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

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

(74) Agent: **WEICKMANN & WEICKMANN PARTMBB**; Postfach 860 820, 81635 München (DE).

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(54) Title: NON-ACYLATED EXENDIN-4 DERIVATIVES AS DUAL GLP-1/GLUCAGON RECEPTOR 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.



Non-Acylated Exendin-4 Derivatives as Dual GLP-1/Glucagon Receptor Agonists

5

Description

FIELD OF THE INVENTION

10 The present invention relates to dual GLP-1 / glucagon receptor agonists and their medical use, for example in the treatment of disorders of the metabolic syndrome, including diabetes and obesity, as well as for reduction of excess food intake. These dual GLP-1 / glucagon receptor agonists show reduced activity on the GIP receptor to reduce the risk of hypoglycemia. They are structurally derived from exendin-4 and
15 supposed to show high stability under acidic conditions.

BACKGROUND OF THE INVENTION

Kosinski et al. (Obesity 2012;20:1566–1571), Pocai et al. (Diabetes 2009, 58, 2258)
20 and Day et al. (Nat Chem Biol 2009;5:749) describe dual agonists of the glucagon-like peptide-1 (GLP-1) and glucagon receptors, e.g. by combining the actions of GLP-1 and glucagon in one molecule, which lead to a therapeutic principle with anti-diabetic action and a pronounced weight lowering effect superior to pure GLP-1 agonists, among others due to glucagon-receptor mediated increased satiety and
25 energy expenditure.

Holst (Physiol. Rev. 2007, 87, 1409) and Meier (Nat. Rev. Endocrinol. 2012, 8, 728) describe that GLP-1 receptor agonists, such as GLP-1, liraglutide and exendin-4, have 3 major pharmacological activities to improve glycemic control in patients with
30 T2DM by reducing fasting and postprandial glucose (FPG and PPG): (i) increased glucose-dependent insulin secretion (improved first- and second-phase), (ii) glucagon suppressing activity under hyperglycemic conditions, (iii) delay of gastric emptying rate resulting in retarded absorption of meal-derived glucose.

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

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-NH₂

5 Liraglutide is a marketed chemically modified GLP-1 analog 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, J.B. et al., Lancet, 374:39-47, 2009).

The amino acid sequence of Liraglutide is shown as SEQ ID NO: 2.

10

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

15 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 as SEQ ID NO: 3.

HSQGTFTSDYSKYLDLRRAQDFVQWLMNT-OH

20 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. Recent publications suggest that glucagon has in addition beneficial effects on reduction of body fat mass, reduction of food intake, and increase of energy expenditure (KM Heppner, Physiology &
25 Behavior 2010, 100, 545–548).

GIP (glucose-dependent insulintropic 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
30 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: 5.

YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-OH

Peptides which are based on the structures of GLP-1 or glucagon, and bind and activate both the glucagon and the GLP-1 receptor (Hjort et al. Journal of Biological Chemistry, 269, 30121-30124, 1994; Day JW et al, Nature Chem Biol, 5: 749-757, 2009) and suppress body weight gain and reduce food intake are described in patent applications WO 2008/071972, WO 2008/101017, WO 2009/155258, WO 2010/096052, WO 2010/096142, WO 2011/075393, WO 2008/152403, WO 2010/070251, WO 2010/070252, WO 2010/070253, WO 2010/070255, WO 2011/160630, WO 2011/006497, WO 2011/087671, WO 2011/087672, WO2011/117415, WO2011/117416, WO 2012/150503, WO2012/158965, WO 2012/177444, WO 2013/004983, WO 2013/092703, WO2014/017843, WO2014/041195, WO 2014/041375, WO2014/081872, WO2014/140222, WO2014/170496, WO2015/055801 and WO2015/055802, the contents of which are herein incorporated by reference. Other peptidic dual agonists are described in WO 2012/177443, WO2013/186240 WO2014/056872 and WO2014/091316, the contents of which are herein incorporated by reference. The body weight reduction was shown to be superior to pure GLP-1 agonists.

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 GLP-1 receptor, whereas it shows 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]
4	exendin-4	0.4	12500.0	>10000000

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

HGEGTFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂

5 Exendin-4 shares many of the glucoregulatory actions observed with GLP-1. Clinical and nonclinical 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-
10 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
15 obesity. Patients with obesity have a higher risk of getting diabetes, hypertension, hyperlipidemia, cardiovascular and musculoskeletal diseases.

Relative to GLP-1, exendin-4 is resistant to cleavage by dipeptidyl peptidase-4 (DPP4) resulting in a longer half-life and duration of action in vivo (Eng J., Diabetes,
20 45 (Suppl 2):152A (abstract 554), 1996).

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
25 chemically labile due to methionine oxidation 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).

Compounds of this invention are exendin-4 derivatives, which in addition to the
30 agonistic activity at the GLP-1 receptor of native exendin-4 show agonistic activity at the glucagon receptor and which have – among others - the following modifications: at position 2 a d-serine (dSer), at position three a glutamine (Gln), at position 17 a glutamine (Gln), at position 18 an arginine (Arg), at position 19 an alanine (Ala) and at position 27 an isoleucine (Ile).

Bloom et al. (WO 2006/134340) disclose that peptides which bind and activate both the glucagon and the GLP-1 receptor can be constructed as hybrid molecules from glucagon and exendin-4, where the N-terminal part (e.g. residues 1-14 or 1-24) originates from glucagon and the C-terminal part (e.g. residues 15-39 or 25-39) originates from exendin-4. Such peptides comprise glucagon's amino acid motif YSKY in position 10-13. Krstenansky et al (Biochemistry, 25, 3833-3839, 1986) show the importance of these residues 10-13 of glucagon for its receptor interactions and activation of adenylate cyclase.

