

Exendin-4 Derivatives as Selective Glucagon Receptor Agonists

5 Description

FIELD OF THE INVENTION

10 The present invention relates to exendin-4 peptide analogues which activate the glucagon receptor and their medical use, for example in the treatment of severe hypoglycemia.

BACKGROUND OF THE INVENTION

15 Exendin-4 is a 39 amino acid peptide which is produced by the salivary glands of the Gila monster (*Heloderma suspectum*) (Eng, J. et al., J. Biol. Chem., 267:7402-05, 1992). Exendin-4 is an activator of the glucagon-like peptide-1 (GLP-1) receptor, whereas it does not activate significantly the glucagon receptor.

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

HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH₂

25 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 2.

HSQGTFTSDYSKYLDSRRAQDFVQWLMNT-OH

30 During hypoglycemia, when blood glucose levels drop below normal, glucagon signals the liver to break down glycogen and release glucose, causing an

increase of blood glucose levels to reach a normal level. Hypoglycemia is a common side effect in diabetics who are treated with insulin due to elevated blood glucose levels. Thus, glucagon's most predominant role in glucose regulation is to counteract insulin action and maintain blood glucose levels.

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Glucagon has an isoelectric point of approximately 7 and is therefore only poorly soluble (< 0.2 mg/ml) in the pH range of 4–8. It is well soluble

(> 10 mg/ml) at pH values below 3 or above 9 (Bromer, W.W., Handbook of Experimental Pharmacology, Vol 66/1, 1983). Consequently, the currently

10 available commercial solutions of glucagon (GlucaGen® HypoKit, Glucagon emergency rescue kit) are acidic and need to be prepared freshly before use due to the chemical and biophysical instability of glucagon in solution at low pH (Joshi, A.B. et al, Int.J.Ph.Sci., 203, 115-125, 2000).

15 The preparation of glucagon formulations with enhanced stability compared to the commercial kit solutions are described in patent applications WO9947160, WO12059762, US2011/0097386, US2011/0237510, US2011/049713, WO12012460, WO12122535, US2012/0071817, and WO13101749, the contents of which are herein incorporated by reference.

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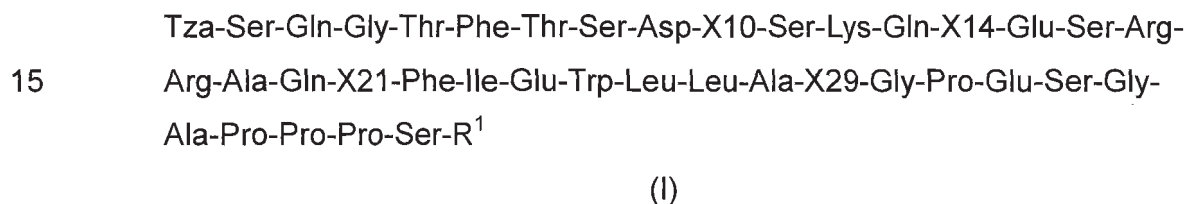
The preparation of stabilized analogues of glucagon is described in patent applications WO14016300, WO11049713, WO07056362, WO08086086, and WO09155257, the contents of which are herein incorporated by reference.

25 The use of 4-Thiazolylalanine in position 1 of a synthetic peptide has been described in WO07140284 for GLP-1 receptor agonists. Conversely, 4-Thiazolylalanine in the present invention surprisingly provides highly active glucagon receptor agonists with reduced activity at the GLP-1 receptor when compared to peptides that carry the natural histidine at position 1 (native
30 glucagon).

BRIEF SUMMARY OF THE INVENTION

Provided herein are exendin-4 analogues which potently and selectively activate the glucagon receptor and show a higher solubility at a near neutral pH and an enhanced chemical stability in solution compared to natural glucagon. All the compounds carry the artificial amino acid 4-Thiazolylalanine at position 1. This surprisingly results in a higher selectivity towards the glucagon receptor versus the GLP1 receptor when identical compounds are compared to each other differing only at position 1 (Tza in position 1 instead of His). The present invention therefore provides highly selective glucagon receptor agonists.

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



X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phe, Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine, Cyclohexylglycine and tert-Leucine

X14 represents an amino acid residue selected from Leu and Nle

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

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

R¹ represents OH or NH₂
or a salt or solvate thereof.

The compounds of the invention are glucagon receptor agonists as determined by the observation that they are capable of stimulating intracellular cAMP formation upon binding at the receptor for glucagon. The compounds exhibit at

least a relative activity of 0.1%, preferably 0.5%, more preferably 1.0% and even more preferably 10.0% compared to that of natural glucagon at the glucagon receptor.

- 5 The compounds of the invention also activate the GLP1 receptor as determined by the observation that they are capable of stimulating intracellular cAMP formation upon binding at the receptor for GLP1. The activity of a given compound of this invention (expressed by its activity relative to the activity of GLP1 at the GLP1 receptor) is below 10%, more preferably below 5% and even
10 more preferably below 2% compared to the activity of the same compound at the glucagon receptor (expressed by its activity relative to the activity of glucagon at the glucagon receptor).

- Surprisingly, it was found that peptidic compounds of the formula I with
15 4-Thiazolylalanine at position 1 showed increased glucagon receptor activation and increased selectivity towards the activity on the GLP-1 receptor compared to derivatives having a histidine at this position. Histidine is the naturally occurring amino acid in glucagon at position 1 and has been shown to be important for the activation mechanism of the glucagon receptor (Unson, C.G. et al, Arch.
20 Biochem. Biophys., 300, 747-750, 1993).

- Further, the compounds of the invention preferably have an enhanced solubility at acidic and/or physiological pH values, e.g., at pH 4.5 and/or at pH 7.4 at 25°C, preferably at least 0.5 mg/ml, more preferably at least 1.0 mg/ml and even more
25 preferably at least 10.0 mg/ml.

- Furthermore, the compounds of the invention preferably have a high stability when stored for 14 days at 50°C in solution at pH 7,3 (determined by chromatographic analyses as described in the Examples). Preferably, newly
30 formed degradation products are below 40%, more preferably below 30%, even more preferably at below 20%.

In an embodiment, the C-terminal group R^1 is NH_2 .

In a further embodiment, the C-terminal group R^1 is OH.

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

X10 represents Leu,

X14 represents an amino acid residue selected from Leu and Nle,

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

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

10 R^1 represents OH,

or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

X10 represents Tyr,

15 X14 represents an amino acid residue selected from Leu and Nle,

X21 represents Glu,

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

R^1 represents OH,

or a salt or solvate thereof.

