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(54) Title: GLP-1 DERIVATIVES

**(57) Abrégé/Abstract:**

Derivatives of GLP-1 and analogues thereof having a lipophilic substituent have interesting pharmacological properties, in particular they have a more protracted profile of action than GLP-1(7-37).

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(54) Title: GLP-1 DERIVATIVES

(57) Abstract

Derivatives of GLP-1 and analogues thereof having a lipophilic substituent have interesting pharmacological properties, in particular they have a more protracted profile of action than GLP-1(7-37).

**GLP-1 DERIVATIVES**

This application is a divisional of Application Serial No. 2,264,243 filed August 22, 1997.

**FIELD ON THE INVENTION**

- 5 The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments thereof and analogues of such fragments which have a protracted profile of action and to methods of making and using them.

**10 BACKGROUND OF THE INVENTION**

- Peptides are widely used in medical practice, and since they can be produced by recombinant DNA technology it can be expected that their importance will increase also in the years to come. When native peptides or analogues thereof are used in therapy it is generally found that they have a high clearance. A high clearance of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level thereof over a prolonged period of time since repeated administrations will then be necessary. Examples of peptides which have a high clearance are: ACTH, corticotropin-releasing factor, angiotensin, calcitonin, insulin, glucagon, glucagon-like peptide-1, glucagon-like peptide-2, insulin-like growth factor-1, insulin-like growth factor-2, gastric inhibitory peptide, growth hormone-releasing factor, pituitary adenylate cyclase activating peptide, secretin, enterogastrin, somatostatin, somatotropin, somatomedin, parathyroid hormone, thrombopoietin, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, oxytocin, opioids and analogues thereof, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase and ribonuclease. In some cases it is possible to influence the release profile of peptides by applying suitable pharmaceutical compositions, but this approach has various shortcomings and is not generally applicable.
- 30 The hormones regulating insulin secretion belong to the so-called enteroinsular axis, designating a group of hormones, released from the gastrointestinal mucosa in response to the presence and absorption of nutrients in the gut, which promote an early and potentiated release of insulin. The enhancing effect on insulin secretion, the so-called incretin effect, is probably essential for a normal glucose tolerance. Many of the 35 gastrointestinal hormones, including gastrin and secretin (cholecystokinin is not

- insulinotropic in man), are insulinotropic, but the only physiologically important ones, those that are responsible for the incretin effect, are the glucose-dependent insulinotropic polypeptide, GIP, and glucagon-like peptide-1 (GLP-1). Because of its insulinotropic effect, GIP, isolated in 1973 (1) immediately attracted considerable interest among diabetologists.
- 5 However, numerous investigations carried out during the following years clearly indicated that a defective secretion of GIP was not involved in the pathogenesis of insulin dependent diabetes mellitus (IDDM) or non insulin-dependent diabetes mellitus (NIDDM) (2). Furthermore, as an insulinotropic hormone, GIP was found to be almost ineffective in NIDDM (2). The other incretin hormone, GLP-1 is the most potent insulinotropic substance
- 10 known (3). Unlike GIP, it is surprisingly effective in stimulating insulin secretion in NIDDM patients. In addition, and in contrast to the other insulinotropic hormones (perhaps with the exception of secretin) it also potently inhibits glucagon secretion. Because of these actions it has pronounced blood glucose lowering effects particularly in patients with NIDDM.
- 15 GLP-1, a product of the proglucagon (4), is one of the youngest members of the secretin-VIP family of peptides, but is already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism (5). The glucagon gene is processed differently in the pancreas and in the intestine. In the pancreas (9), the processing leads to the formation and parallel secretion of 1) glucagon
- 20 itself, occupying positions 33-61 of proglucagon (PG); 2) an N-terminal peptide of 30 amino acids (PG (1-30)) often called glicentin-related pancreatic peptide, GRPP (10, 11); 3) a hexapeptide corresponding to PG (64-69); 4) and, finally, the so-called major proglucagon fragment (PG (72-158)), in which the two glucagon-like sequences are buried (9). Glucagon seems to be the only biologically active product. In contrast, in the intestinal
- 25 mucosa, it is glucagon that is buried in a larger molecule, while the two glucagon-like peptides are formed separately (8). The following products are formed and secreted in parallel: 1) glicentin, corresponding to PG (1-69), with the glucagon sequence occupying residues Nos. 33-61 (12); 2) GLP-1(7-36)amide (PG (78-107))amide (13), not as originally believed PG (72-107)amide or 108, which is inactive). Small amounts of C-terminally
- 30 glycine-extended but equally bioactive GLP-1(7-37), (PG (78-108)) are also formed (14); 3) intervening peptide-2 (PG (111-122)amide) (15); and 4) GLP-2 (PG (126-158)) (15, 16). A fraction of glicentin is cleaved further into GRPP (PG (1-30)) and oxyntomodulin (PG (33-69)) (17, 18). Of these peptides, GLP-1, has the most conspicuous biological activities.
- 35 Being secreted in parallel with glicentin/enteroglucagon, it follows that the many studies of enteroglucagon secretion (6, 7) to some extent also apply to GLP-1 secretion, but GLP-1 is metabolised more quickly with a plasma half-life in humans of 2 min (19). Carbohydrate

or fat-rich meals stimulate secretion (20), presumably as a result of direct interaction of yet unabsorbed nutrients with the microvilli of the open-type L-cells of the gut mucosa. Endocrine or neural mechanisms promoting GLP-1 secretion may exist but have not yet been demonstrated in humans.

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The incretin function of GLP-1(29-31) has been clearly illustrated in experiments with the GLP-1 receptor antagonist, exendin 9-39, which dramatically reduces the incretin effect elicited by oral glucose in rats (21, 22). The hormone interacts directly with the  $\beta$ -cells via the GLP-1 receptor (23) which belongs to the glucagon/VIP/calcitonin family of G-protein-coupled 7-transmembrane spanning receptors. The importance of the GLP-1 receptor in regulating insulin secretion was illustrated in recent experiments in which a targeted disruption of the GLP-1 receptor gene was carried out in mice. Animals homozygous for the disruption had greatly deteriorated glucose tolerance and fasting hyperglycaemia, and even heterozygous animals were glucose intolerant (24). The signal transduction mechanism (25) primarily involves activation of adenylate cyclase, but elevations of intracellular  $\text{Ca}^{2+}$  are also essential (25, 26). The action of the hormone is best described as a potentiation of glucose stimulated insulin release (25), but the mechanism that couples glucose and GLP-1 stimulation is not known. It may involve a calcium-induced calcium release (26, 27). As already mentioned, the insulinotropic action of GLP-1 is preserved in diabetic  $\beta$ -cells. The relation of the latter to its ability to convey "glucose competence" to isolated insulin-secreting cells (26, 28), which respond poorly to glucose or GLP-1 alone, but fully to a combination of the two, is also not known. Equally importantly, however, the hormone also potently inhibits glucagon secretion (29). The mechanism is not known, but seems to be paracrine, via neighbouring insulin or somatostatin cells (25).  
Also the glucagonostatic action is glucose-dependent, so that the inhibitory effect decreases as blood glucose decreases. Because of this dual effect, if the plasma GLP-1 concentrations increase either by increased secretion or by exogenous infusion the molar ratio of insulin to glucagon in the blood that reaches the liver via the portal circulation is greatly increased, whereby hepatic glucose production decreases (30). As a result blood glucose concentrations decrease. Because of the glucose dependency of the insulinotropic and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore, does not cause hypoglycaemia regardless of dose (31). The effects are preserved in patients with diabetes mellitus (32), in whom infusions of slightly supraphysiological doses of GLP-1 may completely normalise blood glucose values in spite of poor metabolic control and secondary failure to sulphonylurea (33). The importance of the glucagonostatic effect is illustrated by the finding that GLP-1 also lowers blood glucose in type-1 diabetic patients without residual  $\beta$ -cell secretory capacity (34).

In addition to its effects on the pancreatic islets, GLP-1 has powerful actions on the gastrointestinal tract. Infused in physiological amounts, GLP-1 potently inhibits pentagastrin-induced as well as meal-induced gastric acid secretion (35, 36). It also  
5 inhibits gastric emptying rate and pancreatic enzyme secretion (36). Similar inhibitory effects on gastric and pancreatic secretion and motility may be elicited in humans upon perfusion of the ileum with carbohydrate- or lipid-containing solutions (37, 38). Concomitantly, GLP-1 secretion is greatly stimulated, and it has been speculated that GLP-1 may be at least partly responsible for this so-called "ileal-brake" effect (38). In fact,  
10 recent studies suggest that, physiologically, the ileal-brake effects of GLP-1 may be more important than its effects on the pancreatic islets. Thus, in dose response studies GLP-1 influences gastric emptying rate at infusion rates at least as low as those required to influence islet secretion (39).

15 GLP-1 seems to have an effect on food intake. Intraventricular administration of GLP-1 profoundly inhibits food intake in rats (40, 42). This effect seems to be highly specific. Thus, N-terminally extended GLP-1 (PG 72-107)amide is inactive and appropriate doses of the GLP-1 antagonist, exendin 9-39, abolish the effects of GLP-1 (41). Acute, peripheral administration of GLP-1 does not inhibit food intake acutely in rats (41, 42). However, it  
20 remains possible that GLP-1 secreted from the intestinal L-cells may also act as a satiety signal.

Not only the insulinotropic effects but also the effects of GLP-1 on the gastrointestinal tract are preserved in diabetic patients (43), and may help curtailing meal-induced glucose  
25 excursions, but, more importantly, may also influence food intake. Administered intravenously, continuously for one week, GLP-1 at 4 ng/kg/min has been demonstrated to dramatically improve glycaemic control in NIDDM patients without significant side effects (44). The peptide is fully active after subcutaneous administration (45), but is rapidly degraded mainly due to degradation by dipeptidyl peptidase IV-like enzymes (46, 47).

30 The amino acid sequence of GLP-1 is given *i.a.* by Schmidt *et al.* (*Diabetologia* 28 704-707 (1985)). Although the interesting pharmacological properties of GLP-1(7-37) and analogues thereof have attracted much attention in recent years only little is known about the structure of these molecules. The secondary structure of GLP-1 in micelles has been  
35 described by Thorton *et al.* (*Biochemistry* 33 3532-3539 (1994)), but in normal solution, GLP-1 is considered a very flexible molecule. Surprisingly, we found that derivatisation of this relatively small and very flexible molecule resulted in compounds

whose plasma profile were highly protracted and still had retained activity.

GLP-1 and analogues of GLP-1 and fragments thereof are potentially useful *i.a.* in the treatment of type 1 and type 2 diabetes. However, the high clearance limits the usefulness of 5 these compounds, and thus there still is a need for improvements in this field. Accordingly, it is one object of the present invention to provide derivatives of GLP-1 and analogues thereof which have a protracted profile of action relative to GLP-1(7-37). It is a further object of the invention to provide derivatives of GLP-1 and analogues thereof which have a lower clearance than GLP-1(7-37). It is a further object of the invention to provide a pharmaceutical 10 composition comprising a compound according to the invention and to use a compound of the invention to provide such a composition. Also, it is an object of the present invention to provide a method of treating insulin dependent and non-insulin dependent diabetes mellitus.

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- 20
- SUMMARY OF THE INVENTION**
- Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised *i.a.* in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1(7-36)amide, GLP-1(7-37) and GLP-2 occurs mainly in the L-cells. A simple system is used to describe fragments and analogues of this peptide. Thus, for example, Gly<sup>8</sup>-GLP-1(7-37) designates a fragment of GLP-1 formally derived from GLP-1 by deleting the amino acid residues Nos. 1 to 6 and substituting the naturally occurring amino acid residue in position 8 (Ala) by Gly. Similarly, Lys<sup>34</sup>(N<sup>ε</sup>-tetradecanoyl)-GLP-1(7-37) designates GLP-1(7-37) wherein the ε-amino group of the Lys residue in position 34 has been tetradecanoylated. Where reference in this text is made to C-terminally extended GLP-1 analogues, the amino acid residue in position 38 is Arg unless otherwise indicated, the optional amino acid residue in position 39 is also Arg unless otherwise indicated and the

optional amino acid residue in position 40 is Asp unless otherwise indicated. Also, if a C-terminally extended analogue extends to position 41, 42, 43, 44 or 45, the amino acid sequence of this extension is as in the corresponding sequence in human preproglucagon unless otherwise indicated.