In the exendin-4 derivatives described in this invention, several of the underlying residues are different from glucagon and the peptides described in WO 2006/134340. In particular residues Tyr10 and Tyr13, which are known to contribute to the fibrillation of glucagon (DE Otzen, Biochemistry, 45, 14503-14512, 2006) are replaced by Leu in position 10 and Gln, 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 behaviour 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 glucagon receptor, keeping their activity on the GLP-1 receptor (see also WO2013/186240).

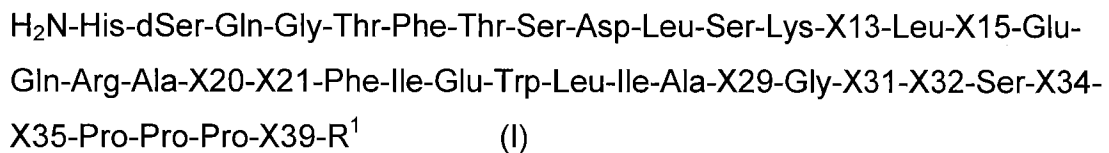
Compounds of this invention are designed to be more resistant to cleavage by neutral endopeptidase (NEP) and dipeptidyl peptidase-4 (DPP4), resulting in a longer half-life and duration of action in vivo, when compared with native GLP-1 and glucagon.

Compounds of this invention preferably are chemically stable not only at neutral pH, but also at pH 4.5. This property potentially allows co-formulation for a combination therapy with an insulin or insulin derivative.

BRIEF SUMMARY OF THE INVENTION

Provided herein are exendin-4 derivatives which potently activate the GLP1 and the glucagon receptor. In these exendin-4 derivatives – among other substitutions - methionine at position 14 is replaced by leucin

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



10

X13 represents an amino acid residue selected from Gln and Leu,

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

X20 represents an amino acid residue selected from Arg and Lys,

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

15

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

X31 represents an amino acid residue selected from Pro and His,

X32 represents an amino acid residue selected from His and Pro,

X34 represents an amino acid residue selected from Gly and dAla,

X35 represents an amino acid residue selected from Ala and Pro,

20

X39 represents Ser or Pro-Pro-Pro,

R¹ is NH₂ or OH,

or a salt or solvate thereof.

- 25 The compounds of the invention are GLP-1 and glucagon receptor agonists as determined by the observation that they are capable of stimulating intracellular cAMP formation.

According to another embodiment the peptidic compounds of the invention exhibit a
30 relative activity of at least 0.1% (i.e. EC₅₀ <700 pM), preferably at least 0.7% (i.e. EC₅₀ <100 pM), more preferably at least 1.4% (i.e. EC₅₀ <50 pM), more preferably at least 7% (i.e. EC₅₀ <10 pM), and even more preferably at least 10% (i.e. EV₅₀ <7 pM) compared to that of GLP-1(7-36) at the GLP-1 receptor (EC₅₀ = 0.7 pM).

According to another embodiment the peptidic compounds of the invention exhibit a relative activity of at least 0.1% (i.e. $EC_{50} < 1000$ pM), preferably of at least 0.33% (i.e. $EC_{50} < 300$ pM), more preferably at least 1% (i.e. $EC_{50} < 100$ pM), more preferably at least 2% (i.e. $EC_{50} < 50$ pM) and even more preferably at least 5 % (i.e. $EC_{50} < 20$ pM) compared to that of natural glucagon at the glucagon receptor ($EC_{50} = 1.0$ pM).

The term "activity" as used herein preferably refers to the capability of a compound to activate the human GLP-1 receptor and 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.

The compounds of the invention preferably have an EC_{50} for hGLP-1 receptor of 100 pmol or less, more preferably of 90 pmol or less, more preferably of 80 pmol or less, more preferably of 70 pmol or less, more preferably of 60 pmol or less, more preferably of 50 pmol or less, more preferably of 40 pmol or less, more preferably of 30 pmol or less, more preferably of 25 pmol or less, more preferably of 20 pmol or less, more preferably of 15 pmol or less, more preferably of 10 pmol or less, more preferably of 9 pmol or less, more preferably of 8 pmol or less, more preferably of 7 pmol or less, more preferably of 6 pmol or less, more preferably of 5 pmol or less and/or an EC_{50} for hGlucagon receptor of 100 pmol or less, more preferably of 90 pmol or less, more preferably of 80 pmol or less, more preferably of 70 pmol or less, more preferably of 60 pmol or less, more preferably of 50 pmol or less, more preferably of 40 pmol or less, more preferably of 30 pmol or less, more preferably of 25 pmol or less, more preferably of 20 pmol or less, more preferably of 15 pmol or less. It is particularly preferred that the EC_{50} for both receptors is 100 pmol or less, more preferably of 90 pmol or less, more preferably of 80 pmol or less, more preferably of 70 pmol or less, more preferably of 60 pmol or less, more preferably of 50 pmol or less, more preferably of 40 pmol or less, more preferably of 30 pmol or less, more preferably of 25 pmol or less, more preferably of 20 pmol or less, more

preferably of 15 pmol or less. The EC₅₀ for hGLP-1, hGlucagon and hGIP receptor may be determined as described in the Methods herein and as used to generate the results described in Example 4.

- 5 The compounds of the invention have the ability to reduce the intestinal passage, 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.
- 10 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.
- 15 The compounds of the invention 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.

20 Surprisingly, it was found that peptidic compounds of the formula (I) showed very potent GLP-1 and Glucagon receptor activation

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).

25

In one embodiment the 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 40°C in solution at acidic and/or physiological pH values, e.g., at an acidity range from pH 4 to 5, especially pH 4.5 and/or a more physiological range
30 from pH 6 to 8, especially at pH 7.4 at 25°C or 40°C. The remaining amount of peptide is determined by chromatographic analyses as described in the Methods. Preferably, after 7 days at 40°C in solution at pH 4.5 or pH 7.4 the purity loss is no more than 20%, more preferably no more than 15%, even more preferably no more than 10% and even more preferably no more than 8.

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

A further embodiment relates to a group of compounds, wherein R^1 is NH_2 .