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A further embodiment relates to a group of compounds, wherein

X10 represents Val,

X14 represents Leu,

X21 represents Glu,

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

R^1 represents OH,

or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

30 X10 represents Ile,

X14 represents an amino acid residue selected from Leu and Nle,

X21 represents Glu,

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

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A further embodiment relates to a group of compounds, wherein

X10 represents 1-Naphthylalanine,

X14 represents an amino acid residue selected from Leu and Nle,

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

10 X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

15 X10 represents 2-Fluorophenylalanine,

X14 represents an amino acid residue selected from Leu and Nle,

X21 represents Asp,

X29 represents Thr,

R¹ represents OH,

20 or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

X10 represents Cyclohexylglycine,

X14 represents an amino acid residue selected from Leu and Nle,

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

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

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

X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine and Cyclohexylglycine,

X14 represents Leu,

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

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

R¹ represents OH

or a salt or solvate thereof.

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

X10 represents an amino acid residue selected from Tyr, Leu, Ile, Phe, 1-Naphthylalanine, Cyclohexylglycine and tert-Leucine,

X14 represents Nle,

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

15 X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

20 X10 represents an amino acid residue selected from Leu, Phe, 1-Naphthylalanine, 2-Fluorophenylalanine and Cyclohexylglycine,

X14 represents an amino acid residue selected from Leu and Nle

X21 represents Asp,

X29 represents Thr,

25 R¹ represents OH,

or a salt or solvate thereof.

A further embodiment relates to a group of compounds, wherein

30 X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phenylglycine, 1-Naphthylalanine, Cyclohexylglycine and tert-Leucine,

X14 represents an amino acid residue selected from Leu and Nle

X21 represents Glu,

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

R¹ represents OH,

or a salt or solvate thereof.

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A further embodiment relates to a group of compounds, wherein

X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phe, Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine, Cyclohexylglycine and tert-Leucine,

10

X14 represents an amino acid residue selected from Leu and Nle

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

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

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A further embodiment relates to a group of compounds, wherein

X10 represents an amino acid residue selected from Tyr, Leu and Val,

X14 represents Leu,

X21 represents Glu,

20

X29 represents Gly,

R¹ represents OH,

or a salt or solvate thereof.

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

25

SEQ ID NO: 3 - 25 as well as salts or solvates thereof.

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

SEQ ID NO: 3, 5, 6, 9, 15, 20, 23, 24, and 25 as well as salts or solvates thereof.

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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.

- 5 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
- 10 hydrate. In still a further aspect, the present invention provides a composition for use in a method of medical treatment, particularly in human medicine.

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

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The compounds of formula (I) are suitable for therapeutic application without an additionally therapeutically effective agent. In other embodiments, however, the compounds are used together with at least one additional therapeutically active agent, as described in "combination therapy".

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Compounds of this invention and formulation thereof may primarily be used to treat hypoglycemia, increase blood glucose levels, as adjunctive therapy with insulin, but also to reduce and maintain body weight, as antidote for beta-blockers and calcium-channel blockers toxication and to induce temporary

25 relaxation of the gastro-intestinal system for radiological uses.

DETAILED DESCRIPTION OF THE INVENTION

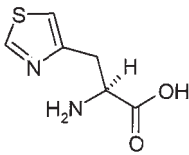
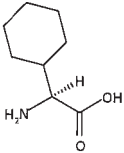
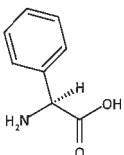
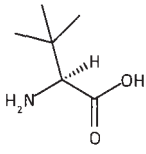
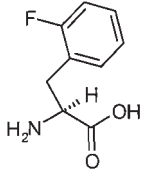
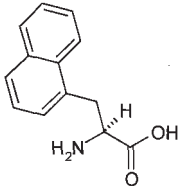
Definitions

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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 Nle (Norleucine).

- 5 Furthermore, the following codes were used for the amino acids shown in Table 1:

Structure	Name	Code
	L-4-Thiazolylalanine	Tza
	L-Cyclohexylglycine	Chg
	L-Phenylglycine	Phg
	L-tert-Leucine	Tle
	L-2-Fluorophenylalanine	2F-Phe
	L-1-Naphthylalanine	1-Nal

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

The invention provides peptidic compounds as defined above.

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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

10 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 differs from native exendin-4 at least at one of those positions which are stated to allow variation. Amino acids

15 within the peptide moiety 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 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

20 Ser at position 39.

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.

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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 herein.

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

acceptable carrier.

Peptide synthesis

- 5 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
- 10 gene expression in a host cell in which a DNA sequence encoding the peptide has been introduced. Alternatively, the gene expression can be achieved without utilizing a cell system. The methods described above may also be combined in any way.
- 15 A preferred way to prepare the peptides of the present invention is solid phase synthesis on a suitable resin. Solid phase peptide synthesis is a well established methodology (see for example: Stewart and Young, Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, Ill., 1984; E. Atherton and R. C. Sheppard, Solid Phase Peptide Synthesis. A Practical Approach, Oxford-IRL
- 20 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 chlorotriyl resin, a Wang resin or a Rink resin in which the linkage of the carboxy group (or carboxamide
- 25 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
- 30 protecting group of this amino acid is removed. The remaining protected amino acids are then coupled one after the other in the order represented by the peptide

sequence using appropriate amide coupling reagents, for example BOP, HBTU, HATU or DIC (N,N'-diisopropylcarbodiimide) / HOBt (1-hydroxybenzotriazol), wherein BOP, HBTU and HATU are used with tertiary amine bases. Alternatively, the liberated N-terminus can be functionalized with groups other than amino
5 acids, for example carboxylic acids, etc.

Finally the peptide is cleaved from the resin and deprotected. 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
10 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 or glucagon in a cell-based assay. Numerically, it is expressed as the "EC50 value", which is the effective concentration of a compound that induces a half maximal increase of response (e.g. formation of intracellular cAMP) in a dose-response experiment.
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20 Therapeutic uses

The compounds of the invention are agonists of the glucagon receptor. Such agonists may at first provide therapeutic benefit to address a clinical need for targeting hypoglycemia.

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Hypoglycemia induced by anti-hyperglycemic medication, e.g. insulin treatment, is an important risk in the therapy of T1DM and T2DM to maintain glycemic control. The attempt to achieve tight glucose control can increase the risk of hypoglycemia in the outpatient and in the critical care setting. In a healthy state, fasting plasma glucose concentrations are usually above 70 mg/dL. If blood
30 sugar levels drop below this threshold, mild hypoglycemia occurs at first with

symptoms that can still be self-treated. These symptoms can include weakness, sleepiness, faintness, blurred vision or a feeling of sadness and unhappiness.

Hypoglycemic symptoms also depend on the age of the patient and are

predominantly neurological in older people whereas in children a change in

5 behavior is frequently observed. Hypoglycemic events during the night can result in morning headache, poor sleep quality, vivid dreams, nightmares, profuse sweating in bed and restless behavior. Sleepwalking has also been reported during nocturnal hypoglycemia. If blood sugar levels drop even further, an event of severe hypoglycemia may be the consequence. Severe hypoglycemia is

10 associated with a serum glucose value below 40-50 mg/dL and this event can result in neuroglycopenic symptoms such as seizure or coma which requires the assistance of a second person. Hypoglycemia can affect the brain resulting in confusion (abnormal behavior or both, such as the inability to complete routine tasks), visual disturbances, seizures and sometimes loss of consciousness. The

15 frequent occurrence of hypoglycemia can result in reduced awareness thus increasing the risk of severe hypoglycemia significantly. Profound and prolonged severe hypoglycemia can result in death, whereas potential mechanisms responsible for hypoglycemia-induced death include brain death and cardiac arrhythmias. On average, patients with T1DM experience 2 episodes of

20 symptomatic hypoglycemia per week and 1 episode of severe hypoglycemia per year. The incidence of hypoglycemia in patients with T2DM treated with insulin is about one-third of that seen in T1DM. This number may increase in patients with a longer duration of insulin treatment, the occurrence of comorbidities and the age of the patients.