5

In its broadest aspect, the present invention relates to derivatives of GLP-1 and analogues thereof. The derivatives according to the invention have interesting pharmacological properties, in particular they have a more protracted profile of action than the parent peptides.

10

In the present text, the designation "an analogue" is used to designate a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the 15 parent peptide. Such addition can take place either at the N-terminal end or at the C-terminal end of the parent peptide or both.

The term "derivative" is used in the present text to designate a peptide in which one or more of the amino acid residues of the parent peptide have been chemically modified, e.g. by 20 alkylation, acylation, ester formation or amide formation.

The term "a GLP-1 derivative" is used in the present text to designate a derivative of GLP-1 or an analogue thereof. In the present text, the parent peptide from which such a derivative is formally derived is in some places referred to as the "GLP-1 moiety" of the derivative.

25

In a preferred embodiment, as described in Claim 1, the present invention relates to a GLP-1 derivative wherein at least one amino acid residue of the parent peptide has a lipophilic substituent attached with the proviso that if only one lipophilic substituent is present and this substituent is attached to the N-terminal or to the C-terminal amino acid residue of the parent 30 peptide then this substituent is an alkyl group or a group which has an  $\omega$ -carboxylic acid group.

In another preferred embodiment, as described in Claim 2, the present invention relates to a GLP-1 derivative having only one lipophilic substituent.

In another preferred embodiment, as described in Claim 3, the present invention relates to a GLP-1 derivative having only one lipophilic substituent which substituent is an alkyl group or a group which has an  $\omega$ -carboxylic acid group and is attached to the N-terminal amino acid residue of the parent peptide.

In another preferred embodiment, as described in Claim 4, the present invention relates to a GLP-1 derivative having only one lipophilic substituent which substituent is an alkyl group or a group which has an  $\omega$ -carboxylic acid group and is attached to the C-terminal amino acid residue of the parent peptide.

In another preferred embodiment, as described in Claim 5, the present invention relates to a GLP-1 derivative having only one lipophilic substituent which substituent can be attached to any one amino acid residue which is not the N-terminal or C-terminal amino acid residue of the parent peptide.

In another preferred embodiment, as described in Claim 6, the present invention relates to a GLP-1 derivative wherein two lipophilic substituents are present.

- 20 In another preferred embodiment, as described in Claim 7, the present invention relates to a GLP-1 derivative wherein two lipophilic substituents are present, one being attached to the N-terminal amino acid residue while the other is attached to the C-terminal amino acid residue.
- 25 In another preferred embodiment, as described in Claim 8, the present invention relates to a GLP-1 derivative wherein two lipophilic substituents are present, one being attached to the N-terminal amino acid residue while the other is attached to an amino acid residue which is not N-terminal or the C-terminal amino acid residue.
- 30 In another preferred embodiment, as described in Claim 9, the present invention relates to a GLP-1 derivative wherein two lipophilic substituents are present, one being attached to the C-terminal amino acid residue while the other is attached to an amino acid residue which is not the N-terminal or the C-terminal amino acid residue.

In further preferred embodiment, as described in Claim 10, the present invention relates to a derivative of GLP-1(7-C), wherein C is selected from the group comprising 38, 39, 40, 41, 42, 43, 44 and 45 which derivative has just one lipophilic substituent which is attached to the C-terminal amino acid residue of the parent peptide.

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In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the lipophilic substituent comprises from 4 to 40 carbon atoms, more preferred from 8 to 25 carbon atoms.

10 In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to an amino acid residue in such a way that a carboxyl group of the lipophilic substituent forms an amide bond with an amino group of the amino acid residue.

15 In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to an amino acid residue in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid residue.

20 In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent - optionally via a spacer - is attached to the  $\epsilon$ -amino group of  
25 a Lys residue contained in the parent peptide.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which is an unbranched alkane  $\alpha,\omega$ -dicarboxylic acid group having from 1 to 7 methylene groups,  
30 preferably two methylene groups which spacer forms a bridge between an amino group of the parent peptide and an amino group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which

is an amino acid residue except Cys, or a dipeptide such as Gly-Lys. In the present text, the expression "a dipeptide such as Gly-Lys" is used to designate a dipeptide wherein the C-terminal amino acid residue is Lys, His or Trp, preferably Lys, and wherein the N-terminal amino acid residue is selected from the group comprising Ala, Arg, Asp, Asn, Gly, Glu, Gln,

5 Ile, Leu, Val, Phe and Pro.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a  
10 carboxyl group of the parent peptide forms an amide bond with an amino group of a Lys residue or a dipeptide containing a Lys residue, and the other amino group of the Lys residue or a dipeptide containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.

15 In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein an amino group of the parent peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide  
20 spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys and wherein a  
25 carboxyl group of the parent peptide forms an amide bond with an amino group of the amino acid residue spacer or dipeptide spacer, and the carboxyl group of the amino acid residue spacer or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.

30 In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein a lipophilic substituent is attached to the parent peptide by means of a spacer which is an amino acid residue except Cys, or is a dipeptide such as Gly-Lys, and wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of a spacer which is Asp or Glu, or a dipeptide spacer containing an Asp or Glu residue, and a carboxyl

group of the spacer forms an amide bond with an amino group of the lipophilic substituent.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which comprises a partially or completely hydrogenated cyclopentanophenanthrene skeleton.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a straight-chain or branched alkyl group.

10 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is the acyl group of a straight-chain or branched fatty acid.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is an acyl group selected from the group comprising CH<sub>3</sub>(CH<sub>2</sub>)<sub>n</sub>CO-, wherein n is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group comprising CH<sub>3</sub>(CH<sub>2</sub>)<sub>6</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>8</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>10</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>12</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>14</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>16</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>18</sub>CO-, CH<sub>3</sub>(CH<sub>2</sub>)<sub>20</sub>CO- and CH<sub>3</sub>(CH<sub>2</sub>)<sub>22</sub>CO-.

20 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is an acyl group of a straight-chain or branched alkane  $\alpha,\omega$ -dicarboxylic acid.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is an acyl group selected from the group comprising HOOC(CH<sub>2</sub>)<sub>m</sub>CO-, wherein m is an integer from 4 to 38, preferably an integer from 4 to 24, more preferred selected from the group comprising HOOC(CH<sub>2</sub>)<sub>14</sub>CO-, HOOC(CH<sub>2</sub>)<sub>16</sub>CO-, HOOC(CH<sub>2</sub>)<sub>18</sub>CO-, HOOC(CH<sub>2</sub>)<sub>20</sub>CO- and HOOC(CH<sub>2</sub>)<sub>22</sub>CO-.

30 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula CH<sub>3</sub>(CH<sub>2</sub>)<sub>p</sub>((CH<sub>2</sub>)<sub>q</sub>COOH)CHNH-CO(CH<sub>2</sub>)<sub>2</sub>CO-, wherein p and q are integers and p+q is an integer of from 8 to 33, preferably from 12 to 28.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $\text{CH}_3(\text{CH}_2)_r\text{CO}-\text{NHCH}(\text{COOH})(\text{CH}_2)_2\text{CO}-$ , wherein r is an integer of from 10 to 24.

5 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $\text{CH}_3(\text{CH}_2)_s\text{CO}-\text{NHCH}((\text{CH}_2)_2\text{COOH})\text{CO}-$ , wherein s is an integer of from 8 to 24.

10 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $\text{COOH}(\text{CH}_2)_t\text{CO}-$  wherein t is an integer of from 8 to 24.

15 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH}-\text{CO}(\text{CH}_2)_u\text{CH}_3$ , wherein u is an integer of from 8 to 18.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH}-\text{COCH}((\text{CH}_2)_2\text{COOH})\text{NH}-\text{CO}(\text{CH}_2)_w\text{CH}_3$ , wherein w is an integer of from 10 to 16.

20

In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH}-\text{CO}(\text{CH}_2)_2\text{CH}(\text{COOH})\text{NH}-\text{CO}(\text{CH}_2)_x\text{CH}_3$ , wherein x is an integer of from 10 to 16.

25 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which is a group of the formula  $-\text{NHCH}(\text{COOH})(\text{CH}_2)_4\text{NH}-\text{CO}(\text{CH}_2)_2\text{CH}(\text{COOH})\text{NHCO}(\text{CH}_2)_y\text{CH}_3$ , wherein y is zero or an integer of from 1 to 22.

30 In a further preferred embodiment, the present invention relates to a GLP-1 derivative having a lipophilic substituent which can be negatively charged. Such a lipophilic substituent can for example be a substituent which has a carboxyl group.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative the parent peptide of which is selected from the group comprising GLP-1(1-45) or an analogue

thereof.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative derived from a GLP-1 fragment selected from the group comprising GLP-1(7-35), GLP-1(7-36), GLP-1(7-36)amide, GLP-1(7-37), GLP-1(7-38), GLP-1(7-39), GLP-1(7-40) and GLP-1(7-41) or an analogue thereof.

In a further preferred embodiment, the present invention relates to a GLP-1 analogue derived from a GLP-1 analogue selected from the group comprising GLP-1(1-35), GLP-1(1-36), GLP-1(1-36)amide, GLP-1(1-37), GLP-1(1-38), GLP-1(1-39), GLP-1(1-40) and GLP-1(1-41) or an analogue thereof.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any  $\alpha$ -amino acid residue.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the designation analogue comprises derivatives wherein a total of up to fifteen, preferably up to ten amino acid residues have been exchanged with any  $\alpha$ -amino acid residue which can be coded for by the genetic code.

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the designation analogue comprises derivatives wherein a total of up to six amino acid residues have been exchanged with another  $\alpha$ -amino acid residue which can be coded for by the genetic code.

In a further preferred embodiment, the present invention relates to a GLP-1(A-B) derivative wherein A is an integer from 1 to 7 and B is an integer from 38 to 45 or an analogue thereof comprising one lipophilic substituent attached to the C-terminal amino acid residue and, optionally, a second lipophilic substituent attached to one of the other amino acid residues.

In a further preferred embodiment, a parent peptide for a derivative according to the invention is selected from the group comprising Arg<sup>26</sup>-GLP-1(7-37); Arg<sup>34</sup>-GLP-1(7-37); Lys<sup>36</sup>-

GLP-1(7-37); Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>39</sup>-GLP-1(7-39); Arg<sup>26,34</sup>Lys<sup>40</sup>-GLP-1(7-40); Arg<sup>26</sup>Lys<sup>36</sup>-GLP-1(7-37); Arg<sup>34</sup>Lys<sup>36</sup>-GLP-1(7-37); Arg<sup>26</sup>Lys<sup>39</sup>-GLP-1(7-39); Arg<sup>34</sup>Lys<sup>40</sup>-GLP-1(7-40); Arg<sup>26,34</sup>Lys<sup>36,39</sup>-GLP-1(7-39); Arg<sup>26,34</sup>Lys<sup>36,40</sup>-GLP-1(7-40); Gly<sup>8</sup>Arg<sup>26</sup>-GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>-GLP-1(7-37); Gly<sup>8</sup>Lys<sup>36</sup>-GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>39</sup>-GLP-1(7-39); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>40</sup>-GLP-1(7-40); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>36</sup>-GLP-1(7-37); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>36</sup>-GLP-1(7-37); Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>39</sup>-GLP-1(7-39); Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>40</sup>-GLP-1(7-40); Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-GLP-1(7-39) and Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,40</sup>-GLP-1(7-40).