10 A further embodiment relates to a group of compounds, wherein
X13 represents Gln,
X15 represents Asp,
X20 represents Arg,
X21 represents Asp,
15 X29 represents an amino acid residue selected from Gly and dAla,
X31 represents Pro,
X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
20 X39 represents Ser or Pro-Pro-Pro,
 R^1 is NH_2 .

A further embodiment relates to a group of compounds, wherein
X13 represents Leu,
25 X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents an amino acid residue selected from Gly and dAla,
X31 represents an amino acid residue selected from Pro and His,
30 X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
 R^1 is NH_2 .

A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,

X15 represents Asp,

5 X20 represents an amino acid residue selected from Arg and Lys,

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

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

X31 represents Pro,

X32 represents an amino acid residue selected from His and Pro,

10 X34 represents an amino acid residue selected from Gly and dAla,

X35 represents an amino acid residue selected from Ala and Pro,

X39 represents Ser or Pro-Pro-Pro,

R¹ is NH₂.

15 A further embodiment relates to a group of compounds, wherein

X13 represents Leu,

X15 represents Glu,

X20 represents Lys,

X21 represents Glu,

20 X29 represents an amino acid residue selected from Gly and dAla,

X31 represents an amino acid residue selected from Pro and His,

X32 represents Pro,

X34 represents an amino acid residue selected from Gly and dAla,

X35 represents Ala,

25 X39 represents Ser.

R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,

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

X20 represents Arg,

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

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

X31 represents Pro,

X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
5 R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents Leu,
X15 represents an amino acid residue selected from Asp and Glu,
10 X20 represents Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents Gly,
X31 represents an amino acid residue selected from Pro and His,
X32 represents an amino acid residue selected from His and Pro,
15 X34 represents Gly,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂.

20 A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,
X15 represents Asp,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents Asp,
25 X29 represents an amino acid residue selected from Gly and dAla,
X31 represents Pro,
X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
30 X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents Leu,

X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents Glu,
X29 represents an amino acid residue selected from Gly and dAla,
5 X31 represents an amino acid residue selected from Pro and His,
X32 represents Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents Ala,
X39 represents Ser,
10 R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
15 X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents Gly,
X31 represents an amino acid residue selected from Pro and His,
X32 represents an amino acid residue selected from His and Pro,
20 X34 represents Gly,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂.

25 A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents Arg,
X21 represents an amino acid residue selected from Asp and Glu,
30 X29 represents dAla,
X31 represents Pro,
X32 represents an amino acid residue selected from His and Pro,
X34 represents dAla,
X35 represents an amino acid residue selected from Ala and Pro,

X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

- 5 X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents an amino acid residue selected from Gly and dAla,
10 X31 represents Pro,
X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
15 R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

- X13 represents an amino acid residue selected from Gln and Leu,
X15 represents Asp,
20 X20 represents an amino acid residue selected from Arg and Lys,
X21 represents Asp,
X29 represents an amino acid residue selected from Gly and dAla,
X31 represents Pro,
X32 represents His,
25 X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂.

30 A further embodiment relates to a group of compounds, wherein

- X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,

X29 represents an amino acid residue selected from Gly and dAla,
X31 represents an amino acid residue selected from Pro and His,
X32 represents Pro,
X34 represents an amino acid residue selected from Gly and dAla,
5 X35 represents Ala,
X39 represents Ser,
R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

10 X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents an amino acid residue selected from Gly and dAla,
15 X31 represents an amino acid residue selected from Pro and His,
X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents Ala,
X39 represents Ser,
20 R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,
X15 represents Asp,
25 X20 represents an amino acid residue selected from Arg and Lys,
X21 represents Asp,
X29 represents an amino acid residue selected from Gly and dAla,
X31 represents Pro,
X32 represents His,
30 X34 represents an amino acid residue selected from Gly and dAla,
X35 represents Pro,
X39 represents Pro-Pro-Pro,
R¹ is NH₂.

A further embodiment relates to a group of compounds, wherein

X13 represents an amino acid residue selected from Gln and Leu,

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

X20 represents an amino acid residue selected from Arg and Lys,

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

X29 represents Gly,

X31 represents His,

X32 represents Pro,

X34 represents an amino acid residue selected from Gly,

10 X35 represents Ala,

X39 represents Ser,

R¹ is NH₂.

Specific examples of peptidic compounds of formula (I) are the compounds of SEQ

15 ID NO: 6-17, as well as salts and solvates thereof.

Specific examples of peptidic compounds of formula (I) are the compounds of SEQ

ID NO: 6-19, as well as salts and solvates thereof.

20 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.

25

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.

30

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
5 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
10 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.

15 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.

20 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
25 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
30 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, 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, serpinopathies, familial amyloidotic neuropathy, senile systemic amyloidosis, serpinopathies, AL (light chain) amyloidosis (primary systemic amyloidosis), AH (heavy chain) amyloidosis, AA (secondary) amyloidosis, aortic medial amyloidosis, ApoA1 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 hyperglycemia, type 2 diabetes, obesity, particularly Type 2 diabetes.

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 occurring amino acids, as well as generally accepted three letter codes for other amino acids, such as Aib (α -aminoisobutyric acid).

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

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 amino carboxylic acids.

For the avoidance of doubt, in the definitions provided herein, it is generally intended that the sequence of the peptidic moiety (I) differs from native exendin-4 at least at ten of those positions which are stated to allow variation. Amino acids within the peptide moiety (I) can be considered to be numbered consecutively from 1 to 39 in

the conventional N-terminal to C-terminal direction. Reference to a „position“ within peptidic moiety (I) 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.

5

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.

10 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 in the specification.