25 The treatment of hypoglycemia depends on the duration and the intensity of the hypoglycemic event. Mild and moderate hypoglycemia can easily be self-treated by drinking or eating sugar-containing beverages or food. Severe hypoglycemia on the other hand requires the help of another person. While the intravenous application of a carbohydrate is restricted to health care professionals the
30 administration of glucagon as a rescue medication can be carried out by any trained person either by subcutaneous or intramuscular injection. Glucagon is a

peptide hormone that is produced by pancreatic alpha cells and released into the bloodstream when circulating glucose is low. As islet hormone with effects counter to those of insulin, glucagon is raising blood glucose levels by stimulating gluconeogenesis and glycogenolysis (while simultaneously inhibiting glycolysis and glycogen synthesis) to circumvent a hypoglycemic state.

Two commercial glucagon emergency kits are approved as rescue medication for severe hypoglycemia. The Glucagon Emergency Kit (Eli Lilly and Co, Indianapolis, IN) and the GlucaGen® Hypokit® (Novo Nordisk A/S, Bagsværd, Denmark). The kits contain a vial of glucagon powder and a syringe filled with solvent. The glucagon kit needs to be reconstituted before use. The solvent is transferred from the syringe into the vial and the vial is shaken until all solid has dissolved. The solution is then pulled back into the syringe and after removal of air bubbles in the syringe the kit is ready for administration into the leg or the abdomen. The recommended dose is 1 mg of glucagon in 1 mL of sterile water for adults and children weighing more than 25 kg and for children aged 6 to 8 or above. For children under 25 kg or younger than 6 to 8 years of age half the dose (0.5 mL) is recommended.

The FDA-approved instructions for both commercially available glucagon products allow only for immediate usage after the lyophilized powder is reconstituted in aqueous solution. Because of the complex procedure comprising different steps to solve the lyophilized powder carefully and complete an injection these products need to be administered to patients by caregivers or relatives of patients in case of an emergency situation. Based on these requirements glucagon remains an underutilized therapeutic approach despite its documented benefit to immediately improve hypoglycemia.

A glucagon receptor agonistic product with improved stability in solution, as described in this invention, could enable a ready-to-use pen device suitable for self-injection of the patient. Beyond its benefit as rescue medication such a product could offer the opportunity to become a therapy component as insulin counterpart for glucose optimization.

A distinct application may be the use in an automated closed loop artificial

pancreas control system with a dual pump delivery of insulin and glucagon receptor agonist as described in this invention. Such an implantable system measures subcutaneously blood glucose and insulin is given to the patient to bring glucose levels back to a normal level. In contrast, a stabilized glucagon
5 receptor agonist is administered by the artificial pancreas system to prevent glucose levels from going too low.

Accordingly, the compounds of the invention may be used for the treatment of mild to moderate hypoglycemia or in an event of severe hypoglycemia.

Furthermore, the following forms of hypoglycemia could be treated with
10 compounds of the invention as such are: induced by anti-diabetic treatments, e.g. insulin therapy, reactive or post-prandial hypoglycemia, fasting hypoglycemia, alcohol-induced hypoglycemia, post gastric-bypass hypoglycemia, non-diabetic hypoglycemia and pregnancy-associated hypoglycemia.

As outlined above glucagon is a hormone with acute effects counter to those of
15 insulin, raising blood glucose levels by stimulating gluconeogenesis and glycogenolysis to circumvent a hypoglycemic state. However, recent data in rodents and humans reveal that glucagon could have also beneficial effects on energy balance, body fat mass and nutrient intake. Therefore, compounds of this invention may be used for variety of conditions or disorders beyond treatment of
20 hypoglycemia. The compounds of this invention may be used in combination with other therapeutic active drugs. Relevant therapeutic use comprises treatment or prevention of hypoglycemia, both acute and chronic, Type 2 diabetes mellitus, delaying progression from prediabetes to type 2 diabetes, e.g. in states of impaired glucose tolerance and/or impaired fasting glucose, gestational diabetes,
25 type 1 diabetes mellitus, obesity, diseases associated with overweight to obesity, metabolic syndrome/diabetes, cardiovascular diseases, regulation of appetite and satiety in the treatment of eating disorders, e.g. bulimia and maintaining a reduced body weight following successful weight loss.

For cases of beta-blocker poisoning where symptomatic bradycardia and
30 hypotension are present, high-dose glucagon is considered the first-line antidote. Therefore, an injection of compounds of the current invention may be used as a

defense in an overdose of beta-blockers and calcium-channel blockers.

An extra-hepatic effect of glucagon is the relaxation of smooth muscles cells in the gastrointestinal tract, comprising stomach, duodenum, small intestine, and colon. Compounds of this invention and pharmaceutical formulation thereof may
5 be used as smooth muscle cell relaxant in combination with diagnostic imaging techniques for the gastro-intestinal tract, e.g. radiography, CT scanning, sonography, MRI imaging and nuclear medicine imaging.

Accordingly, compounds of this invention and formulation thereof may be used to treat hypoglycemia, increase blood glucose levels, as adjunctive therapy with
10 insulin, to reduce and maintain body weight, as antidote for beta-blockers and calcium-channel blockers toxication and to induce temporary relaxation of the gastro-intestinal system for radiological uses.

Pharmaceutical compositions

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The term "pharmaceutical composition" indicates a mixture containing ingredients that are compatible when mixed and which may be administered. A pharmaceutical composition may include one or more medicinal drugs.

Additionally, the pharmaceutical composition may include carriers, solvents,
20 adjuvants, emollients, expanders, stabilizers and other components, whether these are considered active or inactive ingredients. Guidance for the skilled in preparing pharmaceutical compositions may be found, for example, in Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A. R. Gennaro A. R., 2000, Lippencott Williams & Wilkins.

25

The exendin-4 peptide derivatives of the present invention, or salts thereof, are administered in conjunction with an acceptable pharmaceutical carrier, diluent, or excipient as part of a pharmaceutical composition. A "pharmaceutically acceptable carrier" is a carrier which is physiologically acceptable while retaining
30 the therapeutic properties of the substance with which it is administered.

Standard acceptable pharmaceutical carriers and their formulations are known to

one skilled in the art and described, for example, in Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A. R. Gennaro A. R., 2000, Lippencott Williams & Wilkins. One exemplary pharmaceutically acceptable carrier is physiological saline solution.

