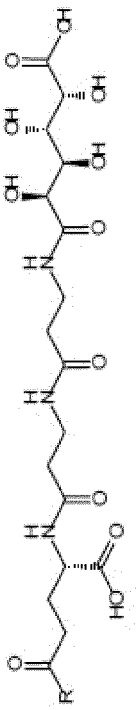
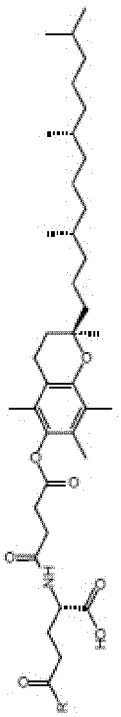
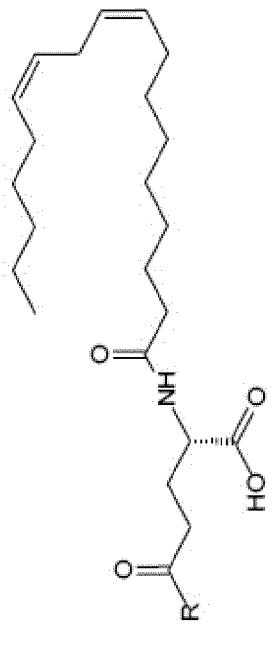
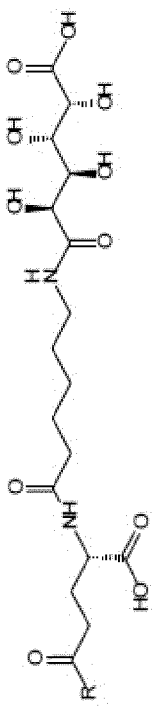
butyrylamino]-butyrylamino}-butyrylamino)-butyryl, 2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-1H-tetrazol-5-yl-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl-, 2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-carboxy-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl-, (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-, and (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-.

Further preferred are stereoisomers, particularly enantiomers of these groups, either S- or R-enantiomers. The term "R" in Table 3 is intended to mean the attachment site of -C(O)-R^5 at the peptide back bone, i.e. particularly the ε-amino group of Lys.

Table 3

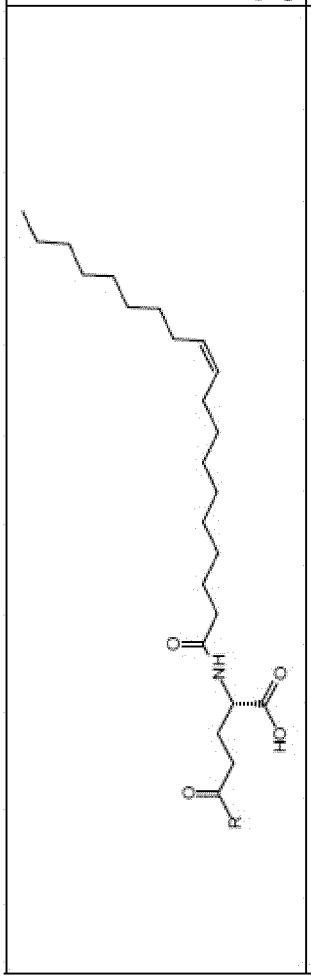
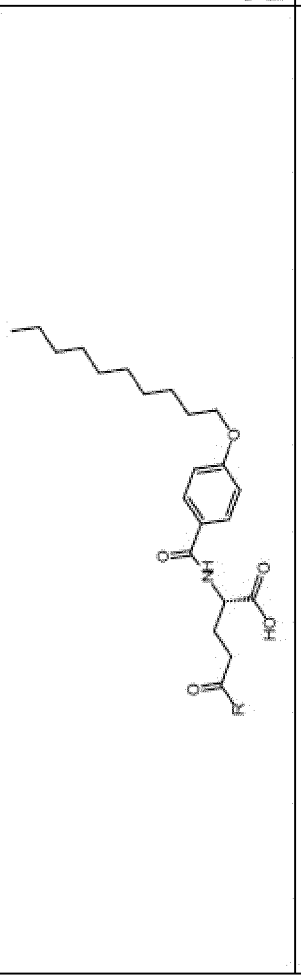
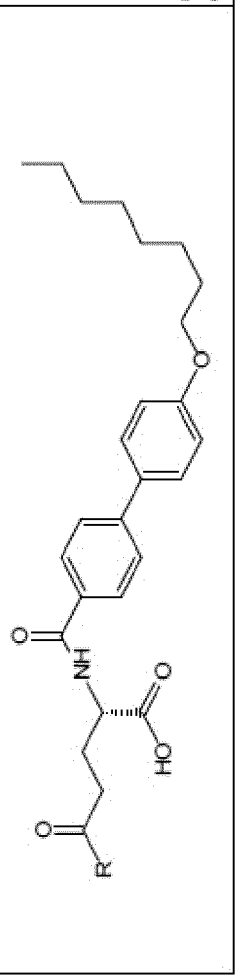
structure	IUPAC	name
	(S)-4-Carboxy-4-hexadecanoylamino-butyryl-	yE-x53
	(S)-4-Carboxy-4-octadecanoylamino-butyryl-	yE-x70
	4-Hexadecanoylamino-butyryl-	GABA-x53
	4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl	GABA-x60
	4-octadecanoylamino-butyryl-	GABA-x70

GABA-x74	4-[(Z)-octadec-9-enoylamino)-butyryl-
Phospho1	6-[(4,4-Diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl-
x53	Hexadecanoyl-
x52	(S)-4-Carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl-

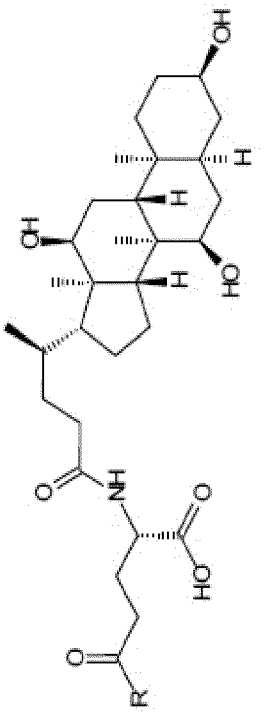
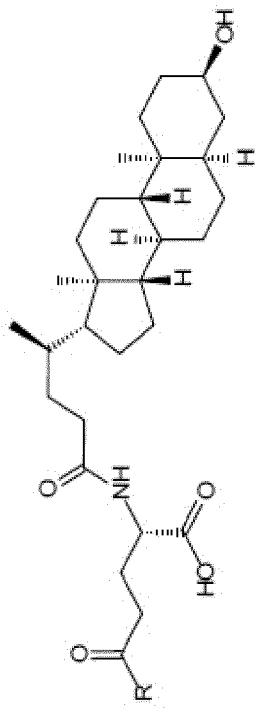
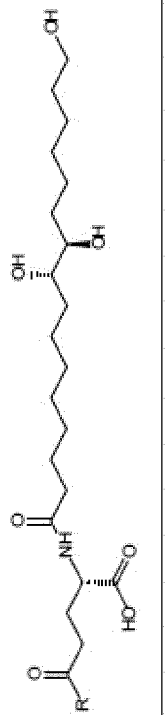
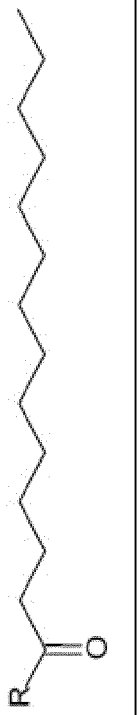
	(S)-4-Carboxy-4-{3-[3-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-propionylamino]-propionylamino}-butyryl	γE-x59
	(S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-	γE-x60
	(S)-4-Carboxy-4-((9Z,12Z)-octadeca-9,12-dienoylamino)-butyryl-	γE-x61
	(S)-4-Carboxy-4-[6-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-hexanoylamino]-butyryl	γE-x64

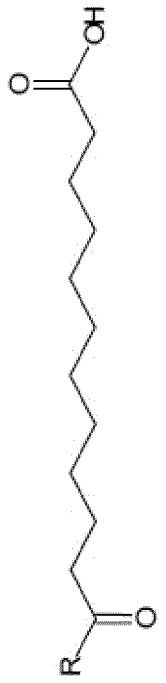
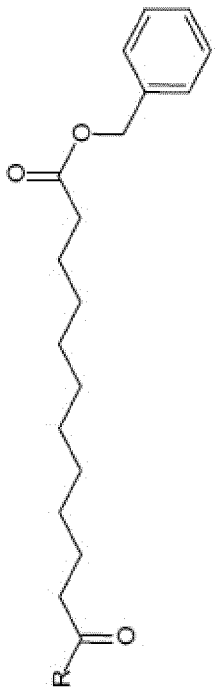
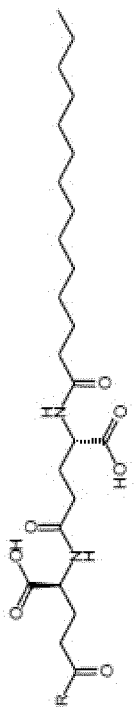
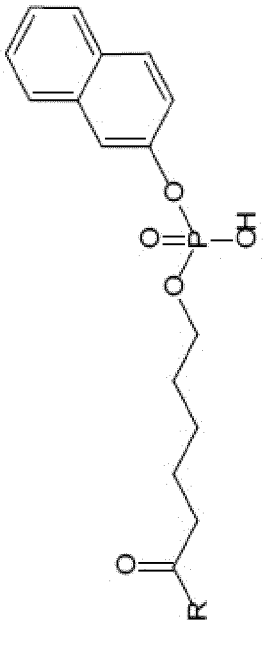
	(S)-4-Carboxy-4-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-butyryl	yE-x65
	(S)-4-Carboxy-4-tetradecanoylamino-butyryl-	yE-x69
	(S)-4-(11-Benzyloxycarbonyl-undecanoylamino)-4-carboxy-butyryl	yE-x72
	(S)-4-Carboxy-4-[11-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexylcarbamoyl)-undecanoylamino]-butyryl-	yE-x73

yE-x74	(S)-4-Carboxy-4-((Z)-octadec-9-enoylamino)-butyryl-
yE-x75	(S)-4-Carboxy-4-(4-dodecyloxy-benzoylamino)-butyryl-
yE-x76	(S)-4-Carboxy-4-henicosanoylamino-butyryl-
yE-x77	(S)-4-Carboxy-4-docosanoylamino-butyryl-

yE-x79	(S)-4-Carboxy-4-((Z)-nonadec-10-enoylamino)-butyryl-	
yE-x80	(S)-4-Carboxy-4-(4-decyloxy-benzoylamino)-butyryl-	
yE-x81	(S)-4-Carboxy-4-[(4'-octyloxy-biphenyl-4-carbonyl)-amino]-butyryl-	

	(S)-4-Carboxy-4-(12-phenyl-dodecanoylamino)-butyryl-	γE-x82
	(S)-4-Carboxy-4-icosanoylamino-butyryl-	γE-X95
	(S)-4-Carboxy-4-((S)-4-carboxy-4-hexadecanoylamino-butyrylamino)-butyryl-	γE-γE-x53
	(S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-	γE-γE-x70
	3-(3-Octadecanoylamino-propionylamino)-propionyl-	β-Ala-β-Ala-x70
	3-(3-Hexadecanoylamino-propionylamino)-propionyl-	β-Ala-β-Ala-x53
	3-Hexadecanoylamino-propionyl-	β-Ala-x53

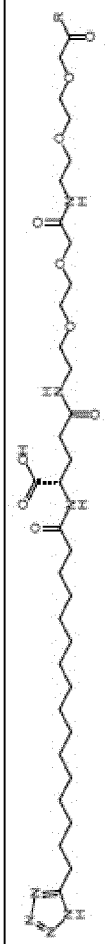
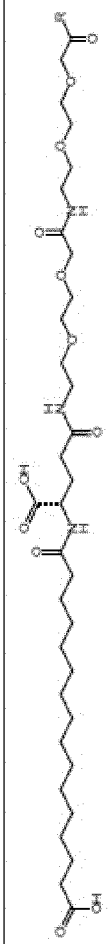
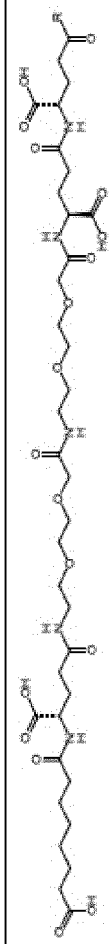
	(S)-4-Carboxy-4-[(R)-4-((3R,5S,7R,8R,9R,10S,12S,13R,14R,17R)-3,7,12-trihydroxy-8,10,13-trimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoylamino]-butyryl- yE-x16
	(S)-4-Carboxy-4-[(R)-4-((3R,5R,8R,9S,10S,13R,14S,17R)-3-hydroxy-10,13-dimethyl-hexadecahydro-cyclopenta[a]phenanthren-17-yl)-pentanoylamino]-butyryl- yE-x19
	(S)-4-Carboxy-4-((9S,10R)-9,10,16-trihydroxy-hexadecanoylamino)-butyryl- yE-x25
	tetradecanoyl- x69

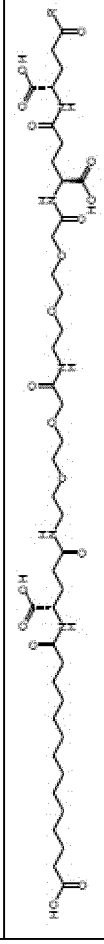
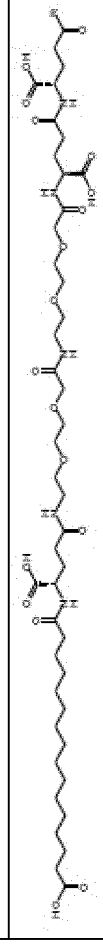
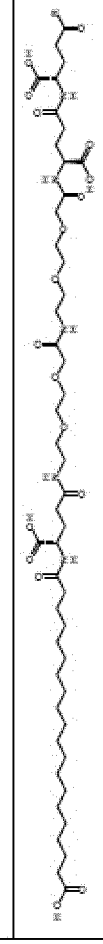
x71	
11-Carboxy-undecanoyl-	
x72	
11-Benzyloxycarbonyl-undecanoyl	
yE-yE-x69	
(S)-4-Carboxy-4-((S)-4-carboxy-4-tetradecanoylamino-butyrylamino)-butyryl-	
Phospho2	
6-[Hydroxy-(naphthalen-2-yloxy)-phosphoryloxy]-hexanoyl-	

Phospho3	6-[Hydroxy-(5-phenyl-pentyloxy)-phosphoryloxy]-hexanoyl-
Sulfonamid 1	4-(Naphthalene-2-sulfonylamino)-4-oxo-butyryl-
Sulfonamid 2	4-(Biphenyl-4-sulfonylamino)-4-oxo-butyryl-
x100	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{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	x101
	(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]-butyrylamino}-butyryl	x102
	(S)-4-Carboxy-2-[2-(2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl	x103
	(S)-4-Carboxy-4-[(S)-4-carboxy-4-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl	x104
	(S)-4-Carboxy-4-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl	x105

	(S)-4-Carboxy-2-{(S)-4-carboxy-2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl	x106
	(S)-4-Carboxy-2-[2-(2-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyryl	x107
	2-(2-{2-[2-(2-[(S)-4-Carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-acetyl-	x108
	2-(2-{2-[(S)-4-Carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetyl	x109
	(S)-4-Carboxy-4-[(S)-4-carboxy-4-{(S)-4-carboxy-4-[(S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)-butyrylamino]-butyrylamino}-butyrylamino)-butyryl	x110

	2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-1H-tetrazol-5-yl-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl	x111
	2-(2-{2-[2-(2-{2-[(S)-4-Carboxy-4-(16-carboxy-hexadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetyl	x112
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-butyrylamino}-butyryl	x113
	(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	x114
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-{(S)-4-carboxy-4-(7-carboxy-heptanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino}-butyrylamino}-butyryl	x115

	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-[(S)-4-carboxy-4-(11-carboxy-undecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl x116
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-[(S)-4-carboxy-4-(13-carboxy-tridecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl x117
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-[(S)-4-carboxy-4-(15-carboxy-pentadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl x118
	(S)-4-Carboxy-4-{(S)-4-carboxy-4-[2-(2-{2-[2-(2-[(S)-4-carboxy-4-(19-carboxy-nonadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-butyryl x119

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In some embodiments, the invention relates to peptidic compounds of Formula (I) as defined above, wherein X14 represents an amino acid residue selected from Lys, Orn, Dab and Dap, wherein the -NH_2 side chain group is functionalized by -C(O)-R^5, X40 represents an amino acid residue selected from Lys, Orn, Dab and Dap, wherein the -NH_2 side chain group can be functionalized by -C(O)-R^5, and R^5 is a lipophilic moiety selected from an acyclic linear or branched (C_4-C_{30}) saturated or unsaturated hydrocarbon group, and/or a cyclic saturated, unsaturated or aromatic group, wherein the lipophilic moiety may be attached to the -NH_2 side chain group by a linker selected from (β-Ala)$_{1-4}$, (γ-Glu)$_{1-4}$, (ϵ-Ahx)$_{1-4}$, or (GABA)$_{1-4}$ in all stereoisomeric forms.