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

Peptide synthesis

20 The skilled person is aware of a variety of different methods to prepare peptides that are described in this invention. These methods include but are not limited to synthetic approaches and recombinant gene expression. Thus, one way of preparing these peptides is the synthesis in solution or on a solid support and subsequent isolation and purification. A different way of preparing the peptides is gene expression in a
25 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
30 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 (benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium), HBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium), HATU (O-(7-azabenzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium) or DIC (N,N'-diisopropylcarbodiimide) / HOBT (1-hydroxybenzotriazol), wherein BOP, HBTU and HATU are used with tertiary amine bases. Alternatively, the liberated N-terminus can be functionalized with groups other than amino acids, for example carboxylic acids, 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, 3d ed., Greene, T. W. and Wuts, P. G. M., Wiley & Sons (New York: 1999).

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

group can be selectively removed using 4% hydrazine in DMF and 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, glucagon or GIP 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

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 apnoea,

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.

5 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 (T2DM), where the body fails to use
10 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”
15 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.

20

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
25 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
30 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 β -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 can be restored with improvement of the diabetic status. While there are many reports that also GIP action on insulin secretion is glucose-dependent, there are also reports in the literature that high plasma levels of GIP might lead to more frequent episodes of hypoglycemia (T McLaughlin et al., J Clin Endocrinol 1983, 56, 648-652). In addition, plasma GIP levels in obese subjects were reported to be higher than normal, suggesting that GIP might induce obesity and insulin resistance (W Creutzfeldt et al. Diabetologia. 1978, 14,15-24). This is supported by reports that the ablation of the GIP receptor might prevent those conditions: GIP receptor knock-out mice fed on high-fat diet actually showed a suppression of body weight compared to wild-type mice (K Miyawaki et al. Nat Med. 2002, 8, 738-42), and long-term administration of the GIP receptor antagonist (Pro3)GIP also prevented obesity and insulin resistance in mice (VA Gault et al. Diabetologia. 2007, 50,1752-62). Therefore, goal of this invention was to provide dual GLP-1/glucagon receptor agonists with reduced activity on the GIP receptor.

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 extra-hepatic tissues such as kidney, heart, adipocytes, lymphoblasts, brain, retina, adrenal gland and
5 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
10 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 pre-formed in preproglucagon and cleaved and secreted in a tissue-specific manner by
15 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 (see Pocai, Molecular Metabolism 2013; 3:241-51).

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

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

30 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.

The compounds of the invention are agonists for the receptors for GLP-1 and for glucagon (e.g. "dual agonists") with reduced activity on the GIP receptor and may provide therapeutic benefit to address a clinical need for targeting the metabolic syndrome by allowing simultaneous treatment of diabetes and 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.

In one embodiment the compounds are useful in the treatment or prevention of hyperglycemia, type 2 diabetes, obesity.

The compounds of the invention are useful in the treatment or prevention of hepatosteatosis, preferably non-alcoholic liver-disease (NAFLD) and non-alcoholic steatohepatitis (*NASH*).

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 DPP4 or NEP), which results in a longer duration of action in vivo. Therefore, the pure GLP-1 receptor agonist exendin-4 might serve as good starting scaffold to obtain exendin-4 analogues with dual GLP-1/glucagon receptor agonism.

Nevertheless, also exendin-4 has been shown to be chemically labile due to methionine oxidation 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.

5 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
10 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
15 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
20 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
25 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.

30 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.

- 5 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.
- 10 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
- 15 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
- 20 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
- 25 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.

- 30 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.

5

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.

10

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

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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.

25

Combination therapy

The compounds of the present invention, dual agonists for the GLP-1 and glucagon receptors, can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2015, e.g. with all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2015, chapter 1, all lipid-lowering agents mentioned in the Rote Liste 2015, chapter 58, all

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antihypertensives and nephroprotectives, mentioned in the Rote Liste 2015, or all diuretics mentioned in the Rote Liste 2015, 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.

10

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

15

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.

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

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Insulin and insulin derivatives (insulinic compounds), 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.

30

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, 5 dulaglutide, rExendin-4 (recombinant exendin-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 10 (xtenylated exenatide) and glucagon-Xten (xtenylated glucagon). The GLP-1 and GLP-1 analogues may optionally also be bound to a polymer.

DPP-4 (also referred to as DDP-IV or dipeptidylpeptidase IV) inhibitors, for example: Alogliptin / Nesina, Trajenta / Linagliptin / BI-1356 / Ondero / Trajenta / 15 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.

20 SGLT2 (sodium glucose transporter 2) inhibitors, for example: Invokana / canagliflozin, Forxiga / dapagliflozin, remogliflozin, sergliflozin, empagliflozin, ipragliflozin, tofogliflozin, luseogliflozin, LX-4211, ertugliflozin / PF-04971729, RO-4998452, EGT-0001442, KGA-3235 / DSP-3235, LIK066, SBM-TFC-039; dual SGLT2/SGLT1 inhibitors;

25 biguanides (e.g. metformin, muformin, 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, 30 repaglinide, mitiglinide), alpha-glucosidase inhibitors (e.g. acarbose, miglitol, voglibose), amylin and amylin analogues (e.g. pramlintide, Symlin).

GPR119 (G protein-coupled receptor 119) 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), GPR120 agonists, GPR142 agonists, systemic or low-absorbable TGR5 (transmembrane G protein-coupled receptor 5) agonists.

- 5 Other suitable combination partners are: Cycloset (bromocriptine mesylate), inhibitors of 11-beta-HSD (11-beta-hydroxysteroid dehydrogenase; 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 (diacylglycerol acyltransferase; e.g. LCQ-908), inhibitors of protein tyrosine-
10 phosphatase 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 (C-C motif receptor 2) antagonists, SGLT-1 inhibitors (e.g. LX-2761), modulators of glucose transporter-
15 4, somatostatin receptor 3 agonists.