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

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

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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.

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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Combination therapy

In addition to its use as medication for hypoglycemic events, the compounds of the present invention, glucagon receptor agonists can be widely combined with other pharmacologically active compounds, such as all drugs mentioned in the Rote Liste 2014, e.g. with all antidiabetics mentioned in the Rote Liste 2014, chapter 12, all weight-reducing agents or appetite suppressants mentioned in the Rote Liste 2014, chapter 1, all lipid-lowering agents mentioned in the Rote Liste 2014, chapter 58, all antihypertensives and nephroprotectives, mentioned in the

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Rote Liste 2014, or all diuretics mentioned in the Rote Liste 2014, 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 add a therapeutic effect to 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.

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

Insulin and Insulin derivatives, for example: Glargin / Lantus® (see www.lantus.com), Glulisin / Apidra®, Detemir / Levemir®, Lispro / Humalog® /

25 Liprolog®, Degludec / DegludecPlus, Aspart, basal insulin and analogues (e.g. LY2963016), PEGylated insulin Lispro (LY2605541), Humulin®, Linjeta, SuliXen®, NN1045, Insulin plus Symlin, 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, 30 Oral-lyn®, Cobalamin® oral insulin, ORMD-0801, NN1953, VIAtab). Additionally

included are also those insulin derivatives which are bonded to albumin or another protein by a bifunctional linker such as HM12460A (LAPS insulin).

- GLP-1, GLP-1 analogues and GLP-1 receptor agonists, for example: Lixisenatide
 5 / AVE0010 / ZP10 / Lyxumia, Exenatide / Exendin-4 / Byetta / Bydureon / ITCA
 650, Liraglutide / Victoza, Semaglutide, Taspoglutide, Albiglutide, Dulaglutide,
 rExendin-4, CJC-1134-PC, PB-1023, TTP-054, HM-11260C, CM-3, GLP-1
 Eligen, ORMD-0901, NN-9924, Nodexen, Viador-GLP-1, CVX-096, ZYOG-1,
 ZYD-1, MAR-701, ZP-2929, ZP-3022, CAM-2036, DA-15864, ARI-2651, ARI-
 10 2255, Exenatide-XTEN and Glucagon-Xten, MAR709, HM1525A, dual
 GLP1R/GlucagonR agonists, dual GLP1R/GIPR agonists, triple
 GLP1R/GlucagonR/GIPR agonists, combinations of GLP1R agonists with insulin
 derivatives such as IDegLira, Lixilan etc.
- 15 DPP-4 inhibitors, for example: Alogliptin / Nesina, Linagliptin / BI-1356 / Ondero /
 Trajenta / Tradjenta / Trayenta / Tradzenta, Saxagliptin / Onglyza, Sitagliptin /
 Januvia / Xelevia / Tesave / Janumet / Velmetia, Vildagliptin, Anagliptin,
 Gemigliptin, Tenegliptin, Melogliptin, Trelagliptin, DA-1229, MK-3102, KM-223.
- 20 SGLT2 inhibitors, for example: Canagliflozin, Dapagliflozin, Remogliflozin,
 Sergliflozin, Empagliflozin, Ipragliflozin, Tofogliflozin, Iuseogliflozin, LX-4211, PF-
 04971729, RO-4998452, EGT-0001442, DSP-3235.
- Biguanides (e.g. Metformin, Buformin, Phenformin), Thiazolidinediones (e.g.
 25 Pioglitazone, Rivoglitazone, Rosiglitazone, Troglitazone), dual PPAR agonists
 (e.g. Aloglitazar, Muraglitazar, Tesaglitazar), Sulfonylureas (e.g. Tolbutamide,
 Glibenclamide, Glimepiride/Amaryl, Glipizide), Meglitinides (e.g. Nateglinide,
 Repaglinide, Mitiglinide), Alpha-glucosidase inhibitors (e.g. Acarbose, Miglitol,
 Voglibose), Amylin and Amylin analogues (e.g. Pramlintide, Symlin).
- 30 GPR119 agonists (e.g. GSK-263A, PSN-821, MBX-2982, APD-597), GPR40

agonists (e.g. TAK-875, TUG-424, P-1736, JTT-851, GW9508).

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

One or more lipid lowering agents are also suitable as combination partners, such as for example: HMG-CoA-reductase inhibitors (e.g. Simvastatin, Atorvastatin), fibrates (e.g. Bezafibrate, Fenofibrate), nicotinic acid and the derivatives thereof (e.g. Niacin),

PPAR-(alpha, gamma or alpha/gamma) agonists or modulators (e.g. Aleglitazar), PPAR-delta agonists, ACAT inhibitors (e.g. Avasimibe), cholesterol absorption inhibitors (e.g. Ezetimibe), bile acid-binding substances (e.g. Cholestyramine), ileal bile acid transport inhibitors, MTP inhibitors, or modulators of PCSK9.

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

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

Other suitable combination partners are:

Further gastrointestinal peptides such as Peptide YY 3-36 (PYY3-36) or analogues thereof, pancreatic polypeptide (PP) or analogues thereof, GIP receptor agonists or antagonists, ghrelin antagonists or inverse agonists, Xenin
5 and analogues thereof.

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

15 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 glucagon receptor.
20 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
25 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
30 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.

- 5 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.

10

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, a ready-to-use formulation in an appropriate syringe or device, a lyophilizate
15 which can be reconstituted prior to injection or separately in two identical or different formulations, for example as so-called kit-of-parts.

LEGENDS TO THE FIGURES

- 20 Figure 1

Blood glucose excursions after subcutaneous administration of GCG or SEQ.ID 5 in terminally anaesthetized rats. Values are mean $\pm$ SEM, n=6-8 rats.

Figure 2

- 25 Blood glucose excursions after subcutaneous administration of GCG or SEQ.ID 6 in terminally anaesthetized rats. Values are mean $\pm$ SEM, n=6-8 rats.