In certain embodiments, X14 represents an amino acid residue with a functionalized -NH_2 side chain group, such as functionalized Lys, Orn, Dab or Dap, wherein at least one H atom of the -NH_2 side chain group is replaced by -C(O)-R^5, which is selected from the group consisting of the substituents according to Table 3 above.

In some embodiments, X14 represents an amino acid residue selected from Lys, Orn, Dab and Dap, wherein the -NH_2 side chain group is functionalized by -C(O)-R^5, X40 represents an amino acid residue selected from Lys, Orn, Dab and Dap, wherein the -NH_2 side chain group can be functionalized by -C(O)-R^5, and -C(O)-R^5 is selected from the group consisting of the substituents according to Table 3 above.

In some embodiments of the invention, position X14 and/or X40 in formula (II) represents Lysine (Lys). According to some embodiments, Lys at position 14 and optionally at position 40 is functionalized, e.g. with a group -C(O)R^5 as described above. In other embodiments, X40 is absent and X14 is Lys functionalized with -C(O)-R^5, -C(O)O-R^5, -C(O)NH-R^5, -$S(O)_2$-R^5 or R^5, preferably by -C(O)-R^5, wherein R^5 is as defined above. In particular, X14 is Lys functionalized with C(O)-R^5, which is selected from the group

consisting of (S)-4-carboxy-4-hexadecanoylamino-butyryl (γE-x53), (S)-4-carboxy-4-octadecanoylamino-butyryl (γE-x70), 4-hexadecanoylamino-butyryl (GABA-x53), 4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-(GABA-x60), 4-octadecanoylamino-butyryl (GABA-x70), 4-((Z)-octadec-9-enoylamino)-butyryl (GABA-x74), 6-[(4,4-Diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl (Phospho1), Hexadecanoyl (x53), (S)-4-Carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl (x52), (S)-4-Carboxy-4-{3-[3-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-propionylamino]-propionylamino}-butyryl (γE-x59), (S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl (γE-x60), (S)-4-Carboxy-4-((9Z,12Z)-octadeca-9,12-dienoylamino)-butyryl (γE-x61), (S)-4-Carboxy-4-[6-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-hexanoylamino]-butyryl (γE-x64), (S)-4-Carboxy-4-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-butyryl (γE-x65), (S)-4-carboxy-4-tetradecanoylamino-butyryl (γE-x69), (S)-4-(11-Benzyloxycarbonyl-undecanoylamino)-4-carboxy-butyryl (γE-x72), (S)-4-carboxy-4-[11-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexylcarbamoyl)-undecanoylamino]-butyryl (γE-x73), (S)-4-Carboxy-4-((Z)-octadec-9-enoylamino)-butyryl (γE-x74), (S)-4-Carboxy-4-(4-dodecyloxy-benzoylamino)-butyryl (γE-x75), (S)-4-Carboxy-4-henicosanoylamino-butyryl (γE-x76), (S)-4-Carboxy-4-docosanoylamino-butyryl (γE-x77), (S)-4-Carboxy-4-((Z)-nonadec-10-enoylamino)-butyryl (γE-x79), (S)-4-Carboxy-4-(4-decyloxy-benzoylamino)-butyryl (γE-x80), (S)-4-Carboxy-4-[(4'-octyloxy-biphenyl-4-carbonyl)-amino]-butyryl (γE-x81), (S)-4-Carboxy-4-(12-phenyl-dodecanoylamino)-butyryl (γE-x82), (S)-4-Carboxy-4-icosanoylamino-butyryl (γE-x95), (S)-4-Carboxy-4-((S)-4-carboxy-4-hexadecanoylamino-butyrylamino)-butyryl (γE-γE-x53), (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl (γE-γE-x70), and 3-(3-Octadecanoylamino-propionylamino)-propionyl (β-Ala-β-Ala-x70).

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In some embodiments, X14 is Lys functionalized with C(O)-R^5, which is selected from the group consisting of (S)-4-carboxy-4-hexadecanoylamino-butyryl (γE-x53) and (S)-4-carboxy-4-octadecanoylamino-butyryl (γE-x70).

A further embodiment relates to a group of compounds, wherein

R^1 is NH_2,

R^2 is NH_2 or

R^1 and R^2 are NH_2.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln, Glu and His,

X12 represents an amino acid residue selected from Ile and Lys,

X14 represents an amino acid residue having a side chain with an -NH_2 group, wherein the -NH_2 side chain group is functionalized by - C(O)-R^5, wherein R^5 is as described above,

X15 represents an amino acid residue selected from Asp and Glu,

X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,

X17 represents an amino acid residue selected from Arg, Lys, Glu, Ile, Gln, Leu, Aib, Tyr and Ala,

X18 represents an amino acid residue selected from Ala, Arg, Aib, Leu, Lys and Tyr,

X19 represents an amino acid residue selected from Ala, Gln, Val and Aib,

X20 represents an amino acid residue selected from Gln, Aib, Phe, Arg, Leu, Lys and His,

X21 represents an amino acid residue selected from Asp, Glu, Tyr, and Leu,

X28 represents an amino acid residue selected from Asn, Ala, Aib , Arg and Lys,

X29 represents an amino acid residue selected from Gly, Thr, Aib, D-Ala and Ala,

X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln, Glu and His,

X12 represents an amino acid residue selected from Ile and Lys,

X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by - C(O)-R^5, wherein R^5 is as described above,

X15 represents an amino acid residue selected from Asp and Glu,

X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,

X17 represents an amino acid residue selected from Arg, Lys, Glu, Gln, Leu, Aib, Tyr and Ala,

X18 represents an amino acid residue selected from Ala, Arg, Aib, Leu and Tyr,

X19 represents an amino acid residue selected from Ala, Val and Aib,

X20 represents an amino acid residue selected from Gln, Aib, Phe, Leu, Lys, His, Pip, (S)MeLys, (R)MeLys and (S)MeOrn,

X21 represents an amino acid residue selected from Asp, Glu and Leu,

X28 represents an amino acid residue selected from Asn, Ala, Aib and Ser,

X29 represents an amino acid residue selected from Gly, Thr, Aib, D-Ala and Ala,

X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln, Glu and His,

X12 represents Ile,

X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by - C(O)-R^5, wherein R^5 is as described above,

X15 represents an amino acid residue selected from Asp and Glu,

X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,

X17 represents an amino acid residue selected from Arg, Lys, Glu, Gln, Leu, Aib, Tyr and Ala,

X18 represents an amino acid residue selected from Ala and Arg,

X19 represents an amino acid residue selected from Ala and Val,

X20 represents an amino acid residue selected from Gln, Aib, Lys, Pip, (S)MeLys, (R)MeLys and (S)MeOrn and His,

X21 represents an amino acid residue selected from Asp, Glu and Leu,

X28 represents an amino acid residue selected from Asn and Ala,

X29 represents an amino acid residue selected from Gly, Thr and D-Ala,

X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln, Glu and His,

X12 represents an amino acid residue selected from Ile and Lys,

X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by $-C(O)-R^5$, wherein R^5 is as described above,

X15 represents an amino acid residue selected from Asp and Glu,

X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,

X17 represents an amino acid residue selected from Arg, Lys, Glu, Gln, Leu, Aib, Tyr and Ala,

X18 represents an amino acid residue selected from Ala and Arg,

X19 represents an amino acid residue selected from Ala and Val,

X20 represents an amino acid residue selected from Gln, Aib, Lys and His,

X21 represents an amino acid residue selected from Asp, Glu and Leu,

X28 represents an amino acid residue selected from Asn and Ala,

X29 represents an amino acid residue selected from Gly, Thr and D-Ala,

X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln and Glu,

X12 represents Ile,

X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl- and 4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-,

X15 represents an amino acid residue selected from Glu and Asp,

X16 represents an amino acid residue selected from Ser and Lys,

X17 represents Arg,

X18 represents Ala,

X19 represents Ala,

X20 represents an amino acid residue selected from Gln and Aib,

X21 represents an amino acid residue selected from Asp and Glu,

X28 represents an amino acid residue selected from Asn and Ala,

X29 represents an amino acid residue selected from Gly and Thr,

X40 is absent.

A further embodiment relates to a group of compounds, wherein

X3 represents Glu,

X12 represents Ile,

X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-

butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl- and 4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-,

X15 represents an amino acid residue selected from Glu and Asp,

X16 represents an amino acid residue selected from Ser and Lys,

X17 represents Arg,

X18 represents Ala,

X19 represents Ala,

X20 represents an amino acid residue selected from Gln and Aib,

X21 represents an amino acid residue selected from Asp and Glu,

X28 represents an amino acid residue selected from Asn and Ala,

X29 represents an amino acid residue selected from Gly and Thr,

X40 is absent.

A further embodiment relates to a group of compounds, wherein

X3 represents Gln,

X12 represents Ile,

X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl- and 4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-,

X15 represents an amino acid residue selected from Glu and Asp,

X16 represents an amino acid residue selected from Ser and Lys,

X17 represents Arg,

X18 represents Ala,

X19 represents Ala,

X20 represents an amino acid residue selected from Gln and Aib,

X21 represents an amino acid residue selected from Asp and Glu,

X28 represents an amino acid residue selected from Asn and Ala,

X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

A further embodiment relates to a group of compounds, wherein
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, 4-octadecanoylamino-butyryl-, Hexadecanoyl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl-.

A further embodiment relates to a group of compounds, wherein
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-octadecanoylamino-butyryl-, 4-octadecanoylamino-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl-.

A further embodiment relates to a group of compounds, wherein
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-.

A further embodiment relates to a group of compounds, wherein
X3 represents an amino acid residue selected from Gln and Glu,
X12 represents Ile,
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-

butyryl-,
X15 represents an amino acid residue selected from Glu and Asp,
X16 represents an amino acid residue selected from Ser and Lys,
X17 represents Arg,
X18 represents Ala,
X19 represents Ala,
X20 represents an amino acid residue selected from Gln and Aib,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Asn and Ala,
X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

A further embodiment relates to a group of compounds, wherein
X3 represents an amino acid residue selected from Gln, His and Glu,
X12 represents Ile,
X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,
X15 represents Glu,
X16 represents an amino acid residue selected from Glu and Lys,
X17 represents Glu,
X18 represents Ala,
X19 represents Val,
X20 represents Arg,
X21 represents Leu,
X28 represents an amino acid residue selected from Asn, Aib and Ala,
X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

A further embodiment relates to a group of compounds, wherein
X3 represents Glu,

X12 represents Ile,

X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,

X15 represents Glu,

X16 represents an amino acid residue selected from Glu and Lys,

X17 represents Glu,

X18 represents Ala,

X19 represents Val,

X20 represents Arg,

X21 represents Leu,

X28 represents an amino acid residue selected from Asn, Aib and Ala,

X29 represents Gly,

X40 is absent.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln, His and Glu,

X12 represents an amino acid residue selected from Ile and Lys,

X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,

X15 represents an amino acid residue selected from Glu and Asp,

X16 represents Glu,

X17 represents an amino acid residue selected from Arg and Gln,

X18 represents an amino acid residue selected from Ala and Arg,

X19 represents Ala,

X20 represents an amino acid residue selected from Pip, (S)MeLys, (R)MeLys and (S)MeOrn,

X21 represents Glu,

X28 represents an amino acid residue selected from Asn, Ser and Ala,

X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

A further embodiment relates to a group of compounds, wherein
X3 represents an amino acid residue selected from Gln, His and Glu,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, hexadecanoyl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,
X15 represents an amino acid residue selected from Glu and Asp,
X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,
X17 represents an amino acid residue selected from Arg, Leu, Aib, Tyr, Glu, Ala and Lys,
X18 represents an amino acid residue selected from Ala, Aib, Leu and Tyr,
X19 represents an amino acid residue selected from Ala, Val and Aib,
X20 represents Aib,
X21 represents an amino acid residue selected from Glu, Leu and Tyr,
X28 represents an amino acid residue selected from Asn, Arg and Ala,
X29 represents an amino acid residue selected from Gly, Ala, D-Ala and Thr,
X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein
X3 represents an amino acid residue selected from Gln, His and Glu,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents Lys, wherein the $-NH_2$ side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,

X15 represents an amino acid residue selected from Glu and Asp,
X16 represents an amino acid residue selected from Ser, Lys and Glu,
X17 represents an amino acid residue selected from Arg, Lys, Ile, Glu and Gln,
X18 represents an amino acid residue selected from Ala, Arg and Lys,
X19 represents an amino acid residue selected from Ala, Val and Gln,
X20 represents an amino acid residue selected from Gln, Phe, Leu, Lys, His and Arg,
X21 represents an amino acid residue selected from Glu, Asp and Leu,
X28 represents an amino acid residue selected from Asn, Arg, Lys and Ala,
X29 represents an amino acid residue selected from Gly, Aib and Thr,
X40 is either absent or represents Lys.

A further embodiment relates to a group of compounds, wherein
X12 represents Ile.