In a further preferred embodiment, a parent peptide for a derivative according to the invention is selected from the group comprising Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(7-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(7-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(7-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(7-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(7-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(7-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(7-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(1-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(1-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(1-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(1-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(1-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(1-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(1-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(1-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(2-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(2-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(2-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(2-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(2-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(2-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(2-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(2-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(3-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(3-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(3-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(3-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(3-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(3-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(3-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(3-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(4-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(4-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(4-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(4-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(4-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(4-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(4-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(4-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(5-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(5-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(5-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(5-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(5-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(5-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(5-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(5-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(6-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(6-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(6-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(6-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(6-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(6-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(6-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(6-45); Arg<sup>26</sup>Lys<sup>38</sup>GLP-1(1-38); Arg<sup>34</sup>Lys<sup>38</sup>GLP-1(1-38); Arg<sup>26,34</sup>Lys<sup>36,38</sup>GLP-1(1-38); Arg<sup>26</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>36,38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26</sup>Lys<sup>39</sup>GLP-1(1-39); Arg<sup>34</sup>Lys<sup>39</sup>GLP-1(1-39); Arg<sup>26,34</sup>Lys<sup>36,39</sup>GLP-1(1-39); Arg<sup>26</sup>Lys<sup>39</sup>GLP-1(7-39); Arg<sup>34</sup>Lys<sup>39</sup>GLP-1(7-39) and Arg<sup>26,34</sup>Lys<sup>36,39</sup>GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative

wherein the parent peptide is selected from the group comprising Arg<sup>26</sup>-GLP-1(7-37), Arg<sup>34</sup>-GLP-1(7-37), Lys<sup>36</sup>-GLP-1(7-37), Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-37), Arg<sup>26</sup>Lys<sup>36</sup>-GLP-1(7-37), Arg<sup>34</sup>Lys<sup>36</sup>-GLP-1(7-37), Gly<sup>8</sup>Arg<sup>26</sup>-GLP-1(7-37), Gly<sup>8</sup>Arg<sup>34</sup>-GLP-1(7-37), Gly<sup>8</sup>Lys<sup>36</sup>-GLP-1(7-37), Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37), Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>36</sup>-GLP-1(7-37) and Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>36</sup>-GLP-1(7-37).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising Arg<sup>26</sup>Lys<sup>38</sup>-GLP-1(7-38), Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38), Arg<sup>26,34</sup>Lys<sup>36,38</sup>-GLP-1(7-38), Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>38</sup>-GLP-1(7-38) and Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,38</sup>-GLP-1(7-38).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising Arg<sup>26</sup>Lys<sup>39</sup>-GLP-1(7-39), Arg<sup>26,34</sup>Lys<sup>36,39</sup>-GLP-1(7-39), Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>39</sup>-GLP-1(7-39) and Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,39</sup>-GLP-1(7-39).

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In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is selected from the group comprising Arg<sup>34</sup>Lys<sup>40</sup>-GLP-1(7-40), Arg<sup>26,34</sup>Lys<sup>36,40</sup>-GLP-1(7-40), Gly<sup>8</sup>Arg<sup>34</sup>Lys<sup>40</sup>-GLP-1(7-40) and Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36,40</sup>-GLP-1(7-40).

20 In a further preferred embodiment, the present invention relates to a GLP-1 derivative which is selected from the group comprising:

- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- 25 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- 30 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- 35 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);

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- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);  
 Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 5 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);  
 10 Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 15 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 20 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36);  
 Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 25 Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 30 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-35);  
 Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;  
 Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;

- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;
- Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;
- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;
- Arg<sup>28</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-36)amide;
- 5 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-37);
- Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37);
- 10 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-38);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-38);
- Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- 15 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-38);
- Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);
- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-39);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-39);
- Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);
- 20 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-39);
- Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);
- Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-40);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-40);
- Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);
- 25 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-40);
- Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- 30 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37);
- Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);
- Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);

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- Lys<sup>28,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>28,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38);  
 5 Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 10 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 15 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 20 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36);  
 Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 25 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-36)amide;  
 Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-35);  
 30 Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-35);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-35);

- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-35);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37);  
 Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 5 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38);  
 10 Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-38);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38);  
 Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38);  
 15 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-39);  
 20 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-39);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))Arg<sup>34</sup>-GLP-1(7-40);  
 25 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 30 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);

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- Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 5 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 10 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 15 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 20 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 25 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 30 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);

- Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-35);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;  
 Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;
- 5 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-36)amide;
- 10 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-37);
- 15 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);
- 20 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-38);
- 25 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-38);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
 Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);
- 30 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-38);

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- Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 5 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 10 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 15 Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(7-deoxycholoyl))Arg<sup>34</sup>-GLP-1(7-40);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(7-deoxycholoyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 20 Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 25 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 30 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-35);

- Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
5 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-35);  
Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
10 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-36)amide;  
Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
15 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-37);  
Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-37);  
Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-37);  
Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
20 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
25 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-38);  
Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-38);  
Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
30 Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-38);  
Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);

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- Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 5 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 10 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 15 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-40);  
 20 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(choloyl))Arg<sup>34</sup>-GLP-1(7-40);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(choloyl))-GLP-1(7-40);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 25 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
 30 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);

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- Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 5 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 10 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-35);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 15 Gly<sup>8</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-36)amide;  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 20 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-37);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
 Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-37);  
 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 25 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-38);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-38);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-38);  
 30 Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);  
 Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-39);  
 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);

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Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-39);

Gly<sup>8</sup>Arg<sup>26</sup>Lys<sup>34</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40);

Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-40);

Gly<sup>8</sup>Lys<sup>26</sup>(N<sup>c</sup>-(lithocholoyl))Arg<sup>34</sup>-GLP-1(7-40);

5 Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40) and

Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(lithocholoyl))-GLP-1(7-40).

In a further preferred embodiment, the present invention relates to a pharmaceutical composition comprising a GLP-1 derivative and a pharmaceutically acceptable vehicle or

10 carrier.

In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament which has a protracted profile of action relative to GLP-1(7-37).

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In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of non-insulin dependent diabetes mellitus.

20 In a further preferred embodiment, the present invention relates to the use of a GLP-1 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of insulin dependent diabetes mellitus.

In a further preferred embodiment, the present invention relates to the use of a GLP-1

25 derivative according to the invention for the preparation of a medicament with protracted effect for the treatment of obesity.

In a further preferred embodiment, the present invention relates to a method of treating insulin dependent or non-insulin dependent diabetes mellitus in a patient in need of such a

30 treatment, comprising administering to the patient a therapeutically effective amount of a GLP-1 derivative according to claim 1 together with a pharmaceutically acceptable carrier.

#### **DETAILED DESCRIPTION OF THE INVENTION**

To obtain a satisfactory protracted profile of action of the GLP-1 derivative, the lipophilic substituent attached to the GLP-1 moiety preferably comprises 4-40 carbon atoms, in particular 8-25 carbon atoms. The lipophilic substituent may be attached to an amino group 5 of the GLP-1 moiety by means of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid residue to which it is attached. Alternatively, the lipophilic substituent may be attached to said amino acid residue in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid residue. As a further option, the lipophilic substituent may be linked 10 to the GLP-1 moiety via an ester bond. Formally, the ester can be formed either by reaction between a carboxyl group of the GLP-1 moiety and a hydroxyl group of the substituent-to-be or by reaction between a hydroxyl group of the GLP-1 moiety and a carboxyl group of the substituent-to-be. As a further alternative, the lipophilic substituent can be an alkyl group which is introduced into a primary amino group of the GLP-1 moiety.

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In one preferred embodiment of the invention, the lipophilic substituent is attached to the GLP-1 moiety by means of a spacer in such a way that a carboxyl group of the spacer forms an amide bond with an amino group of the GLP-1 moiety. Examples of suitable spacers are succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys. When the spacer is succinic 20 acid, one carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the other carboxyl group thereof may form an amide bond with an amino group of the lipophilic substituent. When the spacer is Lys, Glu or Asp, the carboxyl group thereof may form an amide bond with an amino group of the amino acid residue, and the amino group thereof may form an amide bond with a carboxyl group of the lipophilic 25 substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the  $\epsilon$ -amino group of Lys and the lipophilic substituent. In one preferred embodiment, such a further spacer is succinic acid which forms an amide bond with the  $\epsilon$ -amino group of Lys and with an amino group present in the lipophilic substituent. In another preferred embodiment such a further spacer is Glu or Asp which forms an amide bond with 30 the  $\epsilon$ -amino group of Lys and another amide bond with a carboxyl group present in the lipophilic substituent, that is, the lipophilic substituent is a N $\epsilon$ -acylated lysine residue.

In another preferred embodiment of the present invention, the lipophilic substituent has a group which can be negatively charged. One preferred group which can be negatively

charged is a carboxylic acid group.

The parent peptide can be produced by a method which comprises culturing a host cell containing a DNA sequence encoding the polypeptide and capable of expressing the 5 polypeptide in a suitable nutrient medium under conditions permitting the expression of the peptide, after which the resulting peptide is recovered from the culture.

The medium used to culture the cells may be any conventional medium suitable for growing the host cells, such as minimal or complex media containing appropriate supplements. Suitable 10 media are available from commercial suppliers or may be prepared according to published recipes (e.g. in catalogues of the American Type Culture Collection). The peptide produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, 15 e.g. ammonium sulphate, purification by a variety of chromatographic procedures, e.g. ion exchange chromatography, gel filtration chromatography, affinity chromatography, or the like, dependent on the type of peptide in question.

The DNA sequence encoding the parent peptide may suitably be of genomic or cDNA origin, 20 for instance obtained by preparing a genomic or cDNA library and screening for DNA sequences coding for all or part of the peptide by hybridisation using synthetic oligonucleotide probes in accordance with standard techniques (see, for example, Sambrook, J, Fritsch, EF and Maniatis, T, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, New York, 1989). The DNA sequence encoding the peptide 25 may also be prepared synthetically by established standard methods, e.g. the phosphoamidite method described by Beaucage and Caruthers, *Tetrahedron Letters* 22 (1981), 1859 - 1869, or the method described by Matthes et al., *EMBO Journal* 3 (1984), 801 - 805. The DNA sequence may also be prepared by polymerase chain reaction using specific primers, for instance as described in US 4,683,202 or Saiki et al., *Science* 239 (1988), 487 - 30 491.

The DNA sequence may be inserted into any vector which may conveniently be subjected to recombinant DNA procedures, and the choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, i.e.

a vector which exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g. a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

5

The vector is preferably an expression vector in which the DNA sequence encoding the peptide is operably linked to additional segments required for transcription of the DNA, such as a promoter. The promoter may be any DNA sequence which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the DNA encoding the peptide of the invention in a variety of host cells are well known in the art, cf. for instance Sambrook *et al.*, *supra*.

10 The DNA sequence encoding the peptide may also, if necessary, be operably connected to a suitable terminator, polyadenylation signals, transcriptional enhancer sequences, and translational enhancer sequences. The recombinant vector of the invention may further comprise a DNA sequence enabling the vector to replicate in the host cell in question.

15 The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell or one which confers resistance to a drug, e.g. ampicillin, kanamycin, tetracyclin, chloramphenicol, neomycin, hygromycin or methotrexate.

20 To direct a parent peptide of the present invention into the secretory pathway of the host cells, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) may be provided in the recombinant vector. The secretory signal sequence is joined to the DNA sequence encoding the peptide in the correct reading frame. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the peptide. The secretory signal sequence may be that normally associated with the peptide or may be from a gene encoding another secreted protein.

25

25 The procedures used to ligate the DNA sequences coding for the present peptide, the promoter and optionally the terminator and/or secretory signal sequence, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art (cf., for instance, Sambrook *et al.*, *supra*).

The host cell into which the DNA sequence or the recombinant vector is introduced may be any cell which is capable of producing the present peptide and includes bacteria, yeast, fungi and higher eukaryotic cells. Examples of suitable host cells well known and used in the art 5 are, without limitation, *E. coli*, *Saccharomyces cerevisiae*, or mammalian BHK or CHO cell lines.

Examples of compounds which can be useful as GLP-1 moieties according to the present invention are described in International Patent Application No. WO 87/06941 (The General Hospital Corporation) which relates to a peptide fragment which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulinotropic agent.

Further GLP-1 analogues are described in International Patent Application No. 90/11296 (The General Hospital Corporation) which relates to peptide fragments which comprise 15 GLP-1(7-36) and functional derivatives thereof and have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1(1-36) or GLP-1(1-37) and to their use as insulinotropic agents.

International Patent Application No. 91/11457 (Buckley et al.) discloses analogues of the 20 active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37 which can also be useful as GLP-1 moieties according to the present invention.

### Pharmaceutical compositions

25 Pharmaceutical compositions containing a GLP-1 derivative according to the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral 30 administration can be performed by means of an infusion pump. A further option is a composition which may be a powder or a liquid for the administration of the GLP-1 derivative in the form of a nasal or pulmonary spray. As a still further option, the GLP-1 derivatives of the invention can also be administered transdermally, e.g. from a patch, optionally a iontophoretic patch, or transmucosally, e.g. buccally.

Pharmaceutical compositions containing a GLP-1 derivative of the present invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19<sup>th</sup> edition, 1995.

5

Thus, the injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.

- 10 According to one procedure, the GLP-1 derivative is dissolved in an amount of water which is somewhat less than the final volume of the composition to be prepared. An isotonic agent, a preservative and a buffer is added as required and the pH value of the solution is adjusted - if necessary - using an acid, e.g. hydrochloric acid, or a base, e.g. aqueous sodium hydroxide as needed. Finally, the volume of the solution is adjusted with water to give the desired  
15 concentration of the ingredients.