- One or more lipid lowering agents are also suitable as combination partners, such as for example: HMG-CoA (3-hydroxy-3-methyl-glutaryl coenzyme A) reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid
20 and the derivatives thereof (e.g. niacin), nicotinic acid receptor 1 agonists, PPAR (peroxisome proliferator-activated receptor)-(alpha, gamma or alpha/gamma) agonists or modulators (e.g. aleglitazar), PPAR-delta agonists, ACAT (acyl-CoA cholesterol acyltransferase) inhibitors (e.g. avasimibe), cholesterol absorption inhibitors (e.g. ezetimibe), Bile acid-binding substances (e.g. cholestyramine), bile
25 acid-binding substances, ileal bile acid transport (IBAT) inhibitors, MTP (microsomal triglyceride transfer protein) inhibitors, or modulators of PCSK9 (proprotein convertase subtilisin/kexin type 9);

- LDL (low density lipoprotein) receptor up-regulators by liver selective thyroid
30 hormone receptor β agonists, HDL (high density lipoprotein)-raising compounds such as: CETP inhibitors (e.g. torcetrapib, anacetrapid, dalcetrapid, evacetrapid, JTT-302, DRL-17822, TA-8995) or ABC1 regulators; lipid metabolism modulators; PLA2 inhibitors, ApoA-I (apolipoprotein A1) enhancers, thyroid hormone receptor agonists, cholesterol synthesis inhibitors, omega-3 fatty acids and derivatives thereof,

Other suitable combination partners are one or more active substances for the treatment of obesity, such as for example: sibutramine, tesofensine, orlistat (tetrahydrolipstatin), antagonists of the cannabinoid-1 receptor, MCH-1 (melanin-concentrating hormone 1) receptor antagonists, MC4 (melanocortin 4) receptor agonists and partial agonists, NPY5 (neuropeptide Y 5) or NPY2 antagonists (e.g. velneperit), NPY4 agonists, beta-3-agonists, leptin or leptin mimetics, agonists of the 5HT_{2c} receptor (e.g. lorcaserin), or the combinations of bupropione/naltrexone (CONTRAVE), bupropione/zonisamide (EMPATIC), bupropione/phentermine, pramlintide/metreleptin, or phentermine/topiramate (QNEXA).

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, dual GLP-1/GIP agonists, dual GLP-1/glucagon agonists, ghrelin antagonists or inverse agonists, xenin and analogues thereof.

Other suitable combination partners are:

lipase inhibitors, angiogenesis inhibitors, H3 antagonists, AgRP (Agouti-related protein) inhibitors, triple monoamine uptake inhibitors (norepinephrine and acetylcholine), MetAP2 (methionine aminopeptidase type 2) inhibitors, nasal formulation of the calcium channel blocker diltiazem, antisense molecules against production of fibroblast growth factor receptor 4, prohibitin targeting peptide-1. 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 (angiotensin-converting enzyme) inhibitors, ECE (endothelin-converting enzyme) inhibitors, diuretics, beta-blockers, calcium antagonists, centrally acting hypertensives, antagonists of the alpha-2-adrenergic receptor, inhibitors of neutral endopeptidase, thrombocyte aggregation inhibitors and others or combinations thereof are suitable.

In another aspect, this invention relates to the use of a compound according to the

invention or a physiologically acceptable salt thereof combined with at least one of the active substances described above as a combination partner, for preparing a medicament which is suitable for the treatment or prevention of diseases or conditions which can be affected by binding to the receptors for GLP-1 and glucagon and by modulating their activity. This is preferably a disease in the context of the metabolic syndrome, particularly one of the diseases or conditions listed above, most particularly diabetes or obesity or complications thereof.

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

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

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

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

METHODS

Abbreviations employed are as follows:

	AA	amino acid
5	cAMP	cyclic adenosine monophosphate
	Boc	tert-butyloxycarbonyl
	BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
	BSA	bovine serum albumin
10	tBu	tertiary butyl
	dAla	D-alanine
	dSer	D-serine
	Dde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-ethyl
	ivDde	1-(4,4-dimethyl-2,6-dioxocyclohexylidene)3-methyl-butyl
15	DIC	N,N'-diisopropylcarbodiimide
	DIPEA	N,N-diisopropylethylamine
	DMEM	Dulbecco's modified Eagle's medium
	DMF	dimethyl formamide
	EDT	ethanedithiol
20	FBS	fetal bovine serum
	Fmoc	fluorenylmethyloxycarbonyl
	HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
	HBSS	Hanks' Balanced Salt Solution
25	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
30	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
5 TFA	trifluoroacetic acid
Trt	trityl
UPLC	Ultra Performance Liquid Chromatography
UV	ultraviolet

10

General synthesis of peptidic compounds

Materials:

15 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.

20 Fmoc protected natural amino acids were purchased from Protein Technologies Inc., Senn Chemicals, Merck Biosciences, Novabiochem, Iris Biotech, Nagase or Bachem. The following standard amino acids were used throughout the syntheses: Fmoc-L-Ala-OH, Fmoc-L-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-25 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.

30 In addition, the following special amino acids were purchased from the same suppliers as above: Fmoc-L-Lys(ivDde)-OH, Fmoc-Aib-OH, Fmoc-D-Ser(tBu)-OH, Fmoc-D-Ala-OH, Fmoc-beta-Ala-OH, Boc-L-His(Boc)-OH (available as toluene solvate) and Boc-L-His(Trt)-OH, Fmoc-L-Nle-OH, Fmoc-L-Met(O)-OH, Fmoc-L-Met(O2)-OH, Fmoc-(S)MeLys(Boc)-OH, Fmoc-(R)MeLys(Boc)-OH, Fmoc-(S)MeOrn(Boc)-OH and Boc-L-Tyr(tBu)-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.

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 UPLC methods

Method A: detection at 210 - 225 nm, coupled to a mass analyser Waters LCT

Premier, electrospray positive ion mode

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

solvent: H₂O+0.05%TFA : ACN+0.035%TFA (flow 0.5 ml/min)

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

Method B: detection at 214 nm

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

solvent: H₂O+0.05%TFA : ACN+0.035%TFA (flow 0.5 ml/min)

gradient: 80:20 (0 min) to 80:20 (3min) to 25:75 (23 min) to 5:95 (23.5 min) to 5:95 (25.5 min) to 80:20 (26min) to 80:20 (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.