A further embodiment relates to a group of compounds, wherein
X19 represents Ala.

A further embodiment relates to a group of compounds, wherein
X16 represents Glu,
X20 represents an amino acid residue selected from Pip, (S)MeLys, (R)MeLys and (S)MeOrn.

A further embodiment relates to a group of compounds, wherein
X28 represents Ala,
X29 represents Gly.

A further embodiment relates to a group of compounds, wherein
X28 represents Asn,
X29 represents Thr.

A further embodiment relates to a group of compounds, wherein

X3 represents an amino acid residue selected from Gln and Glu,

X12 represents an amino acid residue selected from Ile and Lys,

X14 represents Lys, wherein the -NH_2 side chain group is functionalized by -C(O)-R^5, which is selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- (γE-x53) and (S)-4-Carboxy-4-octadecanoylamino-butyryl- (γE-x70),

X15 represents an amino acid residue selected from Asp and Glu,

X16 represents Glu,

X17 represents an amino acid residue selected from Arg and Gln,

X18 represents an amino acid residue selected from Ala and Arg,

X19 represents Ala,

X20 represents an amino acid residue selected from Pip, (S)-MeLys, (R)-MeLys, and (S)-MeOrn,

X21 represents Glu,

X28 represents an amino acid residue selected from Asn, Ala and Ser,

X29 represents an amino acid residue selected from Gly and Thr,

X40 is absent.

Specific examples of peptidic compounds of formula (I) are the compounds of SEQ ID NO: 8-16 as well as salts and solvates thereof.

Specific examples of peptidic compounds of formula (I) are the compounds of SEQ ID NO: 8-13 and 15 as well as salts and solvates thereof.

In certain embodiments, i.e. when the compound of formula (I) comprises 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, as described in “combination therapy”.

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 suitable 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 improving lipid levels, particularly LDL, as well as HDL levels (e.g. 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 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, 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).

Further medical uses include treatment of bone related disorders, such as osteoporosis or osteoarthritis, etc., where increased bone formation and decreased bone resorption might be beneficial.

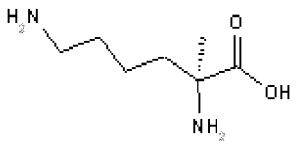
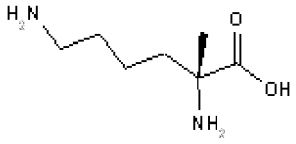
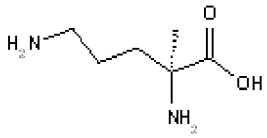
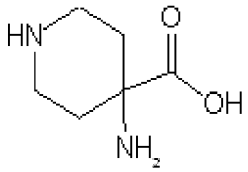
DETAILED DESCRIPTION OF THE INVENTION

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), GABA (γ-aminobutyric acid) or Ahx (ε-aminohexanoic acid).

Furthermore, the following codes were used for the amino acids shown in Table 4:

Table 4:

structure	name	code
 (S)MeLys	(S)-α-methyl-lysine	(S)MeLys
 (R)MeLys	(R)-α-methyl-lysine	(R)MeLys
 (S)MeOrn	(S)-α-methyl-ornithin	(S)MeOrn
 Pip	4-amino-piperidine-4-carboxylic acid	Pip

The term „native exendin-4“ refers to native exendin-4 having the sequence HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2 (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 39-40 amino carboxylic acids.

The peptidic compounds of the present invention may have unmodified side-chains, but 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, e.g., in exendin-4, His is at position 1, Gly at position 2, ..., Met at position 14, ... and Ser at position 39.

The amino acid residues at position 14 and optionally at position 40, having a side chain with an - NH_2 group, e.g. Lys, Orn, Dab or Dap are conjugated to a functional group, e.g. 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 by alkylation, reductive amination or by an amide bond, a carbamate or a sulfonamide bond in case of amino acids carrying an amino group at their side chain.

Nonlimiting examples of lipophilic moieties that can be attached to amino

acid side chains include fatty acids, e.g. C_{8-30} 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, α-glutamic acid, γ-aminobutyric acid and/or ε-aminohexanoic acid or dipeptides, such as β-Ala-β-Ala (also abbreviated βA-βA herein) and/or γ-Glu-γ-Glu (also abbreviated γE-γE herein) in all their stereo-isomer forms (S and R enantiomers).

Thus, one nonlimiting example of a side chain attachment is palmitic acid which is covalently linked to the α-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 the 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 carrying a cleavable linker. This solid support can be any polymer that allows coupling of the initial amino acid, 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, HBTU, HATU 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, etc.

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 removed concomitantly with the cleavage of the desired product 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, 3rd 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 ([1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-3-methylbutyl) 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 group can be selectively removed using 4% hydrazine in DMF and the corresponding free amino group 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, e.g. preparative RP-HPLC, 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, GIP 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 for GIP as well as optionally the glucagon receptor (e.g. "dual or trigonal agonists"). Such peptides that are GIP/GLP-1 co-agonists, or GIP/GLP-1/glucagon tri-agonists may provide therapeutic benefit to address a clinical need for targeting the metabolic syndrome by allowing simultaneous treatment of diabetes and obesity.

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 apnea, 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 high blood sugar levels, 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 GIP as well as glucagon are members of the family of 7-transmembrane-spanning, heterotrimeric G-protein coupled receptors. They are structurally 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, GIP and glucagon share regions of high sequence identity/similarity. GLP-1 and glucagon 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. GIP is derived from a larger proGIP prohormone precursor and is synthesized and released from K-cells located in the small intestine.

The peptidic incretin hormones GLP-1 and GIP are secreted by intestinal

endocrine cells in response to food and account for up to 70% of 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. Also the receptor for GIP is broadly expressed in peripheral tissues including pancreatic islets, adipose tissue, stomach, small intestine, heart, bone, lung, kidney, testis, adrenal cortex, pituitary, endothelial cells, trachea, spleen, thymus, thyroid and brain. Consistent with its biological function as incretin hormone, the pancreatic ß-cell express the highest levels of the receptor for GIP in humans. There is some clinical evidence that the GIP-receptor mediated signaling could be impaired in patients with T2DM but GIP-action is shown to be reversible and could be restored with improvement of the diabetic status. Of note, the stimulation of insulin secretion by both incretin hormones, GIP and GLP-1 is strictly glucosed-dependent ensuring a fail-safe mechanism associated with at low risk for hypoglycemia.

At the beta cell level, GLP-1 and GIP have been shown to promote glucose sensitivity, neogenesis, proliferation, transcription of proinsulin and hypertrophy, as well as antiapoptosis. A peptide with dual agonistic activity for the GLP-1 and the GIP receptor could be anticipated to have additive or synergistic anti-diabetic benefit. 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. Further GIP actions in peripheral tissues beyond the pancreas comprise increased bone formation and decreased bone resorption as well as neuroprotective effects which might be beneficial for the treatment of osteoporosis and cognitive defects like Alzheimer's 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 major 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 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 and GIP are known for their 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 or three 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, 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.

Compared to GLP-1, glucagon and oxyntomodulin, exendin-4 has beneficial physicochemical properties, such as solubility and stability in solution and under physiological conditions (including enzymatic stability towards degradation by enzymes, such as DPP-4 or NEP), which results in a longer duration of action in vivo. Therefore, exendin-4 might serve as good starting

scaffold to obtain exendin-4 analogues with dual or even triple pharmacologies, e.g., GLP-1/GIP and optionally in addition glucagon agonism.

Nevertheless, also exendin-4 has been shown to be chemically labile due to methionine oxdiation in position 14 as well as deamidation and isomerization of asparagine in position 28. Therefore, stability might be further improved by substitution of methionine at position 14 and the avoidance of sequences that are known to be prone to degradation via aspartimide formation, especially Asp-Gly or Asn-Gly at positions 28 and 29.

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, buffers, acidifying agents, alkalizing agents, solvents, adjuvants, tonicity adjusters, emollients, expanders, preservatives, physical and chemical stabilizers e.g. surfactants, antioxidants 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 and in R.C.Rowe et al (Ed), Handbook of Pharmaceutical Excipients, PhP, May 2013 update.

The exendin-4 peptide derivatives 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 (e.g. physiologically acceptable pH) 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 and in R.C.Rowe et al (Ed), Handbook of Pharmaceutical excipients, PhP, May 2013 update. One exemplary pharmaceutically acceptable carrier is physiological saline solution.

In one embodiment carriers are selected from the group of buffers (e.g. citrate/citric acid), acidifying agents (e.g. hydrochloric acid), alkalizing agents (e.g. sodium hydroxide), preservatives (e.g. phenol), co-solvents (e.g. polyethylene glycol 400), tonicity adjusters (e.g. mannitol), stabilizers (e.g. surfactant, antioxidants, amino acids).

Concentrations used are in a range that is physiologically acceptable.

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.

In the pharmaceutical composition, the exendin-4 derivative can be in monomeric or oligomeric form.

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 For example the “therapeutically effective amount” of a compound of the formula (I) is about 0.01 to 50 mg/dose, preferably 0.1 to 10 mg/dose.

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 or multiple 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.

In certain embodiments the pharmaceutical composition may be provided together with a device for application, for example together with a syringe, an injection pen or an autoinjector. Such devices may be provided separate from a pharmaceutical composition or prefilled with the pharmaceutical composition.

Combination therapy

The compounds of the present invention, dual agonists for the GLP-1 and GIP receptors or trigonal agonists for the GLP-1, GIP and glucagon receptors, can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2012 and/or the Rote Liste 2013, e.g. with all antidiabetics mentioned in the Rote Liste 2012, chapter 12, and/or the Rote Liste 2013, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2012, chapter 1, and/or the Rote Liste 2013, chapter 1, all lipid-lowering agents mentioned in the Rote Liste 2012, chapter 58, and/or the Rote Liste 2013, chapter 58, all antihypertensives and nephroprotectives, mentioned in the Rote Liste 2012 and/or the Rote Liste 2013, or all diuretics mentioned in the Rote Liste 2012, chapter 36, and/or the Rote Liste 2013, 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: Glargine / Lantus® , 270 - 330U/mL of insulin glargine (EP 2387989 A), 300U/mL of insulin glargine (EP 2387989 A), Glulisin / Apidra®, Detemir / Levemir®, Lispro / Humalog® / Liprolog®, Degludec / DegludecPlus, Aspart, basal insulin and analogues (e.g.LY-2605541, LY2963016, NN1436), PEGylated insulin Lispro, Humulin®, Linjeta, SuliXen®, NN1045, Insulin plus Symlin, PE0139, fast-acting and short-acting insulins (e.g. Linjeta, PH20, NN1218, HinsBet), (APC-002)hydrogel, oral, inhalable, transdermal and sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza, Tregopil, TPM 02, Capsulin, Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, NN1953, NN1954, NN1956, VIAtab, Oshadi oral insulin). 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 / AC-2993, Liraglutide / Victoza, Semaglutide, Taspoglutide, Syncria / Albiglutide, Dulaglutide, rExendin-4, CJC-1134-PC, PB-1023, TTP-054, Langlenatide / HM-11260C, CM-3, GLP-1 Eligen, ORMD-0901, NN-9924, NN-9926, NN-9927, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1, ZYD-1, GSK-2374697, DA-3091, MAR-701, MAR709, ZP-2929, ZP-3022, TT-401, BHM-034. MOD-6030, CAM-2036, DA-15864, ARI-2651, ARI-2255, Exenatide-XTEN and Glucagon-Xten.

DPP-4 inhibitors, for example: Alogliptin / Nesina, Trajenta / Linagliptin / BI-1356 / Ondero / Trajenta / Tradjenta / Trayenta / Tradzenta, Saxagliptin / Onglyza, Sitagliptin / Januvia / Xelevia / Tesave / Janumet / Velmetia, Galvus / Vildagliptin, Anagliptin, Gemigliptin, Teneligliptin, Melogliptin, Trelagliptin, DA-1229, Omarigliptin / MK-3102, KM-223, Evogliptin, ARI-2243, PBL-1427, Pinoxacin.

SGLT2 inhibitors, for example: Invokana / Canaglifozin, Forxiga / Dapagliflozin, Remoglifozin, Sergliflozin, Empagliflozin, Ipragliflozin, Tofogliflozin, Luseogliflozin, LX-4211, Ertuglifozin / PF-04971729, RO-4998452, EGT-0001442, KGA-3235 / DSP-3235, LIK066, SBM-TFC-039,

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, ZYG-19, DS-8500), GPR40 agonists (e.g. Fasiglifam / 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, GKM-001), 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, SGLT-1 inhibitors (e.g. LX-2761).

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.

LEGENDS TO THE FIGURES

Figure 1. Effect of s.c. administration of compound SEQ ID NO: 11 at 3 µg/kg and 10 µg/kg on body weight in female diet-induced obese (DIO) C57BL/6NCrl mice following 3-weeks chronic treatment once daily. Data are mean ± SEM.

Figure 2. Effect of s.c. administration of compound SEQ ID NO: 11 at 3 µg/kg and 10 µg/kg on body weight in female diet-induced obese (DIO) C57BL/6NCrl mice following 3-weeks chronic treatment once daily. Changes in body weight were calculated as relative change from baseline.Data are mean ± SEM.

Figure 3. Effect of 4 weeks of treatment with SEQ ID NO: 11 at 3 and 10 µg/kg, s.c. on non-fasted glucose in diabetic dbdb-mice, represented as change from baseline (0 mmol/l, day -7). Data are mean+SEM.

Figure 4. Effect of 4 weeks of treatment with SEQ ID NO: 11 at 3 and 10 µg/kg, s.c. on HbA1c in diabetic dbdb-mice, represented as change from baseline (0 %, day -7). Data are mean+SEM.

Figure 5. Effect of 4 weeks of treatment with SEQ ID NO: 11 at 3 and 10 µg/kg, s.c. on oral glucose tolerance in diabetic dbdb-mice, represented as change from baseline (t = 0 min, 0 mmol/l, immediately before glucose administration). Data are mean+SEM.

Figure 6. Effect of 4 weeks of treatment with SEQ ID NO: 11 at 3 and 10 µg/kg, s.c. on oral glucose tolerance in diabetic dbdb-mice, represented as area under the glucose curve (Glucose-AUC). Data are mean+SEM.

Figure 7. Effect of treatment with SEQ ID NO: 11, SEQ ID NO: 12 and SEQ ID NO: 15 at 3 µg/kg, s.c. on glucose lowering in non-fasted female diabetic dbdb-mice, represented as change from baseline. Data are mean+SEM.