Figure 3

Effect of subcutaneous SEQ. ID 5 and human glucagon on blood glucose in dog

30

Figure 4

Effect of subcutaneous and intramuscular SEQ. ID 5 on blood glucose in dog

Figure 5

Effect of subcutaneous SEQ. ID 5 vs. SEQ. ID 6 on blood glucose in dog

5

METHODS

Abbreviations employed are as follows:

10	2F-Phe	2-Fluorophenylalanine
	AA	amino acid
	cAMP	cyclic adenosine monophosphate
	Boc	tert-butyloxycarbonyl
	BOP	(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium
15		hexafluorophosphate
	BSA	bovine serum albumin
	tBu	tertiary butyl
	Chg	Cyclohexylglycine
	CTC	2-Chlorotrityl chloride
20	DIC	N,N'-diisopropylcarbodiimide
	DIPEA	N,N-diisopropylethylamine
	DMEM	Dulbecco's modified Eagle's medium
	DMF	dimethyl formamide
	EDT	ethanedithiol
25	FBS	fetal bovine serum
	Fmoc	fluorenylmethyloxycarbonyl
	GCG	Glucagon
	GLP-1	Glucagon related peptide 1
	HATU	2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium
30		hexafluorophosphate
	HBSS	Hanks' Balanced Salt Solution

	HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate
	HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
	HOBt	1-hydroxybenzotriazole
5	HOSu	N-hydroxysuccinimide
	HPLC	High Performance Liquid Chromatography
	HTRF	Homogenous Time Resolved Fluorescence
	IBMX	3-isobutyl-1-methylxanthine
	Nal	1-Naphthylalanine
10	PBS	phosphate buffered saline
	PEG	polyethylene glycole
	Phg	Phenylglycine
	RP-HPLC	reversed-phase high performance liquid chromatography
	s.c.	subcutaneous
15	TFA	trifluoroacetic acid
	Tle	tert-Leucine
	TRIS	Tris(hydroxymethyl)-aminomethan
	Trt	trityl
	Tza	4-Thiazolylalanine
20	UV	ultraviolet

General synthesis of peptidic compounds

25 Materials:

For solid phase peptide synthesis preloaded Fmoc-Ser(tBu)-Wang resin was used. Fmoc-Ser(tBu)-Wang resin was purchased from Novabiochem with a loading of 0,3 mmol/g.

30 Fmoc protected natural amino acids were purchased from Protein Technologies Inc., Senn Chemicals, Merck Biosciences, Novabiochem, Iris Biotech or Bachem.

The following standard amino acids were used throughout the syntheses: Fmoc-L-Ala-OH, Fmoc-L-Arg(Pbf)-OH, Fmoc-L-Asn(Trt)-OH, Fmoc-L-Asp(OtBu)-OH, Fmoc-L-Gln(Trt)-OH, Fmoc-L-Glu(OtBu)-OH, Fmoc-Gly-OH, Fmoc-L-His(Trt)-OH, Fmoc-L-Ile-OH, Fmoc-L-Leu-OH, Fmoc-L-Lys(Boc)-OH, Fmoc-L-Phe-OH, Fmoc-L-Pro-OH, Fmoc-L-Ser(tBu)-OH, Fmoc-L-Thr(tBu)-OH, Fmoc-L-Trp(Boc)-OH, Fmoc-L-Tyr(tBu)-OH, Fmoc-L-Val-OH.

In addition, the following special amino acids were purchased from the same suppliers as above: Fmoc-L-Tza-OH, Fmoc-L-Phg-OH, Fmoc-L-Nal-OH, Fmoc-L-2F-Phe-OH, Fmoc-L-Chg-OH, Fmoc-L-Tle-OH

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

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 RP-HPLC purification procedure.

25 General Preparative HPLC Purification Procedure:

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

Solubility and stability testing of exendin-4 derivatives:

Prior to the testing of solubility and stability of a peptide batch, its content was determined. Therefore, two parameters were investigated, its purity (HPLC-UV)
5 and the amount of salt load of the batch (ion chromatography).

For solubility testing, the target concentration was 10 mg/mL pure compound. Therefore, solutions from solid samples were prepared in different buffer systems with a concentration of 10 mg/mL compound based on the previously determined
10 content. HPLC-UV was performed after 2 h of gentle agitation from the supernatant, which was obtained by 20 min of centrifugation at 4000 rpm.

The solubility was then determined by comparison with the UV peak areas obtained with a stock solution of the peptide at a concentration of 2 mg/mL in
15 pure water or a variable amount of acetonitrile (optical control that all of the compound was dissolved).

For solubility testing, analytical Chromatography was performed with a Waters UPLC system on a Waters ACQUITY UPLC® CSH™ C18 1.7 µm (150 x 2.1mm)
20 at 50 °C with a gradient elution at a flow rate of 0.5 mL/min and monitored at 210-225 nm. The gradients were set up as 20% B (0-3min) to 75% B (3-23min) followed by a wash step at 98%B (23.5-30.5) and a equilibration period (31-37 min at 20%B). Buffer A = 0.5 % trifluoroacetic acid in water and B = 0.35 % trifluoroacetic acid in acetonitrile. Optionally, the LC was coupled to an Waters
25 LCT Premier ESI-TOF mass spectrometer using the positive ion mode.

For stability testing, the target concentration was 1.0 mg/mL pure compound in a pH 7.3 TRIS buffer (50 mM) containing m-cresol (30 mM), sodium chloride (85 mM) and polysorbate 20 (8 µM). The solution was stored for 14 days at
30 50°C. After that time, the solution was analysed by UPLC.

For stability testing, UPLC was performed on an Waters Acquity UPLC H-Class system with a Waters Acquity UPLC BEH130 C18 1.7 μ m column (2.1 x 100 mm) at 40 °C with a gradient elution at a flow rate of 0.5 mL/min and monitored at 215 and 280 nm. The gradients were set up as 10% B to 90% B over 19.2 min and then 90% B for 0.8 min. Buffer A = 0.1 % formic acid in water and B = 0.1 % formic acid in acetonitrile.

For determination of the amount of the remaining peptide, the peak areas of the target compound at t0 and t14 were compared, resulting in “%Remaining peptide”, following the equation

$$\% \text{Remaining peptide} = [(\text{peak area peptide t14}) \times 100] / \text{peak area peptide t0}.$$

The “%Normalized purity” is defined by the %Relative purity at day 14 in relation to the %Relative purity at t0 following the equation

$$\% \text{Normalized purity} = [(\% \text{Relative purity t14}) \times 100] / \% \text{Relative purity t0}$$

The %Relative purity at t0 was calculated by dividing the peak are of the peptide at t0 by the sum of all peak areas at t0 following the equation

$$\% \text{Relative purity t0} = [(\text{peak area t0}) \times 100] / \text{sum of all peak areas t0}$$

Likewise, the %relative purity t14 was calculated by dividing the peak are of the peptide at t14 by the sum of all peak areas at t14 following the equation

$$\% \text{Relative purity t14} = [(\text{peak area t14}) \times 100] / \text{sum of all peak areas t14}$$

The potential difference between “%Normalized purity” and “%Remaining peptide” reflects the amount of peptide which did not remain soluble upon stress conditions.

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

5 Anion Chromatography:

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

In vitro cellular assays for glucagon receptor efficacy:

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

cAMP content of cells was determined using a kit from Cisbio Corp. (cat. no.
62AM4PEC) based on HTRF (Homogenous Time Resolved Fluorescence). For
preparation, cells were split into T175 culture flasks and grown overnight to near
20 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
25 cells/ml and 25 µl-aliquots dispensed into the wells of 96-well plates. For
measurement, 25 µl of test compound in assay buffer was added to the wells,
followed by incubation for 30 minutes at room temperature. After addition of
HTRF reagents diluted in lysis buffer (kit components), the plates were incubated
for 1 hr, followed by measurement of the fluorescence ratio at 665 / 620 nm. In
30 vitro potency of agonists was quantified by determining the concentrations that
caused 50% activation of maximal response (EC50).