Examples of isotonic agents are sodium chloride, mannitol and glycerol.

- 20 Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol.

Examples of suitable buffers are sodium acetate and sodium phosphate.

- Further to the above-mentioned components, solutions containing a GLP-1 derivative  
25 according to the present invention may also contain a surfactant in order to improve the solubility and/or the stability of the GLP-1 derivative.

A composition for nasal administration of certain peptides may, for example, be prepared as described in European Patent No. 272097 (to Novo Nordisk A/S) or in WO 93/18785.

30

According to one preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection. Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, e.g. a lyophilised product, which has to be dissolved in a solvent before it

can be injected. The injectable solution preferably contains not less than about 2 mg/ml, preferably not less than about 5 mg/ml, more preferred not less than about 10 mg/ml of the GLP-1 derivative and, preferably, not more than about 100 mg/ml of the GLP-1 derivative.

- 5 The GLP-1 derivatives of this invention can be used in the treatment of various diseases. The particular GLP-1 derivative to be used and the optimal dose level for any patient will depend on the disease to be treated and on a variety of factors including the efficacy of the specific peptide derivative employed, the age, body weight, physical activity, and diet of the patient, on a possible combination with other drugs, and on the severity of the case. It is  
10 recommended that the dosage of the GLP-1 derivative of this invention be determined for each individual patient by those skilled in the art.

In particular, it is envisaged that the GLP-1 derivative will be useful for the preparation of a medicament with a protracted profile of action for the treatment of non-insulin dependent  
15 diabetes mellitus and/or for the treatment of obesity.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination  
20 thereof, be material for realising the invention in diverse forms thereof.

#### **EXAMPLES**

- 25 The following acronyms for commercially available chemicals are used:

DMF :	N,N-Dimethylformamide.
NMP :	N-Methyl-2-pyrrolidone.
EDPA :	N-Ethyl-N,N-diisopropylamine.
EGTA :	Ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid.
GTP	Guanosine 5'-triphosphate.
TFA :	Trifluoroacetic acid.
THF :	Tetrahydrofuran

	Myr-ONSu:	Tetradecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	Pal-ONSu:	Hexadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	Ste-ONSu	Octadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	HOOC-(CH <sub>2</sub> ) <sub>6</sub> -COONSu:	ω-Carboxyheptanoic acid 2,5-dioxopyrrolidin-1-yl ester.
5	HOOC-(CH <sub>2</sub> ) <sub>10</sub> -COONSu:	ω-Carboxyundecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	HOOC-(CH <sub>2</sub> ) <sub>12</sub> -COONSu:	ω-Carboxytridecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	HOOC-(CH <sub>2</sub> ) <sub>14</sub> -COONSu:	ω-Carboxypentadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	HOOC-(CH <sub>2</sub> ) <sub>16</sub> -COONSu:	ω-Carboxyheptadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.
	HOOC-(CH <sub>2</sub> ) <sub>18</sub> -COONSu:	ω-Carboxynonadecanoic acid 2,5-dioxopyrrolidin-1-yl ester.

10

**Abbreviations:**

PDMS: Plasma Desorption Mass Spectrometry

15 MALDI-MS: Matrix Assisted Laser Desorption/Ionisation Mass Spectrometry

HPLC: High Performance Liquid Chromatography

amu: atomic mass units

20 Analytical

**Plasma Desorption Mass Spectrometry**Sample preparation:

25 The sample is dissolved in 0.1 % TFA/EtOH (1:1) at a concentration of 1 µg/µl. The sample solution (5-10 µl) is placed on a nitrocellulose target (Bio-ion AB, Uppsala, Sweden) and allowed to adsorb to the target surface for 2 minutes. The target is subsequently rinsed with 2x25 µl 0.1 % TFA and spin-dried. Finally, the nitrocellulose target is placed in a target carrousel and introduced into the mass spectrometer.

30

MS analysis:

PDMS analysis was carried out using a Bio-ion 20 time-of flight instrument (Bio-ion Nordic AB, Uppsala, Sweden). An acceleration voltage of 15 kV was applied and molecular ions

35 formed by bombardment of the nitrocellulose surface with 252-Cf fission fragments were accelerated towards a stop detector. The resulting time-of-flight spectrum was calibrated

into a true mass spectrum using the H<sup>+</sup> and NO<sup>+</sup> ions at m/z 1 and 30, respectively. Mass spectra were generally accumulated for 1.0x10<sup>6</sup> fission events corresponding to 15-20 minutes. Resulting assigned masses all correspond to isotopically averaged molecular masses. The accuracy of mass assignment is generally better than 0.1 %.

5

### MALDI-MS

MALDI-TOF MS analysis was carried out using a Voyager™ RP instrument (perSeptive Biosystems Inc., Framingham, MA) equipped with delayed extraction and operated in linear mode. Alpha-cyano-4-hydroxy-cinnamic acid was used as matrix, and mass assignments were based on external calibration.

15 **Example 1**

Synthesis of Lys<sup>26</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37).

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The title compound was synthesised from GLP-1(7-37). A mixture of GLP-1(7-37) (25 mg, 7.45 µm), EDPA (26.7 mg, 208 µm), NMP (520 µl) and water (260 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (2.5 mg, 7.67 µm) in NMP (62.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. An additional amount of Myr-ONSu (2.5 mg, 7.67 µm) in NMP (62.5 µl) was added and the resulting mixture gently shaken for 5 min. After a total reaction time of 40 min. the reaction was quenched by the addition of a solution of glycine (12.5 mg, 166 µmol) in 50% aqueous ethanol (12.5 ml). The title compound was isolated from the reaction mixture by HPLC using a cyanopropyl column (Zorbax™ 300SB-CN) and a standard acetonitrile/TFA system, yield: 1.3 mg (corresponding to 4.9% of the theoretical yield). The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The isolated product was analysed by PDMS and the m/z value for the protonated molecular ion was found to be 3567.9±3. The resulting molecular weight is thus 3566.9±3 amu (theoretical value: 3565.9 amu). The position of acylation (Lys26) was verified by enzymatic cleavage of the title compound with *Staphylococcus aureus* V8 protease and subsequent mass determination of the peptide fragments by PDMS.

In addition to the title compound two other GLP-1 derivatives were isolated from the reaction mixture by using the same chromatographic column and a more shallow gradient (35-38% acetonitrile in 60 minutes); see Examples 2 and 3.

5

**Example 2**

Synthesis of Lys<sup>34</sup>(N<sup>ε</sup>-tetradecanoyl)-GLP-1(7-37).

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The title compound was isolated by HPLC from the reaction mixture described in Example

- 10 1. PDMS analysis yielded a protonated molecular ion at m/z 3567.7±3. The molecular weight is thus found to be 3566.7±3 amu (theoretical value: 3565.9 amu). The acylation site was determined on the basis of the fragmentation pattern.

**Example 3**

- 15 Synthesis of Lys<sup>26,34</sup>-bis(N<sup>ε</sup>-tetradecanoyl)-GLP-1(7-37).
- 

The title compound was isolated by HPLC from the reaction mixture described in Example

1. PDMS analysis yielded a protonated molecular ion at m/z 3778.4±3. The molecular weight is thus found to be 3777.4±3 amu (theoretical value: 3776.1 amu).

20

**Example 4**

Synthesis of Lys<sup>26</sup>(N<sup>ε</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-37).

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- 25 The title compound was synthesised from Arg<sup>34</sup>-GLP-1(7-37). A mixture of Arg<sup>34</sup>-GLP-1(7-37) (5 mg, 1.47 µm), EDPA (5.3 mg, 41.1 µm), NMP (105 µl) and water (50 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.71 mg, 2.2 µm) in NMP (17.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature and then allowed to stand for 20 min. After a total reaction time of 30 min. the reaction was quenched by the addition of a solution of glycine (25 mg, 33.3 µm) in 50% aqueous ethanol (2.5 ml). The reaction mixture was purified by HPLC as described in Example 1. PDMS analysis yielded a protonated molecular ion at m/z 3594.9±3. The molecular weight is thus found to be 3593.9±3 amu (theoretical value: 3593.9 amu).

**Example 5**

Synthesis of Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37).

- 5 The title compound was synthesised from Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37) which was purchased from QCB. A mixture of Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37) (1.3 mg, 0.39 µm), EDPA (1.3 mg, 10 µm), NMP (125 µl) and water (30 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.14 mg, 0.44 µm) in NMP (3.6 ml), the reaction mixture was gently shaken for 15 min. at room  
10 temperature. The reaction was quenched by the addition of a solution of glycine (0.1 mg, 1.33 µm) in 50% aqueous ethanol (10 µl). The reaction mixture was purified by HPLC, and the title compound (60 µg, 4%) was isolated.

**Example 6**

- 15 Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>c</sup>-tetradecanoyl)-GLP-1(7-37)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37)-OH (5.0 mg, 1.477 µmol), EDPA (5.4 mg, 41.78 µmol), NMP (105 µl) and water (50 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Myr-ONSu (0.721 mg, 2.215 µmol) in  
20 NMP (18 µl). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.5 mg, 33.3 µmol) in 50% aqueous ethanol (250 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The  
25 column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound ( 1.49 mg, 28 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3595 ± 3. The resulting molecular weight is thus 3594 ± 3 amu (theoretical value 3594 amu).

**30 Example 7**

Synthesis of Lys<sup>26,34</sup>bis(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37)-OH.

A mixture of GLP-1(7-37)-OH (70 mg, 20.85 µmol), EDPA (75.71 mg, 585.8 µmol), NMP (1.47 ml) and water (700 µL) was gently shaken for 10 min. at room temperature. To the

resulting mixture was added a solution of HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu (27.44 mg, 62.42 µmol) in NMP (686 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (34.43 mg, 458.7 µmol) in 50% aqueous ethanol (3.44 ml). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound ( 8.6 mg, 10 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 4006 ± 3. The resulting molecular weight is thus 4005 ± 3 amu (theoretical value 4005 amu).

#### Example 8

Synthesis of Arg<sup>28,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-36)-OH.

15 A mixture of Arg<sup>28,34</sup>Lys<sup>36</sup>-GLP-1(7-36)-OH (5.06 mg, 1.52 µmol), EDPA (5.5 mg, 42.58 µmol), NMP (106 µl) and water (100 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu (1.33 mg, 3.04 µmol) in NMP (33.2 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2.5 h at room temperature. The 20 reaction was quenched by the addition of a solution of glycine (2.50 mg, 33.34 µmol) in 50% aqueous ethanol (250 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound ( 0.46 mg, 8 %) was isolated, and the product 25 was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3652 ± 3. The resulting molecular weight is thus 3651 ± 3 amu (theoretical value 3651 amu).

#### Example 9

30 Synthesis of Arg<sup>28,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-38)-OH.

A mixture of Arg<sup>28,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (5.556 mg, 1.57 µmol), EDPA (5.68 mg, 43.96 µmol), NMP (116.6 µl) and water (50 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu (1.38

mg, 3.14 µmol) in NMP (34.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2.5 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.5 mg, 33.3 µmol) in 50% aqueous ethanol (250 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.7 mg, 12 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3866 ± 3. The resulting molecular weight is thus 3865 ± 3 amu (theoretical value 3865 amu).

#### Example 10

Synthesis of Arg<sup>34</sup>Lys<sup>28</sup> (N<sup>c</sup>-(ω-carboxynonadecanoyl))-GLP-1(7-37)-OH.

A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (5.04 mg, 1.489 µmol), EDPA (5.39 mg, 41.70 µmol), NMP (105 µl) and water (50 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>18</sub>-COONSu (1.31 mg, 2.97 µmol) in NMP (32.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 30 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.46 mg, 32.75 µmol) in 50% aqueous ethanol (246 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound ( 1.2 mg, 22 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3709 ± 3. The resulting molecular weight is thus 3708 ± 3 amu (theoretical value 3708 amu).

#### Example 11

Synthesis of Arg<sup>34</sup>Lys<sup>28</sup> (N<sup>c</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH.

A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (5.8 mg, 1.714 µmol), EDPA (6.20 mg, 47.99 µmol), NMP (121.8 µl) and water (58 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu (2.11 mg, 5.142 µmol) in NMP (52.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature,

and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.83 mg, 37.70 µmol) in 50% aqueous ethanol (283 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The 5 column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.81 mg, 13 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3681 ± 3. The resulting molecular weight is thus 3680 ± 3 amu (theoretical value 3680 amu).