Figure 8. Effect of s.c. administration of compound SEQ ID NO: 11 at 1, 10 and 100 µg/kg on gastric emptying and intestinal passage in female NMRI-mice. Data are mean+SEM.
a) → Gastric emptying
b) → Small intestinal passage relative to small intestinal length

METHODS

Abbreviations employed are as follows:

AA	amino acid
cAMP	cyclic adenosine monophosphate
Boc	tert-butyloxycarbonyl
BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BSA	bovine serum albumin
tBu	tertiary butyl
Dde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-ethyl
ivDde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)3-methyl-butyl
DIC	N,N'-diisopropylcarbodiimide
DIPEA	N,N-diisopropylethylamine
DMEM	Dulbecco's modified Eagle's medium
DMF	dimethyl formamide
EDT	ethanedithiol
FA	formic acid
FBS	fetal bovine serum
Fmoc	fluorenylmethyloxycarbonyl
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HBSS	Hanks' Balanced Salt Solution
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
HOBt	1-hydroxybenzotriazole
HOSu	N-hydroxysuccinimide
HPLC	High Performance Liquid Chromatography
HTRF	Homogenous Time Resolved Fluorescence
IBMX	3-isobutyl-1-methylxanthine
LC/MS	Liquid Chromatography/Mass Spectrometry
Palm	palmitoyl
PBS	phosphate buffered saline

PEG	polyethylene glycole
PK	pharmacokinetic
RP-HPLC	reversed-phase high performance liquid chromatography
Stea	stearyl
TFA	trifluoroacetic acid
Trt	trityl
UV	ultraviolet

General synthesis of peptidic compounds

Materials:

Different Rink-Amide resins (4-(2',4'-Dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido-norleucylaminomethyl resin, Merck Biosciences; 4-[(2,4-Dimethoxyphenyl)(Fmoc-amino)methyl]phenoxy acetamido methyl resin, Agilent Technologies) were used for the synthesis of peptide amides with loadings in the range of 0.3-0.4 mmol/g.

Fmoc protected natural amino acids were purchased from Protein Technologies Inc., Senn Chemicals, Merck Biosciences, Novabiochem, Iris Biotech or Bachem. The following standard amino acids were used throughout the syntheses: Fmoc-L-Ala-OH, Fmoc-Arg(Pbf)-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-L-Lys(Mmt)-OH, Fmoc-Aib-OH, Fmoc-D-Ser(tBu)-OH, Fmoc-D-Ala-OH, Boc-L-His(Boc)-OH

(available as toluene solvate) and Boc-L-His(Trt)-OH.

The solid phase peptide syntheses were performed for example on a Prelude Peptide Synthesizer (Protein Technologies Inc) or similar automated synthesizer 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 or Fmoc-L-Lys(Mmt)-OH was used in the corresponding position. After completion of the synthesis, the ivDde group was removed according to a modified literature procedure (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603), using 4% hydrazine hydrate in DMF. The Mmt group was removed by repeated treatment with 1% TFA in dichloromethane. 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 / UPLC

Method A: Analytical UPLC/MS was performed on a Waters UPLC system with a Waters UPLC HSS 1.7 µm C18 column (2.1 x 100 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.

A Waters LCT Premier Time-of-Flight instrument was used as mass analyser equipped with an electrospray in the positive ion mode.

Method B: detection at 210 - 225 nm, optionally coupled to a mass analyser Waters LCT Premier, electrospray positive ion mode

column: Waters ACQUITY UPLC® CSH™ C18 1.7 µm (150 x 2.1mm) at 50 °C

solvent: H_2O+0.5%TFA : ACN+0.35%TFA (flow 0.5 ml/min)

gradient: 80:20 (0 min) to 80:20 (3 min) to 25:75 (23 min) to 2:98 (23.5 min) to 2:98 (30.5 min) to 80:20 (31 min) to 80:20 (37 min)

Method C: detection at 215 nm

column: Aeris Peptide, 3.6 µm, XB-C18 (250 x 4.6 mm) at 60 °C

solvent: H_2O+0.1%TFA : ACN+0.1%TFA (flow 1.5 ml/min)

gradient: 90:10 (0 min) to 90:10 (3 min) to 10:90 (43 min) to 10:90 (48 min) to 90:10 (49 min) to 90:10 (50 min)

Method D: detection at 214 nm

column: Waters X-Bridge C18 3.5 µm 2.1 x 150 mm

solvent: H_2O+0.5%TFA : ACN (flow 0.55 ml/min)

gradient: 90:10 (0 min) to 40:60 (5 min) to 1:99 (15 min)

Method E: detection at 210 - 225 nm, optionally coupled to a mass analyser Waters LCT Premier, electrospray positive ion mode

column: Waters ACQUITY UPLC® BEH™ C18 1.7 µm (150 x 2.1 mm) at 50 °C

solvent: H_2O+1%FA : ACN+1%FA (flow 0.9 ml/min)

gradient: 95:5 (0 min) to 95:5 (2min) to 35:65 (3 min) to 65:35 (23.5 min) to 5:95 (24 min) to 95:5 (26min) to 95:5 (30min)

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 + 0.05 to 0.1% TFA (B) and water + 0.05 to 0.1% TFA (A) were employed as eluents. Alternatively, a buffer system consisting of acetonitrile and water with minor amounts of acetic acid was used. Product-containing fractions were collected and lyophilized to obtain the purified product, typically as TFA or acetate salt.

Solubility and Stability-Testing of exendin-4 derivatives

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 chromatography).

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 was dissolved). This analysis also served as starting point (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.

The chemical stability is expressed as "% remaining peptide".

Anion Chromatography

Instrument: Dionex ICS-2000, pre/column: Ion Pac AG-18 2 x 50 mm (Dionex)/

AS18 2 x 250 mm (Dionex), eluent: aqueous 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 KOH, suppressor: ASRS 300 2 mm, detection: conductivity.

As HPLC/UPLC method method D or E has been used.

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

Agonism of compounds for the receptors was determined by functional assays measuring cAMP response of HEK-293 cell lines stably expressing human GIP, 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).

Bioanalytical screening method for quantification of exendin-4 derivatives in mice and pigs

Mice were dosed 1 mg/kg subcutaneously (s.c.). The mice were sacrified and blood samples were collected after 0.25, 0.5, 1, 2, 4, 8, 16 and 24 hours post application. Plasma samples were analyzed after protein precipitation via liquid chromatography mass spectrometry (LC/MS). PK parameters and half-life were calculated using WinonLin Version 5.2.1 (non-compartment model).

Female Göttinger minipigs were dosed 0.1 mg/kg subcutaneously (s.c.). Blood samples were collected after 0.25, 0.5, 1, 2, 4, 8, 24, 32, 48, 56 and 72 hours post application. Plasma samples were analyzed after protein precipitation via liquid chromatography mass spectrometry (LC/MS). PK parameters and half-life were calculated using WinonLin Version 5.2.1 (non-compartment model).

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. Then, the test compound / reference compound or its vehicle in the control group was administered subcutaneously. 60 min later, to allow the compound to reach relevant plasma exposure, a coloured, non-caloric bolus was instilled via gavage into the stomach. 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 stomach content, calculated as weight of filled subtracted by the weight of emptied stomach, 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 ratio in

percent of the latter distance and the total length of the small intestine.

Statistical analyses were performed with Everstat 6.0 by 1-way-ANOVA, followed by Dunnett's as post-hoc test. Dunnett's Test was applied to compare versus vehicle control. 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 over 22 hours, while data are processed as mean over every 30 min. Repetition of this procedure over several days was possible. Restriction of assessment to 22 hours was for practical reasons 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. Comparable data can be obtained for both female and male mice.

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

Acute and subchronic effects of exendin-4 derivatives after subcutaneous treatment on blood glucose and body weight in female diet-induced obese (DIO) C57BL/6NCrl mice

18 weeks on high-fat diet (method 1)

Female C57BL/6NCrl mice were housed in groups in a specific pathogen-

free barrier facility on a 12 h light/dark cycle with free access to water and high-fat diet. After 18 weeks on high-fat diet, mice were stratified to treatment groups (n = 8), so that each group had similar mean body weight. An aged-matched group with *ad libitum* access to standard chow was included as standard control group.
Before the experiment, mice were subcutaneously (s.c.) injected with vehicle solution and weighed for 3 days to acclimate them to the procedures.

1) Acute effect on blood glucose in fed DIO mice: initial blood samples were taken just before first administration (s.c.) of vehicle (phosphate buffer solution) or the exendin-4 derivatives at doses of 10, 30 and 100 µg/kg (dissolved in phosphate puffer), respectively. The volume of administration was 5 mL/kg. The animals had access to water and their corresponding diet during the experiment, food consumption was determined at all time points of 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 (method: d-glucose hexokinase, hemolysate, AU640 Beckman Coulter). Blood sampling was performed by tail incision without anaesthesia.

2) Subchronic effect on body weight: all animals were treated once daily s.c. in the afternoon, at the end of the light phase (12 h lights on) with either vehicle or exendin-4 derivatives at the abovementioned doses for 4 weeks. Body weight was recorded daily. On days 6 and 28, total fat mass was measured by nuclear magnetic resonance (NMR) using a Bruker minispec (Ettlingen, Germany).

14 weeks of prefeeding with high-fat diet (method 2)
Female C57BL/6NCrl mice were housed in groups in a specific pathogen-free barrier facility on a 12 h light/dark cycle with free access to water and high-fat diet. After 14 weeks on high-fat diet, mice were stratified to treatment groups (n = 8), so that each group had similar mean body weight. An aged-matched group with *ad libitum* access to standard chow and water

was included as standard control group.

Before the experiment, mice were subcutaneously (s.c.) injected with vehicle solution and weighed for 3 days to acclimate them to the procedures.

Subchronic effect on body weight: all animals were treated once daily s.c. late afternoon, at the end of the light phase (LD 12:12) with either vehicle or exendin-4 derivatives at the abovementioned doses for 3 weeks. Body weight was recorded daily.

Statistical analyses were performed with Everstat 6.0 by repeated measures two-way ANOVA and Dunnett's post-hoc analyses (glucose profile) and 1-way-ANOVA, followed by Dunnett's post-hoc test (body weight, body fat). Differences versus vehicle-treated DIO control mice were considered statistically significant at the $p < 0.05$ level.

Acute and subchronic effects of exendin-4 derivatives after subcutaneous treatment on blood glucose and HbA1c in female leptin-receptor deficient diabetic db/db mice (method 3)

Female BKS.Cg-m +/+ Leprdb/J (db/db) and BKS.Cg-m +/+ Leprdb/+ (lean control) mice were obtained from Charles River Laboratories, Germany, at an age of 9 – 10 weeks. The animals were housed in groups in a specific pathogen-free barrier facility on a 12-h light/dark cycle with free access to water and rodent-standard chow. After 1 week of acclimatization, blood samples were drawn from the tail without anaesthesia and blood glucose (method: d-glucose hexokinase, hemolysate, AU640 Beckman Coulter) and HbA1c level (method: hemolysate, Cobas6000 c501, Roche Diagnostics, Germany) were determined.

HbA1c is a glycosylated form of haemoglobin whose level reflects the average level of glucose to which the erythrocyte has been exposed during its lifetime. In mice, HbA1c is a relevant biomarker for the average blood glucose level during the preceding 4 weeks (erythrocyte life span in mouse ~

47 days).

Db/db mice were stratified to treatment groups (n = 8), so that each group had similar baseline blood glucose and HbA1c levels.

1) Acute effect on blood glucose in fed db/db mice: initial blood samples were taken just before first administration (s.c.) of vehicle (phosphate buffer solution) or exendin-4 derivatives at doses of 3, 10, and 100 µg/kg (dissolved in phosphate buffer), respectively. The volume of administration was 5 mL/kg. The animals had access to water and chow during the experiment, food consumption was determined at all time points of 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. Comparable data can be obtained for both female and male mice.

2) Subchronic effect on blood glucose and HbA1c: all animals were treated once daily s.c. in the afternoon, at the end of the light phase (12 h lights on) with either vehicle or exendin-4 derivatives at the abovementioned doses for 4 weeks. At the end of the study, blood samples (tail, no anaesthesia) were analyzed for glucose and HbA1c. Comparable data can be obtained for both female and male mice.

Statistical analyses were performed with Everstat 6.0 by repeated measures two-way ANOVA and Dunnett's post-hoc analyses. Differences versus vehicle-treated db/db control mice were considered statistically significant at the $p < 0.05$ level.

Effects of 4 weeks of treatment on glucose, HbA1c and oral glucose tolerance in female diabetic dbdb-mice (method 4)

8 week old, female diabetic dbdb-mice of mean non-fasted glucose value of

14.5 mmol/l and a body weight of 37-40 g were used. Mice were individually marked and were adapted to housing conditions for at least one week.

7 days prior to study start, baseline values for non-fasted glucose and HbA1c were determined, 5 days prior to study start, mice were assigned to groups and cages (5 mice per cage, 10 per group) according to their HbA1c values to ensure even distribution of lower and higher values between groups (stratification).

Mice were treated for 4 weeks, by once daily subcutaneous administration 3 hours prior to the dark phase (6 pm to 6 am). Blood samples from a tail tip incision were obtained for HbA1c on study day 21 and oral glucose tolerance was assessed in the 4th week. Oral glucose tolerance test was done in the morning without prior extra compound administration to majorly assess the effect of chronic treatment and less of acute compound administration. Mice were fasted for 4 hours prior to oral glucose administration (2 g/kg, t = 0 min). Blood samples were drawn prior to glucose administration and at 15, 30, 60, 90, 120, and 180 min thereafter. Feed was returned after the last blood sampling. Results are represented as change from baseline, glucose in mmol/l and HbA1c in %.

Statistical analyses are performed with Everstat Version 6.0 based on SAS by 1-way-ANOVA, followed by Dunnett's post-hoc test against vehicle-control. Differences are considered statistically significant at the $p < 0.05$ level.

Glucose lowering in non-fasted female diabetic dbdb-mice

Female diabetic dbdb-mice of mean non-fasted glucose value of 20-22 mmol/l and a body weight of 42 g +/- 0.6 g (SEM) were used. Mice were individually marked and were adapted to housing conditions for at least one week.

3-5 days prior to study start mice were assigned to groups and cages (4 mice per cage, 8 per group, control group 16) according to their non-fasted glucose values to ensure even distribution of lower and higher values between groups (stratification). On the study day, mice were weighed and

dosed (t = 0). Immediately prior to compound administration feed was removed while water remained available, and a first blood sample at a tail incision was drawn (baseline). Further blood samples were drawn at the tail incision at 30, 60, 90, 120, 240, 360, and 480 min.

Statistical analyses are performed with Everstat Version 6.0 based on SAS by 2-way-ANOVA on repeated measures, followed by Dunnett's post-hoc test against vehicle-control. Differences are 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: 8

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. N-Boc-4-(Fmoc-amino)piperidine-4-carboxylic acid was used as amino acid in position 20. In position 1 Boc-Tyr(tBu)-OH and in position 14 Fmoc-Lys(ivDde)-OH were used in the solid phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin according to a modified literature procedure (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603), using 4% hydrazine hydrate in DMF. Hereafter Palm-Glu(γOSu)-OtBu was coupled to the liberated amino-group. 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 0.05% TFA). The purified peptide was analysed by LCMS (Method B). Deconvolution of the mass

signals found under the peak with retention time 12.69 min revealed the peptide mass 4618.71 which is in line with the expected value of 4619.21.