Stability-Testing of exendin-4 derivatives

Prior to the stability measurement of a peptide batch, its purity (UPLC-UV) and its identity (MS) were determined through UPLC-MS (analytical method A).

For chemical stability testing the target concentration was 1mg pure compound/ml.

Therefore solutions from solid samples were prepared in two different buffer systems (a+b) with a concentration of 1mg/mL compound based on the previously determined %purity.

Description of the mentioned two buffer systems:

a) Acetate Buffer pH4.5, 100mM sodium acetate trihydrate, 75µg/ml m-Cresol

b) Phosphate Buffer pH7.4, 100mM sodium hydrogen phosphate, 75µg/ml m-Cresol

After 2 hours of gentle agitation the supernatant was obtained through 20min of centrifugation at 3000 RCF (relative centrifugal acceleration).

For chemical stability testing UPLC-UV (analytical method B) was performed with one aliquot of the supernatant just after it was obtained to determine "purity at starting point", "peak area peptide t0" and "peak sum of impurities t0". Another aliquot of the described supernatant was stored for 7 days at 40°C. After the time course the sample was centrifuged for 20 min at 3000 RCF and analyzed by UPLC-UV to determine "purity after 7 days", "peak area peptide t7" and "peak sum of impurities t7".

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:

$$\% \text{ remaining peptide} = [(\text{peak area peptide } t_7) \times 100] / \text{peak area peptide } t_0$$

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 t_0 (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 t_0 , following the equation:

$$\% \text{ new soluble degradation products} = \{[(\text{peak area sum of impurities } t_7) - (\text{peak area sum of impurities } t_0)] \times 100\} / \text{peak area peptide } t_0$$

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 including non-soluble degradation products and oligomers and/or fibrils, which have been removed from analysis by centrifugation, following the equation:

$$\% \text{ mass balance} = ([\% \text{ remaining peptide}] + [\% \text{ new soluble degradation products}]) - 100$$

The chemical stability was rated through the relative loss of purity calculated by the equation:

$$\% \text{ relative purity loss} = [(\text{purity at starting point}) - (\text{purity after 7 days})] / (\text{purity at starting point}) \times 100$$

As UPLC methods, method A and B has been used.

Solubility-Testing of exendin-4 derivatives

Prior to the solubility measurement of a peptide batch, its purity (UPLC-UV) and its identity (MS) were determined through UPLC-MS (analytical method A).

For solubility testing the target concentration was 10mg pure compound/ml.

Therefore solutions from solid samples were prepared in two different buffer systems (a+b) with a concentration of 10mg/mL compound based on the previously

determined %purity.

Description of the mentioned two buffer systems:

- a) Acetate Buffer pH4.5, 100mM sodium acetate trihydrate, 75µg/ml m-Cresol
- b) Phosphate Buffer pH7.4, 100mM sodium hydrogen phosphate, 75µg/ml m-Cresol

5

After 2 hours of gentle agitation the supernatant was obtained through 20min of centrifugation at 3000 RCF (relative centrifugal acceleration).

10

For solubility testing UPLC-UV (analytical method B) was performed with an aliquot of the supernatant attenuated by the dilution factor of 10 with the same stock buffer it was dissolved before. The solubility was then determined by comparison of the UV peak area of the peptide with the UV peak areas obtained of a stock solution of the peptide at a concentration of 1.2 mg/mL in Dimethyl sulfoxide (DMSO) or a variable amount of acetonitrile obtained through 2 hours of gentle agitation, an optical control that all of the compound was dissolved and 20min of centrifugation at 3000 RCF (relative centrifugal acceleration).

15

As UPLC methods, method A and B has been used.

20

Content determination of exendin-4 derivatives

For content determination of a peptide batch its purity (UPLC-UV) and its identity (MS) were determined through UPLC-MS (analytical method A) and in addition its salt loading was determined by ionic chromatography.

25

Anionic chromatography:

Instrument: Dionex ICS-2000, column: AS18 2 x 250 mm (Dionex), column temperature: 30°C, eluent: aqueous potassium hydroxide, flow: 0.38 mL/min, gradient: 0-3 min: 1 mM KOH, 3-20 min: 1-30 mM KOH, 20-24 min: 30-60 mM KOH, 24-32.9min: 60mM KOH, 32.9-33min: 60-2mM KOH, 33-35.5min: 2-1mM KOH, suppressor: ASRS 300 2 mm, suppressor current: 76mA, detection: conductivity

30

Cationic chromatography

Instrument: Dionex ICS-2000, column: CS18 2 x 250 mm (Dionex), column temperature: 30°C, eluent: Dionex EGC III MSA (methane sulfonic acid), isocratic

flow: 0.25 mL/min, duration: 28 min, suppressor: ASRS 300 2 mm, suppressor current: 5mA, detection: conductivity

In vitro cellular assays for GLP-1 receptor, glucagon receptor and GIP 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. 62AM4PEJ) 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 / 616 nm. In vitro potency of agonists was quantified by determining the concentrations that caused 50% activation of maximal response (EC50).

EXAMPLES

The invention is further illustrated by the following examples.

Example 1:

Synthesis of SEQ ID NO: 7

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 0.4 mmol/g. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. The peptide was cleaved from the resin with King's cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (XBridge, BEH130, Prep C18 5µM) using an acetonitrile/water gradient (both buffers with 0.1% TFA). Finally, the molecular mass of the purified peptide was confirmed by LC-MS.

10 Example 2:

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

20 Finally, the molecular mass of the purified peptide was confirmed by LC-MS.

In an analogous way, the other peptides listed in Table 2 were synthesized.