#### 10 Example 12

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>c</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37)-OH (3.51 mg, 1.036 µmol), EDPA (3.75 mg, 29.03 µmol), NMP (73.8 µl) and water (35 µl) was gently shaken for 10 min. at room 15 temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu (1.27 mg, 3.10 µmol) in NMP (31.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h and 10 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (1.71 mg, 22.79 µmol) in 50% aqueous ethanol (171 µl). The reaction mixture was purified by column 20 chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.8 mg, 21 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3682 ± 3. The resulting molecular weight is thus 3681 ± 3 amu (theoretical value 25 3681 amu).

#### Example 13

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-38)-OH.

30 A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (5.168 mg, 1.459 µmol), EDPA (5.28 mg, 40.85 µmol), NMP (108.6 µl) and water (51.8 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu (1.80 mg, 4.37 µmol) in NMP (45 µl), the reaction mixture was gently shaken for 10 min. at room temperature, and then allowed to stand for an additional 2 h and 15 min. at room

temperature. The reaction was quenched by the addition of a solution of glycine (2.41 mg, 32.09 µmol) in 50% aqueous ethanol (241 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 5 0-100% in 60 minutes. The title compound (0.8 mg, 14 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3838 ± 3. The resulting molecular weight is thus 3837 ± 3 amu (theoretical value 3837 amu).

#### 10 Example 14

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>ε</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-36)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-36)-OH (24.44 mg, 7.34 µmol), EDPA (26.56 mg, 205.52 µmol), NMP (513 µl) and water (244.4 µl) was gently shaken for 5 min. at room 15 temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>16</sub>-COONSu (9.06 mg, 22.02 µmol) in NMP (1.21 ml), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 30 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (12.12 mg, 161.48 µmol) in 50% aqueous ethanol (1.21 ml). The reaction mixture was purified by 20 column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (7.5 mg, 28 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3625 ± 3. The resulting molecular weight is thus 3624 ± 3 amu (theoretical value 3624 25 amu).

#### Example 15

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-37)-OH.

30 A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37)-OH (4.2 mg, 1.24 µmol), EDPA (4.49 mg, 34.72 µmol), NMP (88.2 µl) and water (42 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONSu (1.21 mg, 3.72 µmol) in NMP (30.25 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room

temperature. The reaction was quenched by the addition of a solution of glycine (2.04 mg, 27.28 µmol) in 50% aqueous ethanol (204 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 5 0-100% in 60 minutes. The title compound (0.8 mg, 18 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3598 ± 3. The resulting molecular weight is thus 3597 ± 3 amu (theoretical value 3597 amu).

#### 10 Example 16

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-38)-OH.

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A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (5.168 mg, 1.46 µmol), EDPA (5.28 mg, 40.88 µmol), NMP (108.6 µl) and water (51.7 µl) was gently shaken for 10 min. at room 15 temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONSu (1.43 mg, 4.38 µmol) in NMP (35.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.41 mg, 32.12 µmol) in 50% aqueous ethanol (241 µl). The reaction mixture was purified by column 20 chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.85 mg, 16 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3753 ± 3. The resulting molecular weight is thus 3752 ± 3 amu (theoretical value 3752 25 amu).

#### Example 17

##### Synthesis of Lys<sup>26,34</sup>bis(N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-37)-OH.

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30 A mixture of GLP-1(7-37)-OH (10.0 mg, 2.98 µmol), EDPA (10.8 mg, 83.43 µmol), NMP (210 µl) and water (100 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONSu (2.92 mg, 8.94 µmol) in NMP (73 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 50 min. at room temperature. The reaction was

quenched by the addition of a solution of glycine (4.92 mg, 65.56 µmol) in 50% aqueous ethanol (492 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The 5 title compound (1.0 mg, 9 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3781 ± 3. The resulting molecular weight is thus 3780 ± 3 amu (theoretical value 3780amu).

### Example 18

- 10 Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>c</sup>-(ω-carboxyundecanoyl))-GLP-1(7-36)-OH.
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A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-36)-OH (15.04 mg, 4.52 µmol), EDPA (16.35 mg, 126.56 µmol), NMP (315.8 µl) and water (150.4 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONS<sub>u</sub> (4.44 15 mg, 13.56 µmol) in NMP (111 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (7.5 mg, 99.44 µmol) in 50% aqueous ethanol (750 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard 20 acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.45 mg, 22 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3540 ± 3. The resulting molecular weight is thus 3539 ± 3 amu (theoretical value 3539 amu).

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### Example 19

- Synthesis of Arg<sup>34</sup>Lys<sup>26</sup> (N<sup>c</sup>-(ω-carboxyundecanoyl))-GLP-1(7-37)-OH.
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A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (5.87 mg, 1.73 µmol), EDPA (6.27 mg, 48.57 µmol), 30 NMP (123.3 µl) and water (58.7 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>10</sub>-COONS<sub>u</sub> (1.70 mg, 5.20 µmol) in NMP (42.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.86 mg, 286 µmol) in 50% aqueous

ethanol (286 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.27 mg, 20 %) was isolated, and the product was analysed by PDMS.

- 5 The m/z value for the protonated molecular ion was found to be 3597 ± 3. The resulting molecular weight is thus 3596 ± 3 amu (theoretical value 3596 amu).

#### Example 20

##### Synthesis of Arg<sup>34</sup>Lys<sup>28</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37)-OH.

- 10 A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (4.472 mg, 1.32 µmol), EDPA (4.78 mg, 36.96 µmol), NMP (94 µl) and water (44.8 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (1.07 mg, 3.96 µmol) in NMP (26.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and  
15 then allowed to stand for an additional 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.18 mg, 29.04 µmol) in 50% aqueous ethanol (218 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system.  
The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes.  
20 The title compound (0.5 mg, 11 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3540 ± 3. The resulting molecular weight is thus 3539 ± 3 amu (theoretical value 3539 amu).

#### Example 21

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-38)-OH.

- A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (5.168 mg, 1.459 µmol), EDPA (5.28 mg, 40.85 µmol), NMP (108.6 µl) and water (51.6 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (1.18 mg, 4.37 µmol) in NMP (29.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.40 mg, 32.09 µmol) in 50% aqueous ethanol (240 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard

acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.5 mg, 9 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3697 ± 3. The resulting molecular weight is thus 3695 ± 3 amu (theoretical value 3695 amu).

### Example 22

Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>c</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37)-OH.

10 A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-37)-OH (5.00 mg, 1.47 μmol), EDPA (5.32 mg, 41.16 μmol), NMP (105 μl) and water (50 μl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (1.19 mg, 4.41 μmol) in NMP (29.8 μl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The 15 reaction was quenched by the addition of a solution of glycine (2.42 mg, 32.34 μmol) in 50% aqueous ethanol (242 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.78 mg, 15 %) was isolated, and the product 20 was analysed by PDMS. The m/z value for the protonated molecular ion was found to be

3542 ± 3. The resulting molecular weight is thus 3541 ± 3 amu (theoretical value 3541 amu).

### 25 Example 23

Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>c</sup>-(ω-carboxyheptanoyl))-GLP-1(7-36)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>36</sup>-GLP-1(7-36)-OH (5.00 mg, 1.50 μmol), EDPA (5.44 mg, 42.08 μmol), NMP (210 μl) and water (50 μl) was gently shaken for 5 min. at room temperature.

30 To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (1.22 mg, 4.5 μmol) in NMP (30.5 μl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.47 mg, 33.0 μmol) in 50% aqueous ethanol (247 μl). The reaction mixture was purified by column chromatography using a

cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.71 mg, 14 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3484 ± 3. The resulting 5 molecular weight is thus 3483 ± 3 amu (theoretical value 3483 amu).

#### Example 24

Synthesis of Lys<sup>26,34</sup>bis(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37)-OH.

- 10 A mixture of GLP-1(7-37)-OH (10 mg, 2.5 µmol), EDPA (10.8 mg, 83.56 µmol), NMP (210 µl) and water (100 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>6</sub>-COONSu (2.42 mg, 8.92 µmol) in NMP (60.5 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 2 h and 35 min. at room temperature. The reaction was 15 quenched by the addition of a solution of glycine (4.92 mg, 65.54 µmol) in 50% aqueous ethanol (492 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (2.16 mg, 24 %) was isolated, and the product was analysed by PDMS.
- 20 The m/z value for the protonated molecular ion was found to be 3669 ± 3. The resulting molecular weight is thus 3668 ± 3 amu (theoretical value 3668 amu).

#### Example 25

Synthesis of Arg<sup>34</sup>Lys<sup>26</sup> (N<sup>ε</sup>-(ω-carboxypentadecanoyl))-GLP-1(7-37)-OH.

- 25 A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (4.472 mg, 1.321 µmol), EDPA (4.78 mg, 36.99 µmol), NMP (93.9 µl) and water (44.7 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (1.519 mg, 3.963 µmol) in NMP (38 µl), the reaction mixture was gently shaken for 5 min. at room 30 temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.18 mg, 29.06 µmol) in 50% aqueous ethanol (218 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was

0-100% in 60 minutes. The title compound (0.58 mg, 12 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be  $3654 \pm 3$ . The resulting molecular weight is thus  $3653 \pm 3$  amu (theoretical value 3653 amu).

5

### Example 26

Synthesis of Arg<sup>26,34</sup>Lys<sup>36</sup> (N<sup>c</sup>-( $\omega$ -carboxyheptanoyl))-GLP-1(7-36)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-36)-OH (5.00 mg, 1.50  $\mu$ mol), EDPA (5.44 mg, 42.08 10  $\mu$ mol), NMP (210  $\mu$ l) and water (50  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (1.72 mg, 4.5  $\mu$ mol) in NMP (43  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The 15 reaction was quenched by the addition of a solution of glycine (2.48 mg, 33  $\mu$ mol) in 50% aqueous ethanol (248  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.58 mg, 11 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be  $3596 \pm 3$ . The 20 resulting molecular weight is thus  $3595 \pm 3$  amu (theoretical value 3595 amu).

### Example 27

Synthesis of lithocholic acid 2,5-dioxo-pyrrolidin-1-yl ester.

To a mixture of lithocholic acid (5.44 g, 14.34 mmol), N-hydroxysuccinimide (1.78 g, 15.0 25 mmol), anhydrous THF (120 ml) and anhydrous acetonitrile (30 ml), kept at to 10 °C, was added a solution of N,N'-dicyclohexylcarbodiimide (3.44 g, 16.67 mmol) in anhydrous THF. The reaction mixture was stirred at ambient temperature for 16 h, filtered and concentrated in vacuo. The residue was dissolved in dichloromethane (450 ml), washed with a 10% 30 aqueous Na<sub>2</sub>CO<sub>3</sub> solution (2x150 ml) and water (2x150 ml), and dried (MgSO<sub>4</sub>). Filtered and the filtrate concentrated in vacuo to give a crystalline residue. The residue was recrystallised from a mixture of dichloromethane (30 ml) and n-heptane (30 ml to give the title compound (3.46 g, 51%) as a crystalline solid.

**Example 28****Synthesis of Arg<sup>34</sup>Lys<sup>28</sup>(N<sup>ε</sup>-lithocholy)-GLP-1(7-37)-OH.**

A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (4.472 mg, 1.32 µmol), EDPA (4.78 mg, 36.96 µmol), 5 NMP (94 µl) and water (44.8 µl) was gently shaken for 10 min. at room temperature. To the resulting mixture was added a solution of lithocholic acid 2,5-dioxo-pyrrolidin-1-yl ester (1.87 mg, 3.96 µmol) in NMP (46.8 µl), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of a solution of glycine (2.18 mg, 29.04 µmol) 10 in 50% aqueous ethanol (218 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (1.25 mg, 25 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 15 3744 +- 3. The resulting molecular weight is thus 3743 +- 3 amu (theoretical value 3743 amu).

**Example 29****Synthesis of N<sup>ε</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>.**

20 To a suspension of H-Glu(OH)-OBu<sup>t</sup> (2.5 g, 12.3 mmol), DMF (283 ml) and EDPA (1.58 g, 12.3 mmol) was added drop by drop a solution of Myr-ONSu (4.0 g, 12.3 mmol) in DMF (59 ml). The reaction mixture was stirred for 16 h at room temperature and then concentrated in vacuo to a total volume of 20 ml. The residue was partitioned between 5% 25 aqueous citric acid (250 ml) and ethyl acetate (150 ml), and the phases were separated. The organic phase was concentrated in vacuo and the residue dissolved in DMF (40 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (300 ml) kept at 0 °C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (23 30 ml) and HONSu (1.5 g, 13 mmol) was added. To the resulting mixture was added a solution of N,N'-dicyclohexylcarbodiimide (2.44 g, 11.9 mmol) in dichloromethane (47 ml). The reaction mixture was stirred for 16 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title compound (3.03 g, 50%).