Blood glucose profile in anesthetized rats:

The method aimed to study a test compound on the process of hepatic glycogenolysis. The rats had free access to food until the start of the experiment.

5 It can be stated that the rise of blood glucose after administration of glucagon (GCG) or GCG-mimetic, and which lasted for about 60 to 90 minutes, was the result of the GCG- or GCG-mimetic-induced breakdown of hepatic glycogen. The effect of GCG-mimetic on hepatic glycogenolysis and the subsequent hyperglycemic peak in the blood was compared to the effect obtained with a
10 subcutaneous bolus injection of GCG at a dose of 30 µg/kg.

Blood glucose levels were assayed in anaesthetized male Wistar rats as described previously (Herling et al. Am J Physiol. 1998; 274:G1087-93). Rats were anaesthetized with an intraperitoneal injection of pentobarbital sodium (60 mg/kg) and ketamine (10 mg/kg) and tracheotomized. Anesthesia was
15 maintained for up to 5 hours by subcutaneous infusion of pentobarbital sodium (adjusted to the anesthetic depth of the individual animal; about 24 mg/kg/h).

Body temperature was monitored with a rectal probe thermometer, and temperature was maintained at 37° C by means of a heated surgical table. Blood samples for glucose analysis (10 µl) were obtained from the tip of the tail every
20 15 minutes. The rats were allowed to stabilize their blood glucose levels after surgery for up to 2 hours. Then, GCG as reference compound, or the test compound were administered subcutaneously. For GCG a dose of 30 µg/kg was used to induce hepatic glycogenolysis. The test compound SEQ.ID 5 was administered in doses of 10, 20 and 30 µg/kg, and the test compound SEQ.ID 6
25 was administered in doses of 10 and 30 µg/kg.

Blood glucose profile in normoglycemic Beagle dogs:

Male normoglycemic Beagle dogs were fasted overnight before and during the entire experiment. The animals were randomized to groups of n = 6 per group. At
30 time point 0 min the animals were treated with single doses of the test compound or native human glucagon as reference compound. The injection solutions were

prepared freshly prior to the experiment. The test compound was administered as a single injection via three different routes (s.c., i.m. and i.v.) at doses of 1-100 µg/kg. Blood sampling is performed consecutively via puncture of the jugular vein (vena jugularis) before drug administration (= 0 min) and thereafter up to 240 min. Blood glucose was determined enzymatically (hexokinase method) from whole blood, insulin was analyzed from K-EDTA plasma with a dog-specific ELISA assay.

EXAMPLES

The invention is further illustrated by the following examples.

Example 1:

Synthesis of SEQ ID NO: 25

The solid phase synthesis was carried out on preloaded Fmoc-Ser(tBu)-Wang resin. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. In position 1 Fmoc-Tza-OH and in position 10 Fmoc-Tle-OH were used in the solid phase synthesis protocol. The peptide was cleaved from the resin with King's cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (Sunfire, Prep C18) using an acetonitrile/water gradient (both buffers with 0.1% TFA).

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

Example 2:

Synthesis of SEQ ID NO: 24

The solid phase synthesis was carried out on preloaded Fmoc-Ser(tBu)-Wang resin. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. In position 1 Fmoc-Tza-OH and in position 10 Fmoc-Chg-OH were used in the solid phase synthesis protocol. The peptide was cleaved from the resin with King's

cocktail (D. S. King, C. G. Fields, G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (Sunfire, Prep C18) using an acetonitrile/water gradient (both buffers with 0.1% TFA).

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

Example 3:

Synthesis of SEQ ID NO: 5

10

The solid phase synthesis was carried out on preloaded Fmoc-Ser(tBu)-Wang resin. The Fmoc-synthesis strategy was applied with HBTU/DIPEA-activation. In position 1 Fmoc-Tza-OH was used in the solid phase synthesis protocol. The peptide was cleaved from the resin with King's cocktail (D. S. King, C. G. Fields, 15 G. B. Fields, Int. J. Peptide Protein Res. 36, 1990, 255-266). The crude product was purified via preparative HPLC on a Waters column (Sunfire, Prep C18) using an acetonitrile/water gradient (both buffers with 0.1% TFA).

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

- 20 In an analogous way, the peptides SEQ ID NO: 3-36 were synthesized, see table 2.

Table 2: list of synthesized peptides and comparison of calculated vs. found molecular weight.

SEQ ID	calc. mass	found mass
3	4259.68	4259.3
4	4229.66	4229.8
5	4279.67	4279.7
6	4323.73	4323.6
7	4259.68	4259.8
8	4273.71	4273.7

9	4215.63	4216.0
10	4293.70	4295.1
11	4357.80	4358.2
12	4273.71	4272.8
13	4293.70	4293.7
14	4273.71	4274.3
15	4259.68	4259.7
16	4273.71	4273.4
17	4323.73	4323.4
18	4311.69	4311.3
19	4343.70	4343.3
20	4293.70	4293.5
21	4311.69	4311.4
22	4343.76	4343.4
23	4285.72	4285.2
24	4299.69	4299.0
25	4273.65	4273.0
26	4242.64	4242.5
27	4212.61	4212.5
28	4262.56	4262.2
29	4306.68	4306.6
30	4242.64	4240.1
31	4256.66	4256.5
32	4276.65	4276.2
33	4340.75	4340.2
34	4256.66	4256.6
35	4242.64	4242.5
36	4256.66	4254.1

Example 4: Chemical stability and solubility

Solubility and chemical stability of peptidic compounds were assessed as described in Methods. The results are given in Table 3.

5 Table 3: Chemical stability and solubility

SEQ ID	Solubility (pH7.4) [mg/ml]	Stability (pH7.3, 50 °C, 2 w) [%NormalizedPurity]	Stability (pH7.3, 50 °C, 2 w) [% Remaining Peptide]
2	< 0.2	70	n/a
1	> 10.0	37	33
3	> 10.0	94	92
6	> 10.0	92	94
5	> 10.0	96	88
9	> 10.0	83	70
15	> 10.0	86	75
20	> 10.0	90	90
23	> 10.0	94	92
24	> 10.0	95	90
25	> 10.0	89	82

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

- 10 Potencies of peptidic compounds at the GLP-1 and glucagon receptors were determined by exposing cells expressing human glucagon receptor (hGLUC R), and human GLP-1 receptor (hGLP-1 R) to the listed compounds at increasing concentrations and measuring the formed cAMP as described in Methods.
- 15 The results for Exendin-4 derivatives with activity at the human GLP-1 receptor (hGLP-1 R) and the human glucagon receptor (hGLUC R) are shown in Table 4.