Table 2: list of synthesized peptides and comparison of calculated vs. found molecular weight (analyzed with analytical method A)

SEQ ID NO	calc. Mass	found mass	Monoisotopic or average mass
6	4148.0967	4148.0	monoisotopic
7	4231.0835	4231.1	monoisotopic
8	4418.2448	4418.2	monoisotopic
9	4162.1124	4162.0	monoisotopic
10	4176.1280	4176.1	monoisotopic
11	4259.1148	4259.2	monoisotopic
12	4489.2567	4489.3	monoisotopic

13	4216.1342	4216.1	monoisotopic
14	4191.0774	4191.2	monoisotopic
15	4219.1087	4219.3	monoisotopic
16	4232.1655	4232.2	monoisotopic
17	4188.1029	4188.2	monoisotopic
18	4231.1087	4231.2	monoisotopic
19	4231.0835	4231.1	monoisotopic

Example 3: Chemical stability

- 5 Chemical stability of peptidic compounds were assessed as described in Methods. The results are given in Table 3.

Table 3: Chemical stability (analyzed with analytical method B)

SEQ ID NO	Chemical stability [relative purity loss 7 days 40°C] (%)	
	pH4.5	pH7.4
7	5.7	5.3
8	5.7	3.9
9	7.9	4.0
10	18.3	17.1
11	8.3	18.4
13	3.0	3.9

10 Example 4: In vitro data on GLP-1, glucagon and GIP receptor

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

- 15 described in Methods.

The results are shown in Table 4:

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

SEQ ID NO	EC50 hGLP-1R	EC50 hGlucagon-R	EC50 hGIP-R
6	3.9	2.8	1280.0
7	1.6	3.6	9660.0
8	2.3	4.1	2420.0
9	3.1	2.5	810.0
10	4.4	13.2	1390.0
11	1.9	7.8	13400.0
12	1.6	3.4	15100.0
13	4.0	11.6	1650.0
14	2.9	1.8	6410.0
15	1.4	1.2	7230.0
16	2.9	1.6	812.0
17	3.1	12.5	6530.0
18	4.3	29.5	36500.0
19	1.5	1.6	8860.0

5 Table 5. Sequences

SEQ ID	sequence
1	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-NH ₂
2	H-A-E-G-T-F-T-S-D-V-S-S-Y-L-E-G-Q-A-A-K((S)-4-Carboxy-4-hexadecanoylamino-butyl)-E-F-I-A-W-L-V-R-G-R-G
3	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
4	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-NH ₂
5	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-OH
6	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-D-E-Q-R-A-K-D-F-I-E-W-L-I-A-G-G-P-P-S-G-A-P-P-P-S-NH ₂

7	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-G-G-P-H-S-G-A-P-P-P-S-NH ₂
8	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-D-E-Q-R-A-K-D-F-I-E-W-L-I-A-G-G-P-H-S-G-P-P-P-P-P-P-P-NH ₂
9	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-D-E-Q-R-A-K-E-F-I-E-W-L-I-A-G-G-P-P-S-G-A-P-P-P-S-NH ₂
10	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-E-E-Q-R-A-K-E-F-I-E-W-L-I-A-G-G-P-P-S-G-A-P-P-P-S-NH ₂
11	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-dAla-G-P-H-S-dAla-A-P-P-P-S-NH ₂
12	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-dAla-G-P-H-S-dAla-P-P-P-P-P-P-P-NH ₂
13	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-E-E-Q-R-A-K-E-F-I-E-W-L-I-A-G-G-H-P-S-G-A-P-P-P-S-NH ₂
14	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-G-G-P-P-S-G-A-P-P-P-S-NH ₂
15	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-dAla-G-P-P-S-dAla-A-P-P-P-S-NH ₂
16	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-E-E-Q-R-A-R-E-F-I-E-W-L-I-A-dAla-G-P-P-S-dAla-A-P-P-P-S-NH ₂
17	H-dSer-Q-G-T-F-T-S-D-L-S-K-L-L-D-E-Q-R-A-K-D-F-I-E-W-L-I-A-G-G-P-H-S-G-A-P-P-P-S-NH ₂
18	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-K-D-F-I-E-W-L-I-A-dAla-G-P-H-S-dAla-A-P-P-P-S-NH ₂
19	H-dSer-Q-G-T-F-T-S-D-L-S-K-Q-L-D-E-Q-R-A-R-D-F-I-E-W-L-I-A-G-G-H-P-S-G-A-P-P-P-S-NH ₂

Claims

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

5 H₂N-His-dSer-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-X13-Leu-X15-Glu-
Gln-Arg-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-Ala-X29-Gly-X31-X32-Ser-X34-
X35-Pro-Pro-Pro-X39-R¹ (I)

10 X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents an amino acid residue selected from Gly and dAla,
X31 represents an amino acid residue selected from Pro and His,
15 X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro,
R¹ is NH₂ or OH,

20 or a salt or solvate thereof.

2. A compound of claim 1 ,
which is a GLP1 and Glucagon receptor agonist.

- 25
3. A compound according to any one of claims 1 – 2,
wherein R¹ is NH₂.

4. A compound according to any one of claims 1 - 3,
30 wherein the peptidic compound has a relative activity of at least 0.1%
compared to that of natural glucagon at the glucagon receptor.

5. A compound according to any one of claims 1 - 4, wherein the peptidic
compound exhibits a relative activity of at least 0.1% compared to that of GLP-

1(7-36) at the GLP-1 receptor.

6. A compound of any one of claims 1 - 5, wherein

X13 represents Gln,

X15 represents Asp,

X20 represents Arg,

X21 represents Asp,

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

X31 represents Pro,

X32 represents an amino acid residue selected from His and Pro,

X34 represents an amino acid residue selected from Gly and dAla,

X35 represents an amino acid residue selected from Ala and Pro,

X39 represents Ser or Pro-Pro-Pro.

7. A compound of any one of claims 1 - 6, wherein

X13 represents Leu,

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

X20 represents an amino acid residue selected from Arg and Lys,

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

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

X31 represents an amino acid residue selected from Pro and His,

X32 represents an amino acid residue selected from His and Pro,

X34 represents an amino acid residue selected from Gly and dAla,

X35 represents an amino acid residue selected from Ala and Pro,

X39 represents Ser or Pro-Pro-Pro.