**Example 30**

Synthesis of Glu<sup>22,23,30</sup>Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-tetradecanoyl)))-GLP-1(7-38)-OH.

- 5 A mixture of Glu<sup>22,23,30</sup>Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (1.0 mg, 0.272  $\mu$ mol), EDPA (0.98 mg, 7.62  $\mu$ mol), NMP (70  $\mu$ l) and water (70  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 29, (0.41 mg, 0.816  $\mu$ mol) in NMP (10.4  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then  
10 allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (0.448 mg, 5.98  $\mu$ mol) in 50% aqueous ethanol (45  $\mu$ l). A 0.5 % aqueous solution of ammonium acetate (0.9 ml) was added, and the resulting mixture was immobilised on a Varian 500 mg C8 Mega Bond Elut<sup>®</sup> cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally  
15 liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated in vacuo, and the reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.35 mg, 32 %) was isolated, and the product was analysed by PDMS.  
20 The m/z value for the protonated molecular ion was found to be 4012  $\pm$  3. The resulting molecular weight is thus 4011  $\pm$  3 amu (theoretical value 4011 amu).

**Example 31**

Synthesis of Glu<sup>23,26</sup>Arg<sup>34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-tetradecanoyl)))-GLP-1(7-38)-OH.

- 25 A mixture of Glu<sup>23,26</sup>Arg<sup>34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (6.07 mg, 1.727  $\mu$ mol), EDPA (6.25 mg, 48.36  $\mu$ mol), NMP (425  $\mu$ l) and water (425  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in example 29, (2.65 mg, 5.18  $\mu$ mol) in NMP (66.3  $\mu$ l), the reaction mixture was gently shaken for 5 min. at room temperature, and then  
30 allowed to stand for an additional 45 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (2.85 mg, 38.0  $\mu$ mol) in 50% aqueous ethanol (285  $\mu$ l). A 0.5 % aqueous solution of ammonium acetate (5.4 ml) was added, and the resulting mixture was immobilised on a Varian 500 mg C8 Mega Bond Elut<sup>®</sup> cartridge,

the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated *in vacuo*, and the reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The 5 column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.78 mg, 12 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3854 ± 3. The resulting molecular weight is thus 3853 ± 3 amu (theoretical value 3853 amu).

#### 10 Example 32

##### Synthesis of Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(ω-carboxytridecanoyl))-GLP-1(7-37)-OH.

A mixture of GLP-1(7-37)-OH (30 mg, 8.9 μmol), EDPA (32.3 mg, 250 μmol), NMP (2.1 ml) and water (2.1 ml) was gently shaken for 5 min. at room temperature. To the resulting 15 mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>12</sub>-COONSu (12.7 mg, 35.8 μmol) in NMP (318 μl), the reaction mixture was gently shaken for 1 h and 40 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (3.4 mg, 44.7 μmol) in 50% aqueous ethanol (335 μl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The 20 column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (10 mg, 29 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3840 ± 3. The resulting molecular weight is thus 3839 ± 3 amu (theoretical value 3839 amu).

#### 25 Example 33

##### Synthesis of Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(γ-glutamyl(N<sup>a</sup>-tetradecanoyl)))-GLP-1(7-37)-OH. (NNC 90-1167).

A mixture of GLP-1(7-37)-OH (300 mg, 79.8 μmol), EDPA (288.9 mg, 2.24 mmol), NMP 30 (21 ml) and water (21 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 29, (163 mg, 319.3 μmol) in NMP (4.08 ml), the reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 1 h at room temperature. The reaction was quenched by the addition of a

solution of glycine (131.8 mg, 1.76 mmol) in 50% aqueous ethanol (13.2 ml). A 0.5 % aqueous solution of ammonium-acetate (250 ml) was added, and the resulting mixture was divided into four equal portions. Each portion was eluted onto a Varian 500 mg C8 Mega Bond Elut® cartridge, the immobilised compound washed with 0.1% aqueous TFA (3.5 ml),  
 5 and finally liberated from the cartridge by elution with 70% aqueous acetonitrile (4 ml). The combined eluates were diluted with 0.1% aqueous TFA (300 ml). The precipitated compound was collected by centrifugation, washed with 0.1% aqueous TFA (50 ml), and finally isolated by centrifugation. To the precipitate was added TFA (60 ml), and the resulting reaction mixture was stirred for 1 h and 30 min. at room temperature. Excess  
 10 TFA was removed *in vacuo*, and the residue was poured into water (50 ml). The precipitated compound was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (27.3 mg, 8 %) was isolated, and the product was analysed by PDMS. The m/z  
 15 value for the protonated molecular ion was found to be 4036 ± 3. The resulting molecular weight is thus 4035 ± 3 amu (theoretical value 4035 amu).

#### Example 34

##### Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\omega$ -carboxypentadecanoyl))-GLP-1(7-38)-OH.

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A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (30 mg, 8.9  $\mu$ mol), EDPA (32.3 mg, 250  $\mu$ mol), NMP (2.1 ml) and water (2.1 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (13.7 mg, 35.8  $\mu$ mol) in NMP (343  $\mu$ l), the reaction mixture was gently shaken for 1 h at room temperature. The  
 20 reaction was quenched by the addition of a solution of glycine (3.4 mg, 44.7  $\mu$ mol) in 50% aqueous ethanol (335  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes.  
 The title compound (4.8 mg, 14 %) was isolated, and the product was analysed by PDMS.  
 25 The m/z value for the protonated molecular ion was found to be 3894 ± 3. The resulting molecular weight is thus 3893 ± 3 amu (theoretical value 3893 amu).

**Example 35****Synthesis of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>.**

To a suspension of H-Glu(OH)-OBu<sup>t</sup> (4.2 g, 20.6 mmol), DMF (500 ml) and EDPA (2.65 g, 5 20.6 mmol) was added drop by drop a solution of Pal-ONSu (7.3 g, 20.6 mmol) in DMF (100 ml). The reaction mixture was stirred for 64 h at room temperature and then concentrated *in vacuo* to a total volume of 20 ml. The residue was partitioned between 10% aqueous citric acid (300 ml) and ethyl acetate (250 ml), and the phases were separated. The organic phase was concentrated *in vacuo* and the residue dissolved in 10 DMF (50 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (500 ml) kept at 0 °C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in DMF (45 ml) and HONSu (2.15 g, 18.7 mmol) was added. To the resulting mixture was added a solution of N,N'-dicyclohexylcarbodiimide (3.5 g, 17 mmol) in dichloromethane (67 15 ml). The reaction mixture was stirred for 16 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title compound (6.6 g, 72%).

**20 Example 36****Synthesis of Lys<sup>26,34</sup>-bis(N<sup>c</sup>-(γ-glutamyl(N<sup>a</sup>-hexadecanoyl))-GLP-1(7-37)-OH.**

A mixture of GLP-1(7-37)-OH (10 mg, 2.9 μmol), EDPA (10.8 mg, 83.4 μmol), NMP (0.7 ml) and water (0.7 ml) was gently shaken for 5 min. at room temperature. To the resulting 25 mixture was added a solution of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 33, (163 mg, 319.3 μmol) in NMP (4.08 ml), the reaction mixture was gently shaken 1 h and 20 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (4.9 mg, 65.6 μmol) in 50% aqueous ethanol (492 μl). A 0.5 % aqueous solution of ammonium-acetate (9 ml) was added, and the resulting 30 mixture eluted onto a Varian 1g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (10 ml). The eluate was concentrated *in vacuo*, and the residue purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile

gradient was 0-100% in 60 minutes. The title compound (2.4 mg, 20 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be  $4092 \pm 3$ . The resulting molecular weight is thus  $4091 \pm 3$  amu (theoretical value 4091 amu).

5

### Example 37

Synthesis of Arg<sup>34</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-hexadecanoyl))-GLP-1(7-37)-OH.

A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (3.7 mg, 1.1  $\mu$ mol), EDPA (4.0 mg, 30.8  $\mu$ mol), 10 acetonitrile (260  $\mu$ l) and water (260  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 35, (1.8 mg, 3.3  $\mu$ mol) in acetonitrile (44.2  $\mu$ l), and the reaction mixture was gently shaken for 1 h and 20 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (1.8 mg, 24.2  $\mu$ mol) in 50% aqueous 15 ethanol (181  $\mu$ l). A 0.5 % aqueous solution of ammonium-acetate (12 ml) and NMP (300  $\mu$ l) were added, and the resulting mixture eluted onto a Varian 1g C8 Mega Bond Elut<sup>®</sup> cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 2 h at room temperature and then concentrated *in vacuo*. The residue was 20 purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (0.23 mg, 6 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be  $3752 \pm 3$ . The resulting molecular weight is thus  $3751 \pm 3$  amu (theoretical 25 value 3751 amu).

### Example 38

Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-tetradecanoyl))-GLP-1(7-38)-OH.

30 A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (14 mg, 4.0  $\mu$ mol), EDPA (14.3 mg, 110.6  $\mu$ mol), NMP (980  $\mu$ l) and water (980  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 29, (12.1 mg, 23.7  $\mu$ mol) in NMP (303  $\mu$ l), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was

quenched by the addition of a solution of glycine (6.5 mg, 86.9 mmol) in 50% aqueous ethanol (652 µl). A 0.5 % aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (15 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 1 h and 45 min. at room temperature and then concentrated *in vacuo*. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.9 mg, 26 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3881 ± 3. The resulting molecular weight is thus 3880 ± 3 amu (theoretical value 3880 amu).

### Example 39

15 Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>t</sup>-( $\omega$ -carboxypentadecanoyl))-GLP-1(7-38)-OH.

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A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (14 mg, 4.0 µmol), EDPA (14.3 mg, 111 µmol), NMP (980 µl) and water (980 µl) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (4.5 mg, 11.9 µmol) in NMP (114 µl), the reaction mixture was gently shaken for 1 h and 45 min. at room temperature. An additional solution of HOOC-(CH<sub>2</sub>)<sub>14</sub>-COONSu (4.0 mg, 10.4 µmol) in NMP (100 µl) was added, and the resulting mixture was gently shaken for an additional 1 h and 30 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (1.5 mg, 19.8 µmol) in 50% aqueous ethanol (148 µl). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.9 mg, 26 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3809 ± 3. The resulting molecular weight is thus 3808 ± 3 amu (theoretical value 3808 amu).

**Example 40**

Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-hexadecanoyl))-GLP-1(7-38)-OH.

A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (14 mg, 4.0  $\mu$ mol), EDPA (14.3 mg, 110.6  $\mu$ mol), NMP (980  $\mu$ l) and water (980  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-hexadecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 35, (6.4 mg, 11.9  $\mu$ mol) in NMP (160  $\mu$ l), and the reaction mixture was gently shaken for 1 h and 20 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (6.5 mg, 87 mmol) in 50% aqueous ethanol (653  $\mu$ l). A 0.5 % aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1g C8 Mega Bond Elut<sup>®</sup> cartridge, the immobilised compound washed with 5% aqueous acetonitrile (10 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 1 h and 30 min. at room temperature and then concentrated *in vacuo*. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (7.2 mg, 47 %) was isolated, and the product was analysed by PDMS. The m/z value for the protonated molecular ion was found to be 3881  $\pm$  3. The resulting molecular weight is thus 3880  $\pm$  3 amu (theoretical value 3880 amu).

**Example 41**

Synthesis of Arg<sup>18,23,26,30,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-hexadecanoyl)-GLP-1(7-38)-OH.

A mixture of Arg<sup>18,23,26,30,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (1.0 mg, 0.27  $\mu$ mol), EDPA (0.34 mg, 2.7  $\mu$ mol) and DMSO (600  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of Pal-ONSu (0.28 mg, 0.8  $\mu$ mol) in NMP (7  $\mu$ l). The reaction mixture was gently shaken for 5 min. at room temperature, and then allowed to stand for an additional 6 h at room temperature. The reaction was quenched by the addition of a solution of glycine (1.6 mg, 21.7  $\mu$ mol) in 50% aqueous ethanol (163  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound ( 0.17 mg, 16 %) was isolated, and the product was analysed by MALDI-MS. The m/z value for

the protonated molecular ion was found to be  $3961 \pm 3$ . The resulting molecular weight is thus  $3960 \pm 3$  amu (theoretical value 3960 amu).