Example 2:

Synthesis of SEQ ID NO: 11

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. In position 1 Boc-Tyr(tBu)-OH, in position 14 Fmoc-Lys(ivDde)-OH and in position 20 Fmoc-(S)-MeLys(Boc)-OH were used in the solid phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin according to a modified literature procedure (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603), using 4% hydrazine hydrate in DMF. Hereafter Palm-Glu(γOSu)-OtBu was coupled to the liberated amino-group. 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 0.05% TFA). The purified peptide was analysed by LCMS (Method B). Deconvolution of the mass signals found under the peak with retention time 12.88 min revealed the peptide mass 4634.66 which is in line with the expected value of 4635.25.

Example 3:

Synthesis of SEQ ID NO: 15

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. In

position 1 Boc-Tyr(tBu)-OH and in position 14 Fmoc-Lys(ivDde)-OH and in position 20 Fmoc-alpha-methyl-ornithine(Boc)-OH were used in the solid phase synthesis protocol. The ivDde-group was cleaved from the peptide on resin according to a modified literature procedure (S.R. Chhabra et al., Tetrahedron Lett. 39, (1998), 1603), using 4% hydrazine hydrate in DMF. Hereafter Stea-Glu(γOSu)-OtBu was coupled to the liberated amino-group. 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). The purified peptide was analysed by LCMS (Method B). Deconvolution of the mass signals found under the peak with retention time 12.90 min revealed the peptide mass 4603.64 which is in line with the expected value of 4604.24.

In an analogous way, the following peptides SEQ ID NO: 8 - 17 were synthesized and characterized (Method A-E), see Table 5.

Table 5: list of synthesized peptides and comparison of calculated vs. found molecular weight.

SEQ ID NO:	calc. Mass	found mass
8	4619.2	4618.7
9	4635.2	4634.8
10	4621.2	4621.1
11	4635.2	4635.1
12	4649.3	4648.0
13	4634.3	4633.6
14	4649.3	4648.9
15	4604.2	4603.6
16	4548.2	4547.4
17*	4252.7	4251.7

*non-acylated comparison compound

Example 4: Chemical stability and solubility

Solubility and chemical stability of peptidic compounds were assessed as described in Methods. The results are given in Table 6.

Table 6: Chemical stability and solubility

SEQ ID NO:	Stability (pH4.5) [%]	Stability (pH7.4) [%]	Solubility (pH4.5) [µg/ml]	Solubility (pH7.4) [µg/ml]
1 (Exendin-4)	100.0	77.5	933.6	1000
8	93.0	93.0	>1000	>1000
11	100.0	99.0	964.2	899.8
12	98.0	91.0	>1000	983.0
15	98.0	98.0	>1000	>1000

Example 5: In vitro data on GLP-1, GIP and glucagon receptor

Potencies of peptidic compounds at the GLP-1, GIP and glucagon receptors were determined by exposing cells expressing human glucagon receptor (hGLUC R), human GIP (hGIP 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 for Exendin-4 derivatives with activity at the human GIP (hGIP R), human GLP-1 receptor (hGLP-1 R) and human glucagon receptor (hGLUC R) are shown in Table 7.

Table 7. EC50 values of exendin-4 peptide analogues at GLP-1, GIP and Glucagon receptors (indicated in pM)

SEQ ID NO:	EC50 hGIP R [pM]	EC50 hGLP-1 R [pM]	EC50 hGLUC R [pM]

8	16.3	4.7	34700.0
9	93.2	13.5	>1000000
10	7.1	4.9	10400.0
11	7.0	5.1	3160.0
12	27.0	11.6	1.3
13	33.1	13.6	202.0
14	4.5	7.2	4730.0
15	8.9	16.1	4.0
16	2.5	4.1	19800.0

Comparison Testing

A selection of inventive exendin-4 derivatives comprising a functionalized amino acid in position 14 has been tested versus corresponding compounds having in this position 14 a 'non-functionalized' amino acid. The reference pair compounds and the corresponding EC50 values at GLP-1 and GIP receptors (indicated in pM) are given in Table 8. As shown, the inventive exendin-4 derivatives show a superior activity in comparison to the compounds with a 'non-functionalized' amino acid in position 14.

Table 8. Comparison of exendin-4 derivatives comprising a non-functionalized amino acid in position 14 vs. exendin-4 derivatives comprising a functionalized amino acid in position 14. EC50 values at GLP-1 and GIP receptors are indicated in pM. (K=lysine, L=leucine, γE-x53=(S)-4-Carboxy-4-hexadecanoylamino-butyryl-)

SEQ ID NO:	EC50 hGIPR [pM]	EC50 hGLP-1R [pM]	residue in position 14
11	7.0	5.1	K(γE-x53)
17	163	5.9	L

Example 6: Pharmacokinetic testing

Pharmacokinetic profiles were determined as described in Methods. Calculated $T_{1/2}$ and c_{max} values are shown in Table 9.

Table 9. Pharmacokinetic profiles of exendin-4 derivatives.

	Mice (1 mg/kg)		Mini pigs (0.1 mg/kg)	
SEQ ID NO:	$T_{1/2}$ [h]	Cmax [ng/ml]	$T_{1/2}$ [h]	Cmax [ng/ml]
11	4.3	5940	12.6	302
15	2.9	3740		

Example 7:

Subchronic effects of SEQ ID NO: 11 after subcutaneous treatment on body weight in female diet-induced obese (DIO) C57BL/6NCrl mice (14 weeks of prefeeding with high-fat diet, method 2).

Female obese C57BL/6NCrl mice were treated for 3 weeks once daily subcutaneously in the late afternoon, prior at the end of the light phase (12 h lights on) with 3 µg/kg and 10 µg/kg SEQ ID NO: 11 or vehicle. Body weight was recorded daily.

Treatment with SEQ ID NO: 11 reduced body weight, whereas the high-fat diet control group even gained body weight (Fig. 1 and Table 10). Calculating the relative body weight change from baseline values revealed a dose-dependent decrease of body weight, reaching 7.6% at 3 µg/kg and 17.4% at 10 µg/kg (Fig. 2), respectively.

Table 10. Weight change in DIO mice over a 3-week treatment period (mean ± SEM)

Example (Dose)	Overall weight change (g)
Control standard diet	+0.3 ± 0.2
Control high-fat diet	+2.7 ± 0.3
SEQ ID NO: 11 (3 µg/kg)	-3.2 ± 0.6
SEQ ID NO: 11 (10 µg/kg)	-6.8 ± 0.7

Example 8: Effects of 4 weeks of treatment with SEQ ID NO: 11 on glucose, HbA1c and oral glucose tolerance in female diabetic dbdb-mice (method 4)

Female dbdb-mice, received 3 and 10 µg/kg of SEQ ID NO: 11 or phosphate buffered saline (vehicle control) once daily, subcutaneously over four weeks. SEQ ID NO: 11 reduced statistically significant non-fasted glucose compared to vehicle control at the 3 and 10 µg/kg dose. (Fig. 3).

As well, SEQ ID NO: 11 prevented an increase of HbA1c in a statistical significant manner compared to vehicle control at the 3 and 10 µg/kg dose (Fig. 4; $p<0.05$, 1-way-ANOVA, followed by Dunnett's post-hoc test).
Treatment with SEQ ID NO: 11 lead to improved oral glucose tolerance (represented as normalized to 0 mmol/l at 0 min; Fig. 5), and reduction of AUC under the glucose curve reached statistical significance at 3 and 10 µg/kg compared to vehicle control (Fig. 6; $p<0.05$, 1-way- ANOVA, followed by Dunnett's post-hoc test).

Example 9: SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 15 on glucose lowering in non-fasted female diabetic dbdb-mice

Female dbdb-mice, received 3 µg/kg of SEQ ID NO: 11, SEQ ID NO: 12, and SEQ ID NO: 15 or phosphate buffered saline (vehicle control) subcutaneously, at time 0 min. All three compounds immediately lowered glucose values (baseline at 20-22 mmol/l), with SEQ ID NO: 11 and SEQ ID NO: 12 reaching the maximal effect of ~11 mmol/l and SEQ ID NO: 15 of ~12 mmol/l glucose reduction, respectively, at 240 min and keeping it to the end of observation at 480 min (Fig. 7).
All three compounds reached a statistical significant reduction of glucose compared to vehicle control from t = 60 min until end of observation ($p<0.05$, 2-way-ANOVA on repeated measures, followed by Dunnett's post-hoc test).

Example 2: Effect of SEQ ID NO: 11 on gastric emptying and intestinal passage in female NMRI-mice

Female NMRI-mice, weighing on average 25 – 30 g, received 1, 10 and 100 µg/kg of SEQ ID NO: 11, 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 and intestinal passage was done (Fig. 8).

Comparable data can be obtained for both female and male mice.

In these studies, SEQ ID NO: 11 reduced intestinal passage by 44, 68 and 69% ($p<0.0001$) and increased remaining gastric contents by 17, 97 and 106% ($p<0.0001$ versus vehicle control, 1-W-ANOVA, followed by Dunnett's post-hoc test) respectively.

Table 11: sequences

SEQ ID NO:	sequence
1	H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH2
2	H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K-E-F-I-A-W-L-V-K-G-R-NH2
3	H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K(γE-x53)-E-F-I-A-W-L-V-R-G-R-G
4	Y-A-E-G-T-F-I-S-D-Y-S-I-A-M-D-K-I-H-Q-Q-D-F-V-N-W-L-L-A-Q-K-G-K-K-N-D-W-K-H-N-I-T-Q
5	H-S-Q-G-T-F-T-S-D-Y-S-K-Y-L-D-S-R-R-A-Q-D-F-V-Q-W-L-M-N-T
6	Y-G-E-G-T-F-T-S-D-L-S-I-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH2
7	Y-A-E-G-T-F-T-S-D-V-S-I-Y-L-E-G-Q-A-A-K-E-F-I-A-W-L-V-K-G-R-NH2
8	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x53)-E-E-R-A-A-Pip-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2
9	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x53)-E-E-R-A-A-

	(R)MeLys-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2
10	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x53)-E-E-R-A-A-(S)MeOrn-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2
11	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x53)-E-E-R-A-A-(S)MeLys-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2
12	Y-Aib-Q-G-T-F-T-S-D-L-S-K-Q-K(γE-x70)-D-E-Q-R-A-(S)MeLys-E-F-I-E-W-L-K-S-G-G-P-S-S-G-A-P-P-P-S-NH2
13	Y-Aib-Q-G-T-F-T-S-D-L-S-I-Q-K(γE-x70)-D-E-Q-R-A-(R)MeLys-E-F-I-E-W-L-K-S-G-G-P-S-S-G-A-P-P-P-S-NH2
14	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x70)-D-E-R-A-A-(S)MeLys-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2
15	Y-Aib-Q-G-T-F-T-S-D-L-S-I-Q-K(γE-x70)-D-E-Q-R-A-(S)MeOrn-E-F-I-E-W-L-K-A-G-G-P-S-S-G-A-P-P-P-S-NH2
16	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-K(γE-x53)-E-E-R-A-A-(S)MeLys-E-F-I-E-W-L-K-A-G-G-P-S-S-G-A-P-P-P-S-NH2
17	Y-Aib-E-G-T-F-T-S-D-L-S-I-Q-L-E-E-R-A-A-(S)MeLys-E-F-I-E-W-L-K-N-T-G-P-S-S-G-A-P-P-P-S-NH2

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

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

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

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

Tyr-Aib-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-X12-Gln-X14-X15-X16-X17-X18-X19-X20-X21-Phe-Ile-Glu-Trp-Leu-Lys-X28-X29-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-X40 (II)

X3 represents an amino acid residue selected from Gln, Glu and His,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents an amino acid residue having a side chain with an $-NH_2$ group, wherein the $-NH_2$ side chain group is functionalized by $-C(O)-R^5$, wherein R^5 may be a moiety comprising up to 50 or up to 100 carbon atoms and optionally heteroatoms selected from halogen, N, O, S and/or P,
X15 represents an amino acid residue selected from Asp and Glu,
X16 represents an amino acid residue selected from Ser, Lys, Glu and Gln,
X17 represents an amino acid residue selected from Arg, Lys, Glu, Gln, Leu, Aib, Tyr and Ala,
X18 represents an amino acid residue selected from Ala, Arg, Aib, Leu and Tyr,
X19 represents an amino acid residue selected from Ala, Val and Aib,
X20 represents an amino acid residue selected from Gln, Aib, Phe, Leu, Lys, His, Pip, (S)MeLys, (R)MeLys and (S)MeOrn,
X21 represents an amino acid residue selected from Asp, Glu and Leu,
X28 represents an amino acid residue selected from Asn, Ala, Aib and Ser,
X29 represents an amino acid residue selected from Gly, Thr, Aib, D-Ala and Ala,
X40 is either absent or represents Lys,

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R^1 represents NH_2,

R^2 represents the C-terminal group of the peptidic compound and is selected from OH and NH_2,

or a salt or solvate thereof, wherein the compound is a GLP-1 and GIP receptor agonist.

2. A compound of claim 1, wherein X14 represents an amino acid residue with a functionalized -NH_2 side chain group, such as functionalized Lys, Orn, Dab or Dap, wherein at least one H atom of the -NH_2 side chain group is replaced by -C(O)-R^5, which is selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, 4-Hexadecanoylamino-butyryl-, 4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-, 4-octadecanoylamino-butyryl, 4-((Z)-octadec-9-enoylamino)-butyryl-, 6-[(4,4-Diphenyl-cyclohexyloxy)-hydroxy-phosphoryloxy]-hexanoyl-, Hexadecanoyl-, (S)-4-Carboxy-4-(15-carboxy-pentadecanoylamino)-butyryl-, (S)-4-Carboxy-4-{3-[3-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-propionylamino]-propionylamino}-butyryl, (S)-4-Carboxy-4-{3-[(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyl-tridecyl)-chroman-6-yloxycarbonyl]-propionylamino}-butyryl-, (S)-4-Carboxy-4-((9Z,12Z)-octadeca-9,12-dienoylamino)-butyryl-, (S)-4-Carboxy-4-[6-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-hexanoylamino]-butyryl-, (S)-4-Carboxy-4-((2S,3R,4S,5R)-5-carboxy-2,3,4,5-tetrahydroxy-pentanoylamino)-butyryl-, (S)-4-Carboxy-4-tetradecanoylamino-butyryl-, (S)-4-(11-Benzyloxycarbonyl-undecanoylamino)-4-carboxy-butyryl-, (S)-4-Carboxy-4-[11-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxy-hexylcarbamoyl)-undecanoylamino]-butyryl-, (S)-4-Carboxy-4-((Z)-octadec-9-enoylamino)-butyryl-, (S)-4-Carboxy-4-(4-dodecyloxy-benzoylamino)-butyryl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-, (S)-4-Carboxy-4-docosanoylamino-butyryl-, (S)-4-Carboxy-4-((Z)-nonadec-10-enoylamino)-butyryl-, (S)-4-Carboxy-4-(4-decyloxy-benzoylamino)-butyryl-, (S)-4-

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Carboxy-4-[(4'-octyloxy-biphenyl-4-carbonyl)-amino]-butyryl-, (S)-4-Carboxy-4-(12-phenyl-dodecanoylamino)-butyryl-, (S)-4-Carboxy-4-icosanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-hexadecanoylamino-butyrylamino)-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl-, 3-(3-Hexadecanoylamino-propionylamino)-propionyl-, 3-Hexadecanoylamino-propionyl-, (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-, (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-, (S)-4-Carboxy-4-((9S,10R)-9,10,16-trihydroxy-hexadecanoylamino)-butyryl-, tetradecanoyl-, 11-Carboxy-undecanoyl-, 11-Benzyloxycarbonyl-undecanoyl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-tetradecanoylamino-butyrylamino)-butyryl-, 6-[Hydroxy-(naphthalen-2-yloxy)-phosphoryloxy]-hexanoyl-, 6-[Hydroxy-(5-phenyl-pentyloxy)-phosphoryloxy]-hexanoyl-, 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-{2-[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-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-

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[(S)-4-carboxy-4-(17-carboxy-heptadecanoylamino)-butyrylamino]-ethoxy}-ethoxy)-acetylamino]-butyrylamino}-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}-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-, and (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-,

X40 is absent or represents Lys.