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

SEQ ID NO	EC50 hGLP-1 R [pM]	EC50 hGLUC R [pM]
1	0.4	>10000000
2	56.6	1.0
3	44333.3	1.8
4	3300.0	0.7
5	2190.0	0.6
6	9300.0	0.5
7	4190.0	2.4
8	5800.0	2.2
9	12200.0	2.2
10	45000.0	6.0
11	11700.0	0.9
12	20000.0	1.0
13	32100.0	3.1
14	52900.0	1.2
15	34500.0	2.2
16	19700.0	0.9
17	6940.0	1.0
18	25800.0	3.1
19	6640.0	0.7
20	38900.0	3.8
21	49700.0	1.4
22	8570.0	1.0
23	50700.0	3.5
24	8310.0	0.7
25	23100.0	0.8

Example 6: Comparison Testing

A selection of exendin-4 derivatives comprising the artificial amino acid

- 5 4-thiazolylalanine in position 1 has been tested in comparison to corresponding compounds that have histidine in position 1. Histidine at position 1 is essential for the activation of the receptor in glucagon but also in many related peptides including GLP-1 and exendin-4. Therefore it is surprising that the artificial amino acid 4-thiazolylalanine leads to an even higher activation of the receptor
- 10 compared to identical compounds that have the natural histidine at position 1. Furthermore, the activation of the GLP-1 receptor which counterregulates the glucagon effect is surprisingly reduced by the introduction of the artificial amino acid 4-thiazolylalanine. This leads to even more selective glucagon receptor agonists with a higher GCG/GLP-1 activity ratio. The reference pair compounds
- 15 and the corresponding EC50 values at GLP-1 and Glucagon receptors (indicated in pM) are given in Table 5.

Table 5: Comparison of exendin-4 derivatives comprising the artificial amino acid 4-thiazolylalanine in position 1 vs. exendin-4 derivatives having the natural amino

20 acid histidine in position 1. EC50 values at GLP-1 and Glucagon receptors are indicated in pM.

SEQ ID NO	Amino acid in position 1	EC50 hGLP-1R	EC50 hGlucagon-R	Ratio
2	His	56.6	1,0	57 : 1
3	Tza	44333.3	1.8	24630 : 1
26	His	1240.0	9.4	132 : 1
4	Tza	3300.0	0.7	4714 : 1

27	His	80.8	1.3	62 : 1
5	Tza	2190.0	0.6	3650 : 1
28	His	52.4	1.0	52 : 1
6	Tza	9300.0	0.5	18600 : 1
29	His	145.0	0.9	161 : 1
7	Tza	4190.0	2.4	1746 : 1
30	His	1180.0	6.5	182 : 1
8	Tza	5800.0	2.2	2636 : 1
31	His	941.0	4.1	230 : 1
10	Tza	45000.0	6.0	7500 : 1
32	His	18700.0	12.0	1558 : 1
11	Tza	11700.0	0.9	13000 : 1
33	His	159.0	1.1	145 : 1
12	Tza	20000.0	1.0	20000 : 1
34	His	363.0	1.4	259 : 1
15	Tza	34500.0	2.2	15682 : 1
35	His	934.0	7.1	132 : 1
15	Tza	19700.0	0.9	21888 : 1
36	His	358.5	1.4	256 : 1

Example 7: Effect of SEQ.ID 5 and SEQ.ID 6 on glucose release in anesthetized

rats after s.c. injection

During the 2hr pre-treatment period blood glucose stabilized at a level of about 6 mmol/l, representing normal fed values in rats. GCG at the dose of 30 µg/kg caused a rapid rise of blood glucose, which peaked after 30 minutes at blood glucose levels of about 10 to 11 mmol/l. The test compound SEQ.ID 5 at doses of 10, 20 and 30 µg/kg subcutaneously caused a dose-dependent increase of blood glucose, which peaked 30, 45 and 90 min after injection, respectively. The dose of 20 µg/kg of SEQ.ID 5 demonstrated a nearly comparable shape of blood glucose excursion compared to 30 µg/kg GCG (Fig. 1).

The test compound SEQ.ID 6 at doses of 10 and 30 µg/kg caused a dose-dependent increase of blood glucose, which peaked 30 and 60 min after injection, respectively. The dose of 10 µg/kg of SEQ.ID 6 demonstrated a more powerful blood glucose excursion compared to 30 µg/kg GCG (Fig. 2).

Example 8: Effect of SEQ.ID. 5 and SEQ.ID 6 on glucose release in normoglycemic Beagle dogs after s.c. injection

In animals and humans injection of glucagon leads to a rapid recruitment of hepatic glycogen which is immediately broken down to glucose. This results in an acute but short lasting increase in blood glucose. In normoglycemic Beagle dogs subcutaneous (s.c.) injection of 1 µg/kg human glucagon leads to rapid increase of blood glucose by 2-3 mmol/L within 15 min. s.c. injection of SEQ. ID 5 and SEQ. ID 6 mimicked the effect of human glucagon on blood glucose. In the dog the net total glucose response (change in blood glucose AUC(0-240min) from baseline) after injection of 1 µg/kg s.c. SEQ. ID 5 was similar to that of 1 µg/kg s.c. human glucagon. Blood glucose response to SEQ. ID 5 increased depending on the dose until a peak increase of ~3.5-4 mmol/L was reached with 10 µg/kg s.c. (Fig. 3). Beyond this higher doses of s.c. SEQ. ID 5 did no longer result in higher glucose excursion. In dog the onset of glucose response s.c. SEQ. ID 5 was similar to that of human glucagon while the duration of the glucose response

was slightly longer. SEQ. ID 5 was active through all parenteral routes as subcutaneous, intramuscular and intravenous injections resulted in rapid and transient blood glucose increase. There was no difference in activity and blood glucose time-action profile between subcutaneously and intramuscularly
5 injections SEQ. ID 5 in dogs (Fig. 4).

With respect to induction of a blood glucose response SEQ. ID 5 and SEQ. ID 6 were similarly active in normoglycemic dogs (Fig. 5).

Table 10: Sequences

SEQ. ID	sequence
1	H-G-E-G-T-F-T-S-D-L-S-K-Q-M-E-E-E-A-V-R-L-F-I-E-W-L-K-N-G-G-P-S-S-G-A-P-P-P-S-NH ₂
2	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-OH
3	Tza-S-Q-G-T-F-T-S-D-L-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
4	Tza-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-G-G-P-E-S-G-A-P-P-P-S-OH
5	Tza-S-Q-G-T-F-T-S-D-Y-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-G-G-P-E-S-G-A-P-P-P-S-OH
6	Tza-S-Q-G-T-F-T-S-D-Y-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
7	Tza-S-Q-G-T-F-T-S-D-V-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
8	Tza-S-Q-G-T-F-T-S-D-I-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
9	Tza-S-Q-G-T-F-T-S-D-V-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-G-G-P-E-S-G-A-P-P-P-S-OH
10	Tza-S-Q-G-T-F-T-S-D-Phg-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH

11	Tza-S-Q-G-T-F-T-S-D-1Nal-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
12	Tza-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
13	Tza-S-Q-G-T-F-T-S-D-F-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
14	Tza-S-Q-G-T-F-T-S-D-I-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
15	Tza-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
16	Tza-S-Q-G-T-F-T-S-D-L-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
17	Tza-S-Q-G-T-F-T-S-D-Y-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
18	Tza-S-Q-G-T-F-T-S-D-2FPhe-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
19	Tza-S-Q-G-T-F-T-S-D-1Nal-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
20	Tza-S-Q-G-T-F-T-S-D-Chg-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
21	Tza-S-Q-G-T-F-T-S-D-2FPhe-S-K-Q-L-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
22	Tza-S-Q-G-T-F-T-S-D-1Nal-S-K-Q-L-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
23	Tza-S-Q-G-T-F-T-S-D-Chg-S-K-Q-L-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
24	Tza-S-Q-G-T-F-T-S-D-Chg-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
25	Tza-S-Q-G-T-F-T-S-D-Tle-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH

26	H-S-Q-G-T-F-T-S-D-L-S-K-Q-Nle-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
27	H-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-G-G-P-E-S-G-A-P-P-P-S-OH
28	H-S-Q-G-T-F-T-S-D-Y-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-G-G-P-E-S-G-A-P-P-P-S-OH
29	H-S-Q-G-T-F-T-S-D-Y-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
30	H-S-Q-G-T-F-T-S-D-V-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
31	H-S-Q-G-T-F-T-S-D-I-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
32	H-S-Q-G-T-F-T-S-D-Phg-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
33	H-S-Q-G-T-F-T-S-D-1Nal-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
34	H-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
35	H-S-Q-G-T-F-T-S-D-L-S-K-Q-L-E-S-R-R-A-Q-D-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH
36	H-S-Q-G-T-F-T-S-D-L-S-K-Q-Nle-E-S-R-R-A-Q-E-F-I-E-W-L-L-A-T-G-P-E-S-G-A-P-P-P-S-OH

CLAIMS:

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

5 4-thiazolylalanine-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-X10-Ser-Lys-Gln-X14-Glu-Ser-Arg-Arg-Ala-Gln-X21-Phe-Ile-Glu-Trp-Leu-Leu-Ala-X29-Gly-Pro-Glu-Ser-Gly-Ala-Pro-Pro-Pro-Ser-R¹

(I)

10 X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phe, Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine, Cyclohexylglycine and tert-Leucine,

X14 represents an amino acid residue selected from Leu and Nle

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

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

R¹ represents OH or NH₂
or a salt or solvate thereof.

20 2. A compound of claim 1, wherein
the C-terminal group R¹ is OH.

3. A compound according to any one of claims 1 - 2, wherein,

X10 represents Leu,

25 X14 represents an amino acid residue selected from Leu and Nle

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

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

R¹ represents OH,

or a salt or solvate thereof.

30

4. A compound according to any one of claims 1 - 2, wherein,
X10 represents Tyr,
X14 represents an amino acid residue selected from Leu and Nle,
X21 represents Glu,
5 X29 represents an amino acid residue selected from Gly and Thr,
R¹ represents OH,
or a salt or solvate thereof.

5. A compound according to any one of claims 1 - 2, wherein,
10 X10 represents 1-Naphthylalanine,
X14 represents an amino acid residue selected from Leu and Nle,
X21 represents an amino acid residue selected from Asp and Glu,
X29 represents Thr,
R¹ represents OH,
15 or a salt or solvate thereof.

6. A compound according to any one of claims 1 - 2, wherein,
X10 represents Cyclohexylglycine,
X14 represents an amino acid residue selected from Leu and Nle,
20 X21 represents an amino acid residue selected from Asp and Glu,
X29 represents Thr,
R¹ represents OH,
or a salt or solvate thereof.

25 7. A compound according to any one of claims 1 - 2, wherein,
X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile,
Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine and Cyclohexylglycine,
X14 represents Leu,
X21 represents an amino acid residue selected from Asp and Glu,
30 X29 represents an amino acid residue selected from Gly and Thr,
R¹ represents OH,

or a salt or solvate thereof.

8. A compound according to any one of claims 1 - 2, wherein,

X10 represents an amino acid residue selected from Tyr, Leu, Ile, Phe, 1-Naphthylalanine, Cyclohexylglycine and tert-Leucine

X14 represents Nle,

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

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

9. A compound according to any one of claims 1 - 2, wherein,

X10 represents an amino acid residue selected from Leu, Phe, 1-Naphthylalanine, 2-Fluorophenylalanine and Cyclohexylglycine,

X14 represents an amino acid residue selected from Leu and Nle

X21 represents Asp,

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

10. A compound according to any one of claims 1 - 2, wherein,

X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phenylglycine, 1-Naphthylalanine, Cyclohexylglycine and tert-Leucine,

X14 represents an amino acid residue selected from Leu and Nle

X21 represents Glu,

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

R¹ represents OH,

or a salt or solvate thereof.

11. A compound according to any one of claims 1 - 2, wherein,

X10 represents an amino acid residue selected from Tyr, Leu, Val, Ile, Phe, Phenylglycine, 1-Naphthylalanine, 2-Fluorophenylalanine, Cyclohexylglycine and tert-Leucine,

X14 represents an amino acid residue selected from Leu and Nle

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

X29 represents Thr,

R¹ represents OH,

or a salt or solvate thereof.

10 12. A compound according to any one of claims 1 - 2, wherein,

X10 represents an amino acid residue selected from Tyr, Leu and Val,

X14 represents Leu

X21 represents Glu,

X29 represents Gly,

15 R¹ represents OH,

or a salt or solvate thereof.

13. A compound according to any one of claims 1 - 12, selected from the compounds of SEQ ID NO: 3 - 25 as well as salts or solvates thereof.

20

14. A compound according to any one of claims 1 - 13, selected from the compounds of SEQ ID NO: 3, 5, 6, 9, 15, 20, 23, 24, and 25 as well as salts or solvates thereof.

25 15. A compound of any one of claims 1 - 14 for use in medicine, particularly in human medicine.

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

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17. The compound for use according to any one of claims 15 - 16 for treating hypoglycemia, increase blood glucose levels, or as adjunctive therapy with insulin.
- 5 18. The compound for use according to any one of claims 15 - 16 for the treatment or prevention of hypoglycemia, type 2 diabetes mellitus and for delaying progression from prediabetes to type 2 diabetes.
- 10 19. A pharmaceutical composition comprising at least one compound according to any one of claims 1 – 14 or a physiologically acceptable salt or solvents of any of them.
- 15 20. Use of at least one compound of formula I according to any one of claims 1 – 14 in the manufacture of a medicament for treating hypoglycemia.
- 20 21. Use of at least one compound of formula I according to any one of claims 1 – 14 and of at least one other compound useful for treating hypoglycemia in the manufacture of a medicament for treating hypoglycemia.
- 25 22. The use according to claims 20 – 21, wherein the medicament comprising at least one compound of formula I and at least one other compound useful for treating hypoglycemia is to be administered simultaneously, separately or sequentially.
23. The use according to claims 20 – 22 wherein the medicament is to be administered parenterally.