#### Example 42

5 Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>c</sup>-( $\omega$ -carboxytridecanoyl))-GLP-1(7-38)-OH.

---

A mixture of Arg<sup>26,34</sup>Lys<sup>38</sup>-GLP-1(7-38)-OH (14 mg, 4.0  $\mu$ mol), EDPA (14.3 mg, 111  $\mu$ mol), NMP (980  $\mu$ l) and water (980  $\mu$ l) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of HOOC-(CH<sub>2</sub>)<sub>12</sub>-COONSu (4.2 mg, 11.9  $\mu$ mol) in 10 NMP (105  $\mu$ l), the reaction mixture was gently shaken for 1 h and 50 min. at room temperature. The reaction was quenched by the addition of a solution of glycine (6.5 mg, 87  $\mu$ mol) in 50% aqueous ethanol (652  $\mu$ l). The reaction mixture was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 15 0-100% in 60 minutes. The title compound (5.8 mg, 39 %) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to be  $3780 \pm 3$ . The resulting molecular weight is thus  $3779 \pm 3$  amu (theoretical value 3781 amu).

20

#### Example 43

Synthesis of Arg<sup>34</sup>Lys<sup>26</sup>(N<sup>c</sup>-( $\gamma$ -glutamyl(N<sup>a</sup>-tetradecanoyl)))-GLP-1(7-37)-OH.

---

A mixture of Arg<sup>34</sup>-GLP-1(7-37)-OH (15 mg, 4.4  $\mu$ mol), EDPA (16 mg, 124  $\mu$ mol), NMP (25 ml) and water (4.8 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>a</sup>-tetradecanoyl-Glu(ONSu)-OBu<sup>t</sup>, prepared as described in Example 29, (12.1 mg, 23.7  $\mu$ mol) in NMP (303  $\mu$ l), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (6.5 mg, 86.9  $\mu$ mol) in 50% aqueous ethanol (652  $\mu$ l). A 30 0.5 % aqueous solution of ammonium-acetate (50 ml) was added, and the resulting mixture eluted onto a Varian 1g C8 Mega Bond Elut<sup>®</sup> cartridge, the immobilised compound washed with 5% aqueous acetonitrile (15 ml), and finally liberated from the cartridge by elution with TFA (6 ml). The eluate was allowed to stand for 1 h and 45 min. at room temperature and then concentrated in vacuo. The residue was purified by column

chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.9 mg, 26 %) was isolated, and the product was analysed by MALDI-MS. The m/z value for the protonated molecular ion was found to 5 be 3723 ± 3. The resulting molecular weight is thus 3722 ± 3 amu (theoretical value 3723 amu).

#### Example 44

Synthesis of N<sup>α</sup>-octadecanoyl-Glu(ONSu)-OBu<sup>t</sup>.

10 To a suspension of H-Glu(OH)-OBu<sup>t</sup> (2.82 g, 13.9 mmol), DMF (370 ml) and EDPA (1.79 g, 13.9 mmol) was added drop by drop a solution of Ste-ONSu (5.3 g, 13.9 mmol) in DMF (60 ml). Dichloromethane (35 ml) was added, and the reaction mixture was stirred for 24 h at room temperature and then concentrated *in vacuo*. The residue was partitioned between 15 10% aqueous citric acid (330 ml) and ethyl acetate (200 ml), and the phases were separated. The organic phase was concentrated *in vacuo* and the residue dissolved in DMF (60 ml). The resulting solution was added drop by drop to a 10% aqueous solution of citric acid (400 ml) kept at 0 °C. The precipitated compound was collected and washed with iced water and dried in a vacuum drying oven. The dried compound was dissolved in 20 DMF (40 ml) and HONSu (1.63 g, 14.2 mmol) was added. To the resulting mixture was added a solution of DCC (2.66 g, 12.9 mmol) in dichloromethane (51 ml). The reaction mixture was stirred for 64 h at room temperature, and the precipitated compound was filtered off. The precipitate was recrystallised from n-heptane/2-propanol to give the title 25 compound (4.96 g, 68 %).

25

#### Example 45

Synthesis of Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-octadecanoyl))-GLP-1(7-38)-OH.

A mixture of Arg<sup>26,34</sup>-GLP-1(7-38)-OH (28 mg, 7.9 μmol), EDPA (28.6 mg, 221.5 μmol), 30 NMP (1.96 ml) and water (1.96 ml) was gently shaken for 5 min. at room temperature. To the resulting mixture was added a solution of N<sup>α</sup>-octadecanoyl-Glu(ONSu)-OBu<sup>t</sup> (17.93 g, 31.6 μmol), prepared as described in Example 44, in NMP (448 μl), and the reaction mixture was gently shaken for 2 h at room temperature. The reaction was quenched by the addition of a solution of glycine (13.1 mg, 174 μmol) in 50% aqueous ethanol (1.3 ml). A

0.5 % aqueous solution of ammonium-acetate (120 ml) was added, and the resulting mixture was divided into two equal portions. Each portion was eluted onto a Varian 5 g C8 Mega Bond Elut® cartridge, the immobilised compound washed with 5% aqueous acetonitrile (25 ml), and finally liberated from the cartridge by elution TFA (25 ml). The 5 combined eluates were allowed to stand for 1 h and 25 min. at room temperature and then concentrated *in vacuo*. The residue was purified by column chromatography using a cyanopropyl column (Zorbax 300SB-CN) and a standard acetonitrile/TFA system. The column was heated to 65°C and the acetonitrile gradient was 0-100% in 60 minutes. The title compound (3.6 mg, 11-%) was isolated, and the product was analysed by MALDI-MS.

10 The m/z value for the protonated molecular ion was found to be 3940 ± 3. The resulting molecular weight is thus 3939 ± 3 amu (theoretical value 3937 amu).

## BIOLOGICAL FINDINGS

15

### **Protraction of GLP-1 derivatives after s.c. administration**

The protraction of a number GLP-1 derivatives of the invention was determined by monitoring the concentration thereof in plasma after sc administration to healthy pigs, using the method described below. For comparison also the concentration in plasma of 20 GLP-1(7-37) after sc. administration was followed. The results are given in Table 1. The protraction of other GLP-1 derivatives of the invention can be determined in the same way.

Pigs (50% Duroc, 25% Yorkshire, 25% Danish Landrace, app 40 kg) were fasted from the beginning of the experiment. To each pig 0.5 nmol of test compound per kg body weight 25 was administered in a 50 µM isotonic solution (5 mM phosphate, pH 7.4, 0.02% Tween®-20 (Merck), 45 mg/ml mannitol (pyrogen free, Novo Nordisk). Blood samples were drawn from a catheter in vena jugularis at the hours indicated in Table 1. 5 ml of the blood samples were poured into chilled glasses containing 175 µl of the following solution: 0.18 M EDTA, 1500 KIE/ml aprotinin (Novo Nordisk) and 3% bacitracin (Sigma), pH 7.4. Within 30 min, the samples were centrifuged for 10 min at 5-6000\*g. Temperature was kept at 4°C. The supernatant was pipetted into different glasses and kept at minus 20°C until use.

The plasma concentrations of the peptides were determined by RIA using a monoclonal antibody specific for the N-terminal region of GLP-1(7-37). The cross reactivities were less

than 1% with GLP-1(1-37) and GLP-1(8-36)amide and < 0.1% with GLP-1(9-37), GLP-1(10-36)amide and GLP-1(11-36)amide. The entire procedure was carried out at 4°C.

The assay was carried out as follows: 100 µl plasma was mixed with 271 µl 96% ethanol,  
5 mixed using a vortex mixer and centrifuged at 2600\*g for 30 min. The supernatant was  
decanted into Minisorp™ tubes and evaporated completely (Savant Speedvac™ AS290). The  
evaporation residue was reconstituted in the assay buffer consisting of 80 mM  
NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.1 % HSA (Orpha 20/21, Behring), 10 mM EDTA, 0.6 mM thiomersal  
(Sigma), pH 7.5. Samples were reconstituted in volumes suitable for their expected  
10 concentrations, and were allowed to reconstitute for 30 min. To 300 µl sample, 100 µl  
antibody solution in dilution buffer containing 40 mM NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.1 % HSA, 0.6  
mM thiomersal, pH 7.5, was added. A non-specific sample was prepared by mixing 300 µl  
buffer with 100 µl dilution buffer. Individual standards were prepared from freeze dried  
stocks, dissolved in 300 µl assay buffer. All samples were pre-incubated in Minisorp tubes  
15 with antibody as described above for 72 h. 200 µl tracer in dilution buffer containing 6-7000  
CPM was added, samples were mixed and incubated for 48 h. 1.5 ml of a suspension of  
200 ml per litre of heparin-stabilised bovine plasma and 18 g per litre of activated carbon  
(Merck) in 40 mM NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, 0.6 mM thiomersal, pH 7.5, was added to each  
tube. Before use, the suspension was mixed and allowed to stand for 2 h at 4°C. All  
20 samples were incubated for 1 h at 4°C and then centrifuged at 3400\*g for 25 min.  
Immediately after the centrifugation, the supernatant was decanted and counted in a γ-  
counter. The concentration in the samples was calculated from individual standard curves.  
The following plasma concentrations were found, calculated as % of the maximum  
concentration for the individual compounds (n=2):

25

30

35

Table 1

Test compound <sup>a</sup>	Hours after sc. administration								
	0.75	1	2	4	6	8	10	12	24
GLP-1(7-37)		100	9	1					
Example 25	73	92	100	98	82	24	16	16	16
Example 17	76	71	91	100	84	68	30		9
Example 43		39	71	93	100	91	59	50	17
Example 37		26	38	97	100	71	81	80	45
Example 11	24	47	59	71	100	94	100		94
Example 12	36	54	65	94	80	100	85		93
Example 32	55	53	90	83	88	70	98	100	100
Example 14	18	25	32	47	98	83	97		100
Example 13	15	22	38	59	97	85	100		76
Example 38	60	53	100	66	48	39	25	29	0
Example 39	38	100	70	47	33	33	18	27	14
Example 40	47	19	50	100	51	56	34	14	0
Example 34	19	32	44	84	59	66	83	84	100

<sup>a</sup>The test compounds are the title compounds of the examples with the numbers given

5

As it appears from Table 1, the GLP-1 derivatives of the invention have a protracted profile of action relative to GLP-1(7-37) and are much more persistent in plasma than GLP-1(7-37). It also appears from Table 1 that the time at which the peak concentration in plasma is achieved varies within wide limits, depending on the particular GLP-1 derivative selected.

10

#### Stimulation of cAMP formation in a cell line expressing the cloned human GLP-1 receptor

In order to demonstrate efficacy of the GLP-1 derivatives, their ability to stimulate formation of cAMP in a cell line expressing the cloned human GLP-1 receptor was tested.

15 An EC<sub>50</sub> was calculated from the dose-response curve.

Baby hamster kidney (BHK) cells expressing the human pancreatic GLP-1 receptor were used (Knudsen and Pridal, 1996, Eur. J. Pharm. 318, 429-435). Plasma membranes were prepared (Adelhorst et al, 1994, J. Biol. Chem. 269, 6275) by homogenisation in buffer (10 mmol/l Tris-HCl and 30 mmol/l NaCl pH 7.4, containing, in addition, 1 mmol/l dithiothreitol, 5 mg/l leupeptin (Sigma, St. Louis, MO, USA), 5 mg/l pepstatin (Sigma, St. Louis, MO, USA), 100 mg/l bacitracin (Sigma, St. Louis, MO, USA), and 16 mg/l aprotinin (Novo Nordisk A/S,

Bagsvaerd, Denmark)). The homogenate was centrifuged on top of a layer of 41 w/v% sucrose. The white band between the two layers was diluted in buffer and centrifuged. Plasma membranes were stored at -80°C until used.