3. A compound of any one of claims 1 - 2, wherein X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-, 4-octadecanoylamino-butyryl-, Hexadecanoyl-, (S)-4-Carboxy-4-henicosanoylamino-butyryl-, (S)-4-Carboxy-4-((S)-4-carboxy-4-octadecanoylamino-butyrylamino)-butyryl-, 3-(3-Octadecanoylamino-propionylamino)-propionyl-.

4. A compound according to any one of claims 1-3, wherein X14 is Lys functionalized with C(O)-R^5, which is selected from the group consisting of (S)-4-carboxy-4-hexadecanoylamino-butyryl (γE-x53) and (S)-4-carboxy-4-octadecanoylamino-butyryl (γE-x70).

5. A compound of any one of claims 1 - 4, wherein R^2 is NH_2.

6. A compound according to any one of claims 1-5, wherein the peptidic compound has a relative activity of at least 0.04%, preferably at least 0.08%, more preferably at least 0.2% compared to that of natural GIP at the GIP receptor.

7. A compound according to any one of claims 1-6, wherein the peptidic compound exhibits a relative activity of at least 0.07%, preferably at least 0.1%, more preferably at least 0.14%, more preferably at least 0.35% and even more preferably at least 0.4% compared to that of GLP-1(7-36) at the GLP-1 receptor.

8. A compound according to any one of claims 6 or 7, wherein the peptidic compound further exhibits a relative activity of at least 0.1%, preferably at least 0.2%, more preferably at least 0.3%, more preferably at least 0.4% and even more preferably at least 0.5% compared to that of natural glucagon at the glucagon receptor.

9. A compound of any one of claims 1 – 8, wherein
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl-, (S)-4-Carboxy-4-octadecanoylamino-butyryl-.

10. A compound of any one of claims 1 - 9, wherein
X3 represents an amino acid residue selected from Gln, His and Glu,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by one of the groups selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- and (S)-4-Carboxy-4-octadecanoylamino-butyryl-,
X15 represents an amino acid residue selected from Glu and Asp,
X16 represents Glu,
X17 represents an amino acid residue selected from Arg and Gln,
X18 represents an amino acid residue selected from Ala and Arg,
X19 represents Ala,
X20 represents an amino acid residue selected from Pip, (S)MeLys,(R)MeLys and (S)MeOrn,
X21 represents Glu,
X28 represents an amino acid residue selected from Asn, Ser and Ala,
X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

11. A compound of any one of claims 1 - 10, wherein X19 represents Ala.

12. A compound of any one of claims 1 - 11, wherein
X16 represents Glu,
X20 represents an amino acid residue selected from Pip, (S)MeLys, (R)MeLys and (S)MeOrn.

13. A compound of any one of claims 1 - 12, wherein
X28 represents Ala,
X29 represents Gly.

14. A compound of any one of claims 1 - 12, wherein
X28 represents Asn,
X29 represents Thr.

15. A compound of any one of claims 1 - 14, wherein
X3 represents an amino acid residue selected from Gln and Glu,
X12 represents an amino acid residue selected from Ile and Lys,
X14 represents Lys, wherein the -NH_2 side chain group is functionalized by - C(O)-R^5, which is selected from (S)-4-Carboxy-4-hexadecanoylamino-butyryl- (γE-x53) and (S)-4-Carboxy-4-octadecanoylamino-butyryl- (γE-x70),
X15 represents an amino acid residue selected from Asp and Glu,
X16 represents Glu,
X17 represents an amino acid residue selected from Arg and Gln,
X18 represents an amino acid residue selected from Ala and Arg,
X19 represents Ala,
X20 represents an amino acid residue selected from Pip, (S)-MeLys, (R)-MeLys, and (S)-MeOrn,
X21 represents Glu,
X28 represents an amino acid residue selected from Asn, Ala and Ser,
X29 represents an amino acid residue selected from Gly and Thr,
X40 is absent.

16. The compound of any one of claims 1-15, selected from the compounds of SEQ ID NO.: 8-16 or a salt or solvate thereof.

17. The compound of any one of claims 1-15, selected from the compounds of SEQ ID NO.: 8-13 and 15 or a salt or solvate thereof.

18. A pharmaceutical composition comprising a compound according to any one of claims 1-17 in adjunct with least one pharmaceutically acceptable carrier or excipient.

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19. The composition according to claim 18 further comprising at least one additional therapeutically active agent, wherein the additional therapeutically active agent is selected from the series of Insulin and Insulin derivatives, GLP-1, GLP-1 analogues and GLP-1 receptor agonists, polymer bound GLP-1 and GLP-1 analogues, dual GLP1/glucagon agonists, PYY3-36 or analogues thereof, pancreatic polypeptide or analogues thereof, Glucagon receptor agonists, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, Xenin and analogues thereof, DDP-IV inhibitors, SGLT2 inhibitors, dual SGLT2 / SGLT1 inhibitors, Biguanides Thiazolidinediones, dual PPAR agonists, Sulfonylureas, Meglitinides, alpha-glucosidase inhibitors, Amylin and Amylin analogues, GPR119 agonists, GPR40 agonists, GPR120 agonists, GPR142 agonists, systemic or low-absorbable TGR5 agonists, Cycloset, inhibitors of 11-beta-HSD, activators of glucokinase, inhibitors of DGAT, inhibitors of protein tyrosinephosphatase 1, 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 dehydrogenase kinase, alpha2-antagonists, CCR-2 antagonists, modulators of glucose transporter-4, Somatostatin receptor 3 agonists, HMG-CoA-reductase inhibitors, fibrates, nicotinic acid and the derivatives thereof, nicotinic acid receptor 1 agonists, PPAR-alpha, gamma or alpha/gamma) agonists or modulators, PPAR-delta agonists, ACAT inhibitors, cholesterol absorption inhibitors, bile acid-binding substances, IBAT inhibitors, MTP inhibitors, modulators of PCSK9, LDL receptor up-regulators by liver selective thyroid hormone receptor ß agonists, HDL-raising compounds, lipid metabolism modulators, PLA2 inhibitors , ApoA-I enhancers, thyroid hormone receptor agonists, cholesterol synthesis inhibitors, omega-3 fatty acids and derivatives thereof, active substances for the treatment of obesity, such as Sibutramine, Tesofensine, Orlistat, CB-1receptor antagonists, MCH-1 antagonists, MC4 receptor agonists and partial agonists, NPY5 or NPY2 antagonists, NPY4 agonists, beta-3-

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agonists, leptin or leptin mimetics, agonists of the 5HT2c receptor, or the combinations of bupropione/naltrexone (CONTRAVE), bupropione/zonisamide (EMPATIC), bupropione/phentermine or pramlintide/metreleptin, QNEXA (Phentermine+ topiramate), lipase inhibitors, angiogenesis inhibitors, H3 antagonists, AgRP inhibitors, triple monoamine uptake inhibitors (norepinephrine and acetylcholine), MetAP2 inhibitors, nasal formulation of the calcium channel blocker diltiazem, antisense against production of fibroblast growth factor receptor 4, prohibitin targeting peptide-1, drugs for influencing high blood pressure, chronic heart failure or atherosclerosis, such as angiotensin II receptor antagonists, 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.

20. The composition as claimed in claim 18 or 19 further comprising at least one additional therapeutically active agent, wherein the additional therapeutically active agent particularly is a GLP-1 agonist and/or insulin or an insulin analogue and/or a gastrointestinal peptide.

21. A method of the treatment or prevention, through GLP-1, GIP and/or GCG receptor modulation 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, decreasing food intake, increasing 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, IGT, dyslipidemia, coronary heart disease, hepatic steatosis, beta-blocker poisoning; or for inhibiting the motility of the gastro-intestinal tract in connection with investigations of the gastro-

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intestinal tract using techniques such as X-ray, CT- and NMR-scanning, comprising administering to a patient in need a compound according to any one of claims 1-17 or a pharmaceutical composition according to any one of claims 18-20.

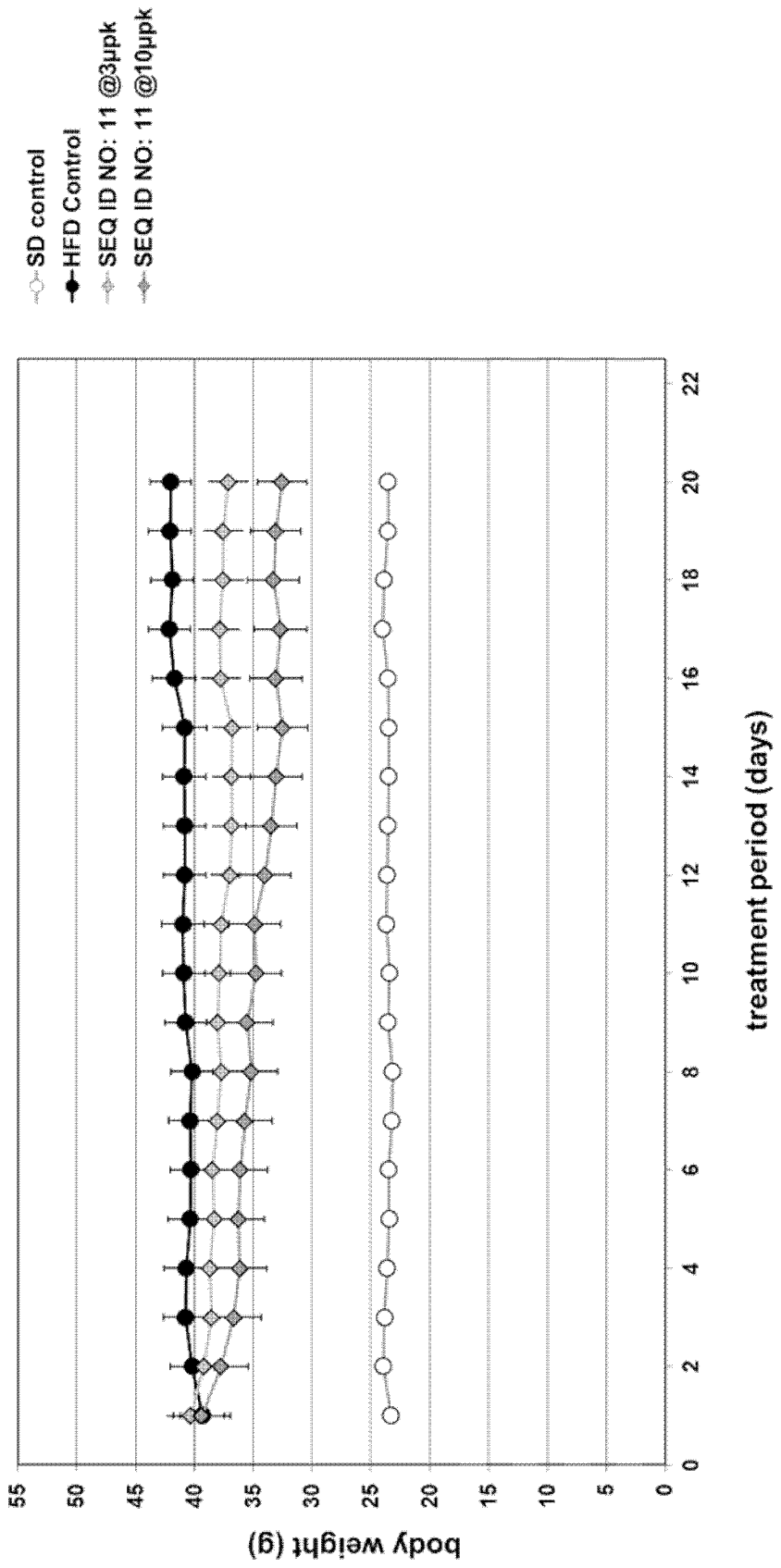
22. The method of claim 21 for the treatment or prevention of hyperglycemia, type 2 diabetes, obesity and metabolic syndrome or reducing body weight.

23. Use of a compound according to any one of claims 1-17 for the preparation of a medicament for treatment, through GLP-1, GIP and/or GCG receptor modulation 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, decreasing food intake, increasing 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, IGT, dyslipidemia, coronary heart disease, hepatic steatosis, beta-blocker poisoning; or for inhibition of the motility of the gastro-intestinal tract in connection with investigations of the gastro-intestinal tract using techniques such as X-ray, CT- and NMR-scanning.