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

X13 represents an amino acid residue selected from Gln and Leu,

X15 represents Asp,

X20 represents an amino acid residue selected from Arg and Lys,

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

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

X31 represents Pro,

X32 represents an amino acid residue selected from His and Pro,

X34 represents an amino acid residue selected from Gly and dAla,

X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro.

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

5 X13 represents Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents Glu,
X29 represents an amino acid residue selected from Gly and dAla,
10 X31 represents an amino acid residue selected from Pro and His,
X32 represents Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents Ala,
X39 represents Ser.

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10. A compound of any one of claims 1 - 9, wherein

X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
20 X21 represents an amino acid residue selected from Asp and Glu,
X29 represents Gly,
X31 represents an amino acid residue selected from Pro and His,
X32 represents an amino acid residue selected from His and Pro,
X34 represents Gly,
25 X35 represents an amino acid residue selected from Ala and Pro,
X39 represents Ser or Pro-Pro-Pro.

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

30 X13 represents an amino acid residue selected from Gln and Leu,
X15 represents an amino acid residue selected from Asp and Glu,
X20 represents an amino acid residue selected from Arg and Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents an amino acid residue selected from Gly and dAla,
X31 represents an amino acid residue selected from Pro and His,

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X32 represents an amino acid residue selected from His and Pro,
X34 represents an amino acid residue selected from Gly and dAla,
X35 represents Ala,
X39 represents Ser.

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12. The compound of any one of claims 1 - 11, selected from the compounds of
SEQ ID NO: 6-17, as well as salts and solvates thereof.

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13. The compound of any one of claims 1 - 11, selected from the compounds of
SEQ ID NO: 6-19, as well as salts and solvates thereof.

14. The compound of any one of claims 1 - 13 for use in medicine, particularly in
human medicine.

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15. The compound for use according to claim 14 which is present as an active
agent in a pharmaceutical composition together with at least one
pharmaceutically acceptable carrier.

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16. The compound for use according to claim 14 or 15 together with 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, dual GLP1/GIP 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

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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 β 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-1 receptor antagonists, MCH-1 antagonists, MC4 receptor agonists and partial agonists, NPY5 or NPY2 antagonists, NPY4 agonists, beta-3-agonists, leptin or leptin mimetics, agonists of the 5HT_{2c} receptor, or the combinations of bupropione/naltrexone, bupropione/zonisamide, bupropione/phentermine or pramlintide/metreleptin, 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.

17. The compound for use according to any one of claims 14 - 16 for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, metabolic syndrome and neurodegenerative disorders, particularly for delaying or preventing disease progression in type 2 diabetes, treating metabolic syndrome, treating obesity or preventing overweight, for decreasing food intake, increase energy

expenditure, reducing body weight, delaying the progression from impaired glucose tolerance (IGT) to type 2 diabetes; delaying the progression from type 2 diabetes to insulin-requiring diabetes; regulating appetite; inducing satiety; preventing weight regain after successful weight loss; treating a disease or state related to overweight or obesity; treating bulimia; treating binge eating; treating atherosclerosis, hypertension, IGT, dyslipidemia, coronary heart disease, hepatic steatosis, treatment of beta-blocker poisoning, use for inhibition of the motility of the gastro-intestinal tract, useful in connection with investigations of the gastro-intestinal tract using techniques such as X-ray, CT- and NMR-scanning.

18. The compound for use according to any one of claims 14 - 17 for the treatment or prevention of hyperglycemia, type 2 diabetes, obesity.

19. The compound for use according to any one of claims 14 - 16 for the treatment or prevention of hepatosteatosis, preferably non-alcoholic liver-disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

20. A pharmaceutical composition comprising at least one compound according to any one of claims 1 – 13 or a physiologically acceptable salt or solvate of any of them, for use as a pharmaceutical.

21. A method of treating hyperglycemia, type 2 diabetes or obesity in a patient, the method comprising administering to the patient an effective amount of at least one compound of formula I according to any one of claims 1 – 13 and an effective amount of at least one other compound useful for treating hyperglycemia, type 2 diabetes or obesity.

22. A method as claimed in claim 21 wherein the effective amount of at least one compound of formula I according to claims 1 – 13 and the additional active ingredient are administered to the patient simultaneously.

23. A method as claimed in claim 21 wherein the effective amount of at least one compound of formula I according to claims 1 – 13 and the additional active ingredient are administered to the patient sequentially.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063339

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/435
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

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

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

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2013/336893 A1 (HAACK TORSTEN [DE] ET AL) 19 December 2013 (2013-12-19) paragraphs [0012], [0040], [0046], [0061], [0213]; claims 1-3,21,29,34 -----	1-23
A	LORENZ MARTIN ET AL: "Recent progress and future options in the development of GLP-1 receptor agonists for the treatment of diabetes", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 23, no. 14, 16 May 2013 (2013-05-16), pages 4011-4018, XP028573319, PERGAMON, AMSTERDAM, NL ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2013.05.022 the whole document ----- -/-	1-23



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search

25 July 2016

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Strobel, Andreas

INTERNATIONAL SEARCH REPORT

International application No

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A	HADJI-GEORGOPOULOS A ET AL: "INCREASED GASTRIC INHIBITORY POLY PEPTIDE LEVELS IN PATIENTS WITH SYMPTOMATIC POST PRANDIAL HYPO GLYCEMIA", JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 56, no. 4, 1983, pages 648-652, XP009185725, ISSN: 0021-972X abstract Discussion section -----	1-23
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/063339

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A	TASYUREK HALE M ET AL: "Incretins: Their physiology and application in the treatment of diabetes mellitus", DIABETES-METABOLISM RESEARCH AND REVIEWS, vol. 30, no. 5, July 2014 (2014-07), pages 354-371, XP002743283, the whole document -----	1-23
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/063339

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/063339

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