SANOFI

WATERMARK INTELLECTUAL PROPERTY PTY LTD

P40476AU00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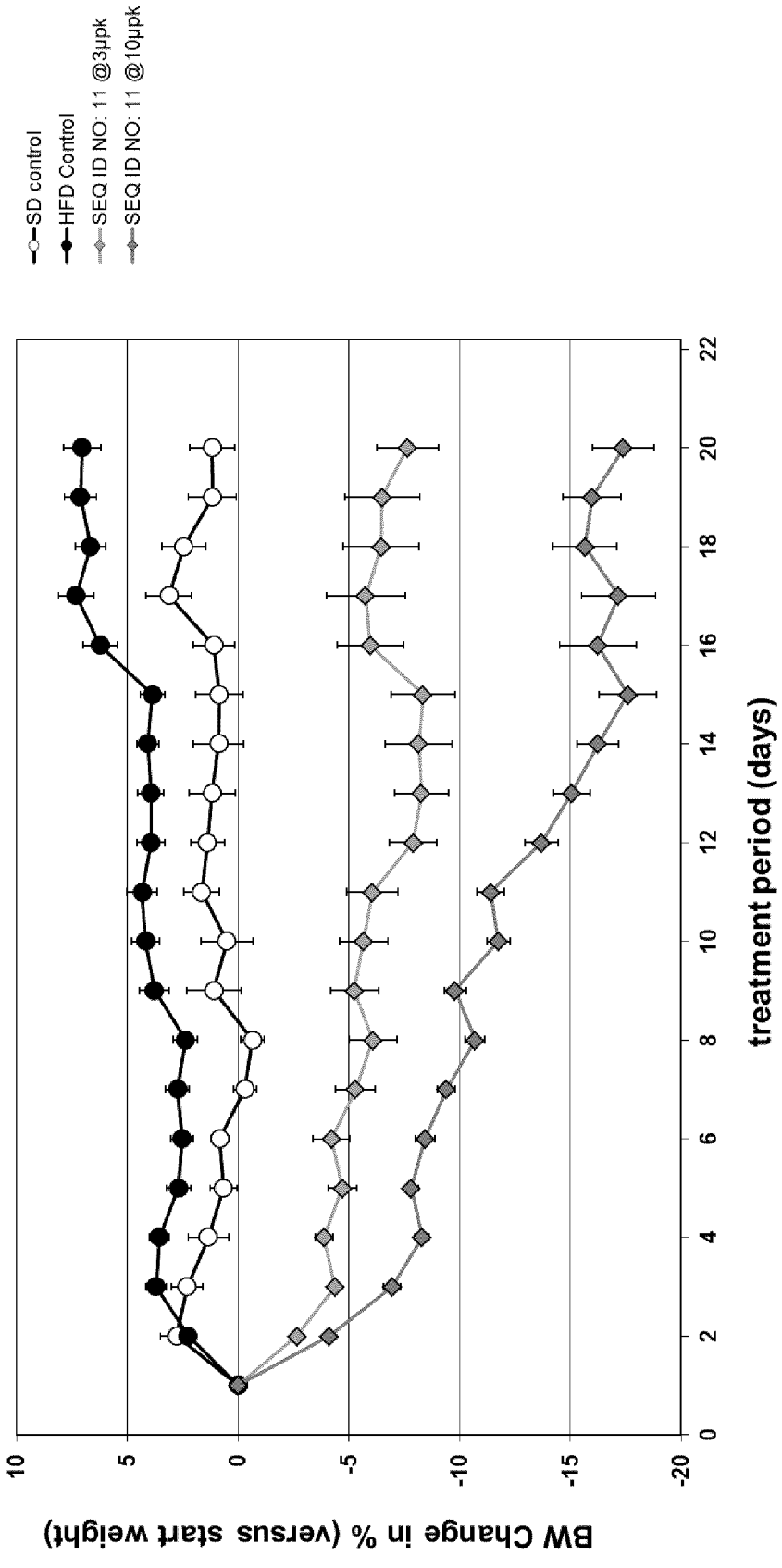
12
14
16
18
20
22
treatment period (days)

Fig. 1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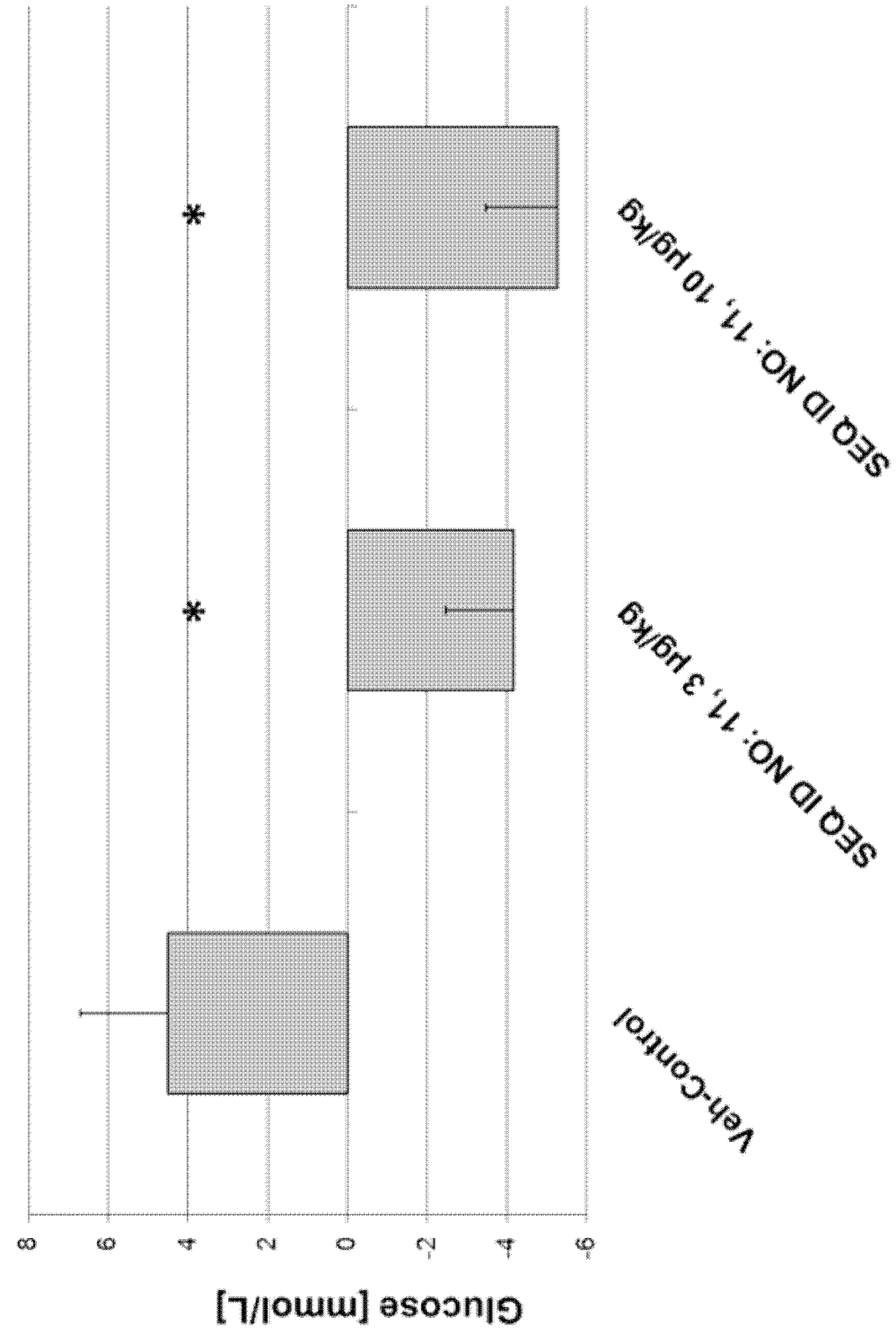
12
14
16
18
20
22
treatment period (days)

Fig. 2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6
4
2
0
-2
-4
-6
*
*
Veh-Control
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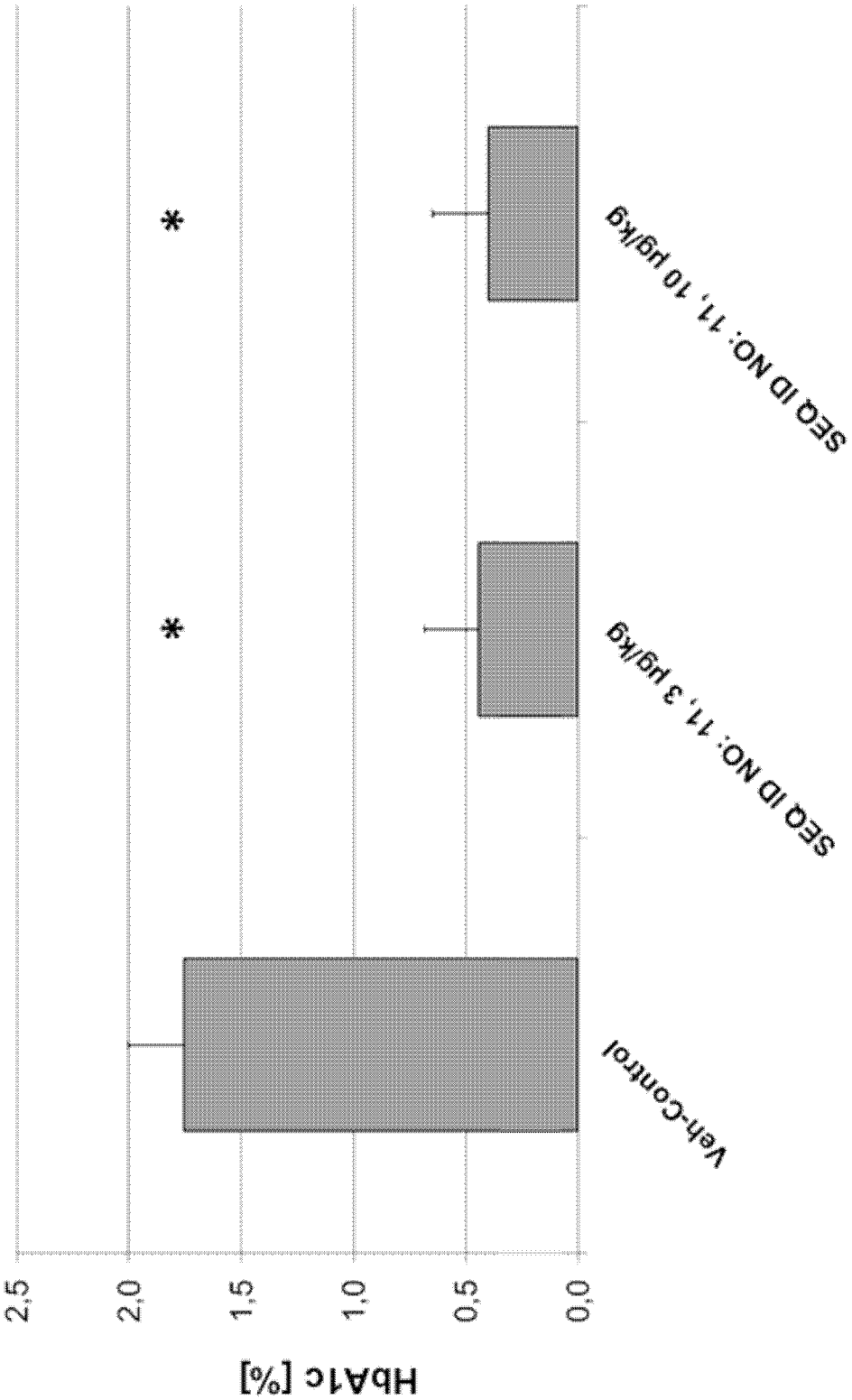
SEQ ID NO: 11, 10 µg/kg

Fig. 3: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2,0
1,5
1,0
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0,0
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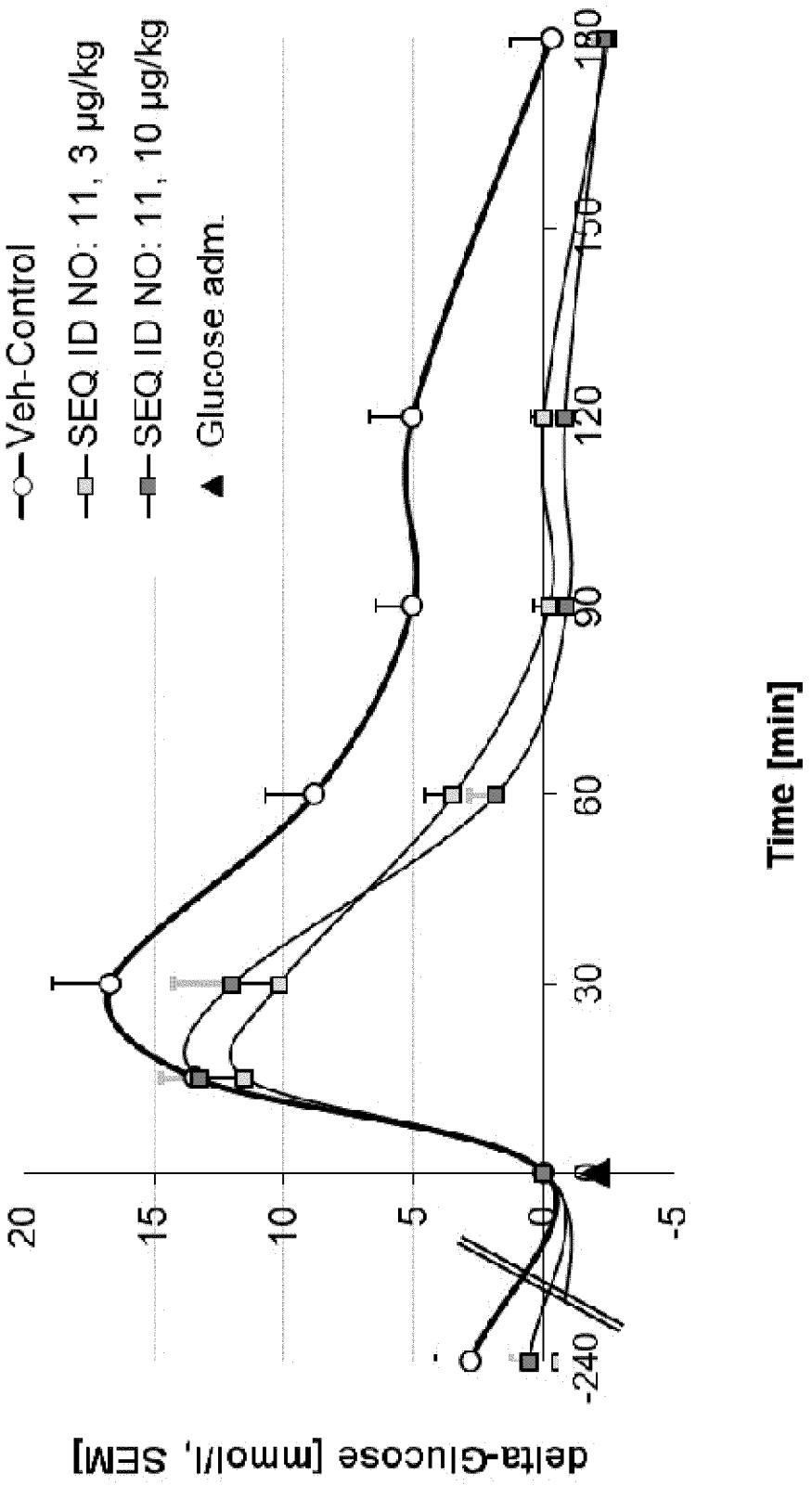
*
*

Fig. 4: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SEQ ID NO: 11, 10 µg/kg
Glucose adm.
delta-Glucose [mmol/l, SEM]
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30
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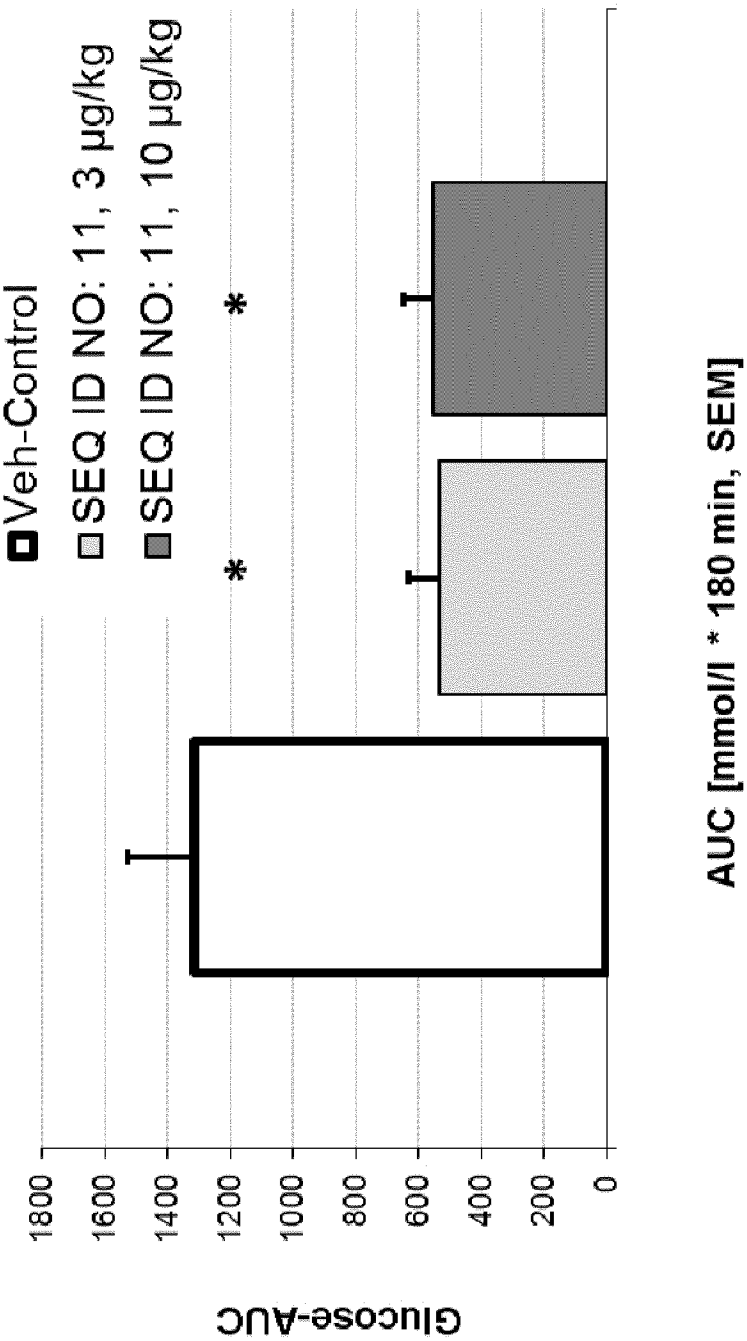
150
180

Fig. 5: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SEQ ID NO: 11, 10 µg/kg
*
*
Glucose-AUC
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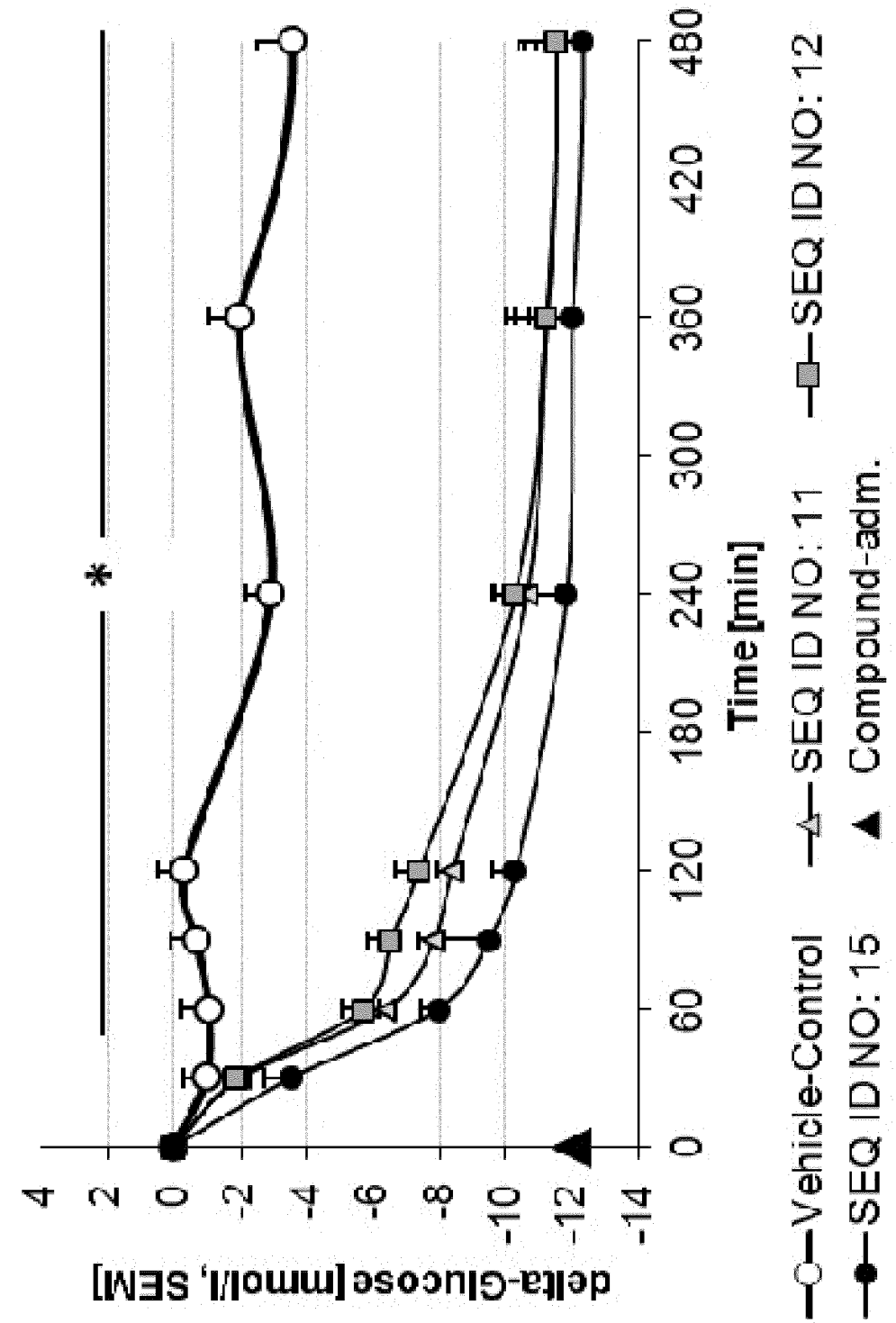
1400
1200
1000
800
600
400
200
0
AUC [mmol/l * 180 min, SEM]

Fig. 6: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0
-2
-4
-6
-8
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-12
-14
0
60
120
180
240
300
360
420
480
Time [min]
*
1
3
Vehicle-Control
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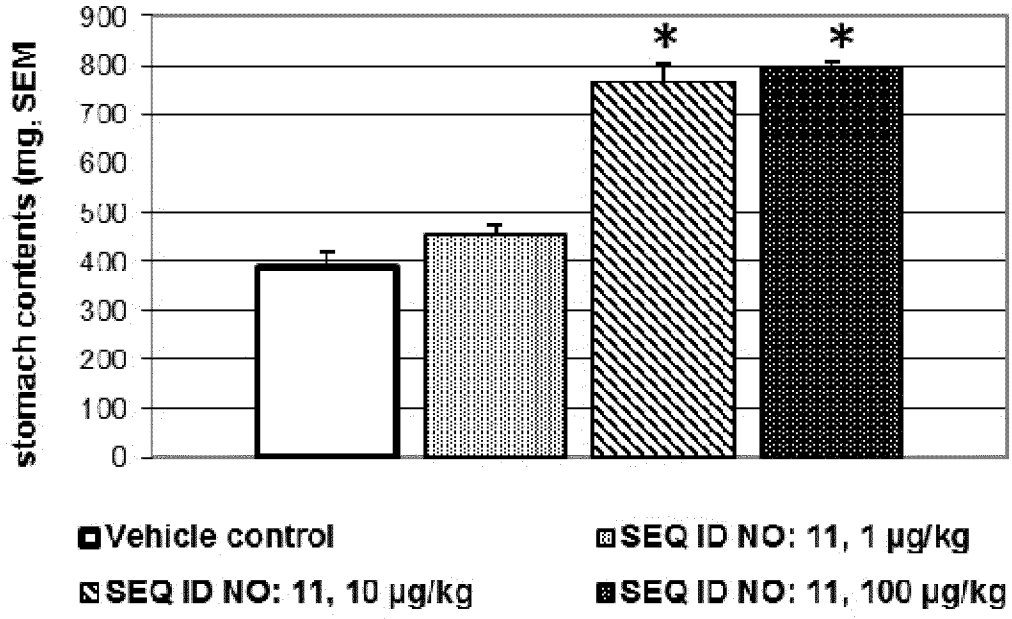
SEQ ID NO: 11
SEQ ID NO: 12
Compound-adm.

Fig. 7

Fig. 8

a)


stomach contents (mg, SEM
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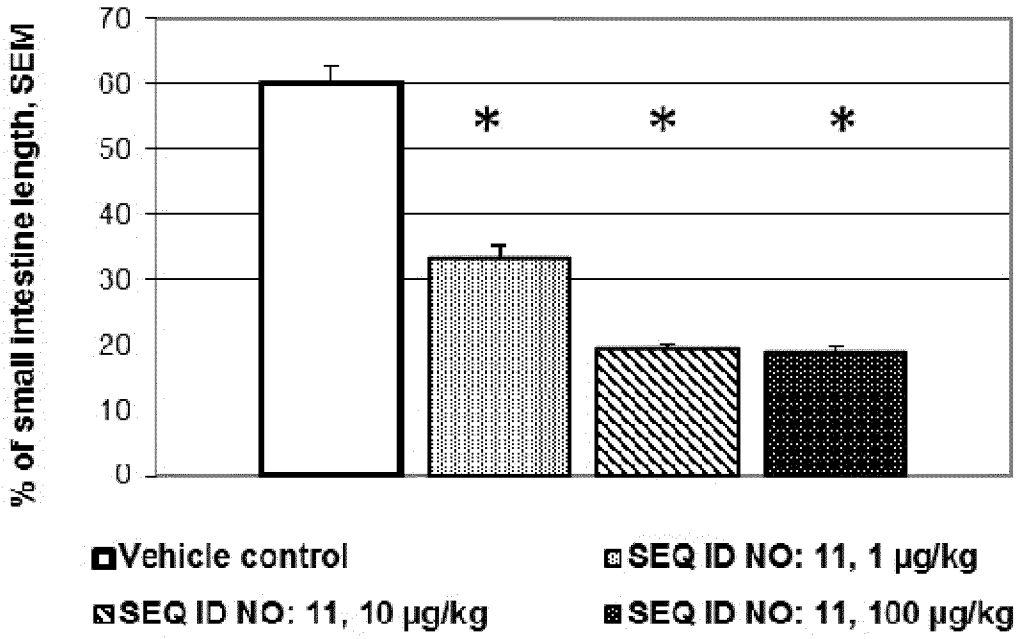
800
700
600
500
400
300
200
100
0
*
*
Vehicle control
SEQ ID NO: 11, 1 µg/kg
SEQ ID NO: 11, 10 µg/kg
SEQ ID NO: 11, 100 µg/kg

b)


% of small intestine length, SEM
70
60
50
40
30
20
10
0
*
*
*
Vehicle control
SEQ ID NO: 11, 1 µg/kg
SEQ ID NO: 11, 10 µg/kg
SEQ ID NO: 11, 100 µg/kg

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Ser Gly Ala Pro Pro Pro Ser
        35
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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
            20                  25                  30
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       (S)-4-carboxy-4-hexadecanoylamino-butyryl

<400> 3

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1   5   10   15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly
            20   25   30

<210> 4
<211> 42
<212> PRT
<213> Homo sapiens

<400> 4

Tyr Ala Glu Gly Thr Phe Ile Ser Asp Tyr Ser Ile Ala Met Asp Lys
1   5   10   15

Ile His Gln Gln Asp Phe Val Asn Trp Leu Leu Ala Gln Lys Gly Lys
            20   25   30

Lys Asn Asp Trp Lys His Asn Ile Thr Gln
        35   40

<210> 5
<211> 29
<212> PRT
<213> Homo sapiens

<400> 5

His Ser Gln Gly Thr Phe Thr Ser Asp Tyr Ser Lys Tyr Leu Asp Ser
1   5   10   15

Arg Arg Ala Gln Asp Phe Val Gln Trp Leu Met Asn Thr
            20   25

<210> 6
<211> 39
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<220>
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<223> Amidated C-terminus

<400> 6

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Tyr Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Met Glu Glu
1               5                   10                  15


Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30


Ser Gly Ala Pro Pro Pro Ser
        35


<210>  7
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<220>
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<400>  7

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ile Tyr Leu Glu Gly
1               5                   10                  15


Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg
            20                  25                  30


<210>  8
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<220>
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<223>  2-Methylalanine

<220>
<221>  MOD_RES
<222>  (14)..(14)
<223>  Lys derivatized at N6 with
       (S)-4-carboxy-4-hexadecanoylamino-butyryl

<220>
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<223>  Xaa is 4-aminopiperidine-4-carboxylic acid

<220>
<221>  MOD_RES
<222>  (39)..(39)
<223>  Amidated C-terminus

<400>  8
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Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Glu Glu
1 5 10 15

Arg Ala Ala Xaa Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

<210> 9
<211> 39
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<220>
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<222> (14)..(14)
<223> Lys derivatized at N6 with
(S)-4-carboxy-4-hexadecanoylamino-butyryl

<220>
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<223> (R)-alpha-methyl lysine

<220>
<221> MOD_RES
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<223> Amidated C-terminus

<400> 9

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Glu Glu
1 5 10 15

Arg Ala Ala Lys Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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(S)-4-carboxy-4-hexadecanoylamino-butyryl

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<223> Xaa is (S)-alpha-methyl ornithine

<220>
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<223> Amidated C-terminus

<400> 10

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Glu Glu
1 5 10 15

Arg Ala Ala Xaa Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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(S)-4-carboxy-4-hexadecanoylamino-butyryl

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<400> 11

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Glu Glu
1 5 10 15

Arg Ala Ala Lys Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

<210> 12
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<400> 12

Tyr Ala Gln Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Lys Asp Glu
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Gln Arg Ala Lys Glu Phe Ile Glu Trp Leu Lys Ser Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<210> 13
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<220>
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<223> (R)-alpha-methyl lysine

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<400> 13

Tyr Ala Gln Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Asp Glu
1 5 10 15

Gln Arg Ala Lys Glu Phe Ile Glu Trp Leu Lys Ser Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

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<223> (S)-alpha-methyl lysine

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<400> 14

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Asp Glu
1 5 10 15

Arg Ala Ala Lys Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

<210> 15
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<220>
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<400> 15

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Gln Arg Ala Xaa Glu Phe Ile Glu Trp Leu Lys Ala Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
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<210> 16
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<223> (S)-alpha-methyl lysine

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<400> 16

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Lys Glu Glu
1   5   10   15

Arg Ala Ala Lys Glu Phe Ile Glu Trp Leu Lys Ala Gly Gly Pro Ser
            20   25   30

Ser Gly Ala Pro Pro Pro Ser
        35

<210> 17
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<220>
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<223> Amidated C-terminus

<400> 17

Tyr Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Ile Gln Leu Glu Glu
1   5   10   15

Arg Ala Ala Lys Glu Phe Ile Glu Trp Leu Lys Asn Thr Gly Pro Ser
            20   25   30

Ser Gly Ala Pro Pro Pro Ser
        35