- 5 The assay was carried out in 96-well microtiter plates in a total volume of 140 µl. The buffer used was 50 mmol/l Tris-HCl, pH 7.4 with the addition of 1 mmol/l EGTA, 1.5 mmol/l MgSO<sub>4</sub>, 1.7 mmol/l ATP, 20 mM GTP, 2 mmol/l 3-isobutyl-1-methylxanthine, 0.01 % Tween-20 and 0.1 % human serum albumin (Reinst, Behringwerke AG, Marburg, Germany). Compounds to be tested for agonist activity were dissolved and diluted in buffer, added to the membrane
- 10 preparation and the mixture was incubated for 2 h at 37°C. The reaction was stopped by the addition of 25 µl of 0.05 mol/l HCl. Samples were diluted 10 fold before analysis for cAMP by a scintillation proximity assay (RPA 538, Amersham, UK). The following results were found:

Test compound <sup>1)</sup>	EC <sub>50</sub> , pM	Test compound <sup>1)</sup>	EC <sub>50</sub> , pM
GLP-1(7-37)	61	Example 31	96
Example 45	120	Example 30	41
Example 43	24	Example 26	8.8
Example 40	55	Example 25	99
Example 39	5.1	Example 19	79
Example 38	54	Example 16	3.5
Example 37	60		

- 15 <sup>1)</sup> The test compounds are the title compounds of the examples with the numbers given.

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## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANT: NOVO NORDISK A/S

(ii) TITLE OF INVENTION: GLP-1 DERIVATIVES

(iii) NUMBER OF SEQUENCES: 96

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## (v) COMPUTER READABLE FORM:

- (A) MEDIUM TYPE: Diskette
- (B) COMPUTER: IBM Compatible
- (C) OPERATING SYSTEM: Windows
- (D) SOFTWARE: FastSEQ for Windows Version 2.0b

## (vi) CURRENT APPLICATION DATA:

- (A) APPLICATION NUMBER: 2,264,243
- (B) FILING DATE: 22-AUG-1997
- (C) CLASSIFICATION:

## (vii) PRIOR APPLICATION DATA:

- (A) APPLICATION NUMBER: DK 0931/96
- (B) FILING DATE: 30-AUG-1996

- (A) APPLICATION NUMBER: DK 1259/96
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- (B) FILING DATE: 20-DEC-1996

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- (B) REGISTRATION NUMBER: 4166
- (C) REFERENCE/DOCKET NUMBER: 11667-10 FC/ntb

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- (C) TELEX:

## (2) INFORMATION FOR SEQ ID NO:1:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid

64b

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly				
20	25	30		

(2) INFORMATION FOR SEQ ID NO:2:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly				
20	25	30		

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Lys Gly				
20	25	30		

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

64c

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly							
1	5	10	15				
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly							
20		25	30				

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly							
1	5	10	15				
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Arg							
20		25	30				

## (2) INFORMATION FOR SEQ ID NO:6:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly							
1	5	10	15				
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg							
20		25	30				

Lys

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

64d

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg  
 20 25 30  
 Arg Lys

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Lys Gly Lys Gly  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:9:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

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

64e

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

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg  
 20 25 30  
 Arg Lys

## (2) INFORMATION FOR SEQ ID NO:12:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Arg  
 20 25 30  
 Lys

## (2) INFORMATION FOR SEQ ID NO:13:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

64f

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Arg  
 20 25 30  
 Arg Lys

## (2) INFORMATION FOR SEQ ID NO:14:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:16:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 31 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

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

64g

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

## (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg  
 20 25 30  
 Lys

## (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 34 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg  
 20 25 30  
 Arg Lys

64h

## (2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly
1				5					10				15		
Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Lys	Gly	
									25				30		

## (2) INFORMATION FOR SEQ ID NO:21:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 31 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly
1				5					10				15		
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Lys	Gly	
									25				30		

## (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly
1				5					10				15		
Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Lys	Gly	Arg	Gly	Arg
									25				30		
Lys															

## (2) INFORMATION FOR SEQ ID NO:23:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly	
1														15		
Gln	Ala	Ala	Lys	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg	Gly	Arg	
														30		
20															25	
Arg Lys																

## (2) INFORMATION FOR SEQ ID NO:24:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly	
1														15		
Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Lys	Gly	Arg	
														30		
20															25	
Lys																

## (2) INFORMATION FOR SEQ ID NO:25:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

His	Gly	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu	Gly	
1														15		
Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Lys	Gly	Arg	
														30		
20															25	
Arg Lys																

64j

## (2) INFORMATION FOR SEQ ID NO:26:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Lys				
20	25	30		

## (2) INFORMATION FOR SEQ ID NO:27:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg				
20	25	30		
Lys				

## (2) INFORMATION FOR SEQ ID NO:28:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly				
1	5	10	15	
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg				
20	25	30		
Arg Lys				

## (2) INFORMATION FOR SEQ ID NO:29:

64k

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly						
1	5	10	15			
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg						
20	25	30				
Arg Glu Lys						
35						

## (2) INFORMATION FOR SEQ ID NO:30:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly						
1	5	10	15			
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg						
20	25	30				
Arg Glu Phe Lys						
35						

## (2) INFORMATION FOR SEQ ID NO:31:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly						
1	5	10	15			
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg						
20	25	30				
Arg Glu Phe Pro Lys						
35						

## (2) INFORMATION FOR SEQ ID NO:32:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg			
20	25	30	
Arg Glu Phe Pro Glu Lys			
35			

## (2) INFORMATION FOR SEQ ID NO:33:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Arg			
20	25	30	
Arg Glu Phe Pro Glu Glu Lys			
35			

## (2) INFORMATION FOR SEQ ID NO:34:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val			
1	5	10	15
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu			
20	25	30	
Val Arg Gly Arg Gly Lys			
35			

64m

## (2) INFORMATION FOR SEQ ID NO:35:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

His	Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val
1		5				10							15		
Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
			20				25						30		
Val	Arg	Gly	Arg	Gly	Arg	Lys									
						35									

## (2) INFORMATION FOR SEQ ID NO:36:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

His	Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val
1		5				10							15		
Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
			20				25						30		
Val	Arg	Gly	Arg	Gly	Arg	Arg	Lys								
						35	40								

## (2) INFORMATION FOR SEQ ID NO:37:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

His	Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val
1		5				10							15		
Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
			20				25						30		

64n

Val Arg Gly Arg Gly Arg Arg Glu Lys  
 35                           40

## (2) INFORMATION FOR SEQ ID NO:38:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val  
 1                       5                       10                       15  
 Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu  
 20                      25                       30  
 Val Arg Gly Arg Gly Arg Arg Glu Phe Lys  
 35                      40

## (2) INFORMATION FOR SEQ ID NO:39:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val  
 1                       5                       10                       15  
 Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu  
 20                      25                       30  
 Val Arg Gly Arg Gly Arg Arg Glu Phe Pro Lys  
 35                      40

## (2) INFORMATION FOR SEQ ID NO:40:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

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

640

Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
			20				25						30		
Val	Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys				
			35				40								

## (2) INFORMATION FOR SEQ ID NO:41:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 45 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

His	Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val
1		5					10						15		
Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
			20				25						30		
Val	Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Glu	Lys			
			35				40						45		

## (2) INFORMATION FOR SEQ ID NO:42:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser
1		5					10						15		
Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val
			20				25						30		
Arg	Gly	Arg	Gly	Lys											
			35												

## (2) INFORMATION FOR SEQ ID NO:43:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

64p

Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser  
 1 5 10 15  
 Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val  
 20 25 30  
 Arg Gly Arg Gly Arg Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:44:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser  
 1 5 10 15  
 Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val  
 20 25 30  
 Arg Gly Arg Gly Arg Arg Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:45:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser  
 1 5 10 15  
 Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val  
 20 25 30  
 Arg Gly Arg Gly Arg Arg Glu Lys  
 35 40

## (2) INFORMATION FOR SEQ ID NO:46:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

64q

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser
1			5						10				15		
Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val
			20						25				30		
Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Lys							
			35						40						

## (2) INFORMATION FOR SEQ ID NO:47:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser
1			5						10				15		
Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val
			20						25				30		
Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Lys						
			35						40						

## (2) INFORMATION FOR SEQ ID NO:48:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser
1			5						10				15		
Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val
			20						25				30		
Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys					
			35						40						

## (2) INFORMATION FOR SEQ ID NO:49:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 44 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

64r

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser
1							5			10					15
Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val
							20			25				30	
Arg	Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Glu	Lys				
						35			40						

## (2) INFORMATION FOR SEQ ID NO:50:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1							5			10					15
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
							20			25				30	
Gly	Arg	Gly	Lys												
			35												

## (2) INFORMATION FOR SEQ ID NO:51:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1							5			10					15
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
							20			25				30	
Gly	Arg	Gly	Arg	Lys											
			35												

## (2) INFORMATION FOR SEQ ID NO:52:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

64s

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1						5				10				15	
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
						20				25				30	
Gly	Arg	Gly	Arg	Arg	Lys										
					35										

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1						5				10				15	
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
						20				25				30	
Gly	Arg	Gly	Arg	Arg	Glu	Lys									
					35										

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1						5				10				15	
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
						20				25				30	
Gly	Arg	Gly	Arg	Arg	Glu	Phe	Lys								
					35		40								

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

64t

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1		5						10				15			
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
								20		25		30			
Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Lys							
					35		40								

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1		5						10				15			
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
								20		25		30			
Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys						
					35		40								

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 43 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser
1		5						10				15			
Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg
								20		25		30			
Gly	Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Glu	Lys					
					35		40								

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single

64u

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5				10					15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
									20				25		30
Arg	Gly	Lys													
									35						

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5				10					15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
									20				25		30
Arg	Gly	Arg	Lys												
									35						

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5				10					15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
									20				25		30
Arg	Gly	Arg	Arg	Lys											
									35						

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid

64v

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5			10						15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
					20			25					30		
Arg	Gly	Arg	Arg	Glu	Lys										
				35											

(2) INFORMATION FOR SEQ ID NO:62:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5			10						15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
					20			25					30		
Arg	Gly	Arg	Arg	Glu	Phe	Lys									
				35											

(2) INFORMATION FOR SEQ ID NO:63:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1					5			10						15	
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
					20			25					30		
Arg	Gly	Arg	Arg	Glu	Phe	Pro	Lys								
				35			40								

(2) INFORMATION FOR SEQ ID NO:64:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 41 amino acids

64W

- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1															15
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
															30
Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys							
															40

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 42 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr
1															15
Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly
															30
Arg	Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys							
															40

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1															15
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
															30
Gly	Lys														

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:

64x

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
				20				25					30		
Gly	Arg	Lys													
		35													

(2) INFORMATION FOR SEQ ID NO:68:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
				20				25					30		
Gly	Arg	Arg	Lys												
		35													

(2) INFORMATION FOR SEQ ID NO:69:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
				20				25					30		
Gly	Arg	Arg	Glu	Lys											
		35													

(2) INFORMATION FOR SEQ ID NO:70:

64y

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: peptide

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:70:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
								20					30		
Gly	Arg	Arg	Glu	Phe	Lys										
								35							

## (2) INFORMATION FOR SEQ ID NO:71:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
								20					30		
Gly	Arg	Arg	Glu	Phe	Pro	Lys									
					35										

## (2) INFORMATION FOR SEQ ID NO:72:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:72:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5				10						15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
								20					30		
Gly	Arg	Arg	Glu	Phe	Pro	Glu	Lys								
					35		40								

## (2) INFORMATION FOR SEQ ID NO:73:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 41 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:73:

Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu
1				5					10					15	
Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg
					20				25					30	
Gly	Arg	Arg	Glu	Phe	Pro	Glu	Glu	Lys							
					35			40							

(2) INFORMATION FOR SEQ ID NO:74:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1 5 10 15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20 25 30  
 Lys

(2) INFORMATION FOR SEQ ID NO:75:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:75:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1 5 10 15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20 25 30  
 Arg Lys

64aa

## (2) INFORMATION FOR SEQ ID NO:76:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:76:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1               5               10               15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20               25               30  
 Arg Arg Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:77:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 36 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1               5               10               15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20               25               30  
 Arg Arg Glu Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:78:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 37 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:78:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1               5               10               15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20               25               30  
 Arg Arg Glu Phe Lys  
 35

64bb

(2) INFORMATION FOR SEQ ID NO:79:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu  
 1                   5                           10                           15  
 Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly  
 20                   25                           30  
 Arg Arg Glu Phe Pro Lys  
 35

(2) INFORMATION FOR SEQ ID NO:80:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:80:

(2) INFORMATION FOR SEO ID NO:81:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 40 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:

Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val	Ser	Ser	Tyr	Leu	Glu
1					5				10				15		
Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu	Val	Arg	Gly	Arg	Gly
							20				25			30	

64cc

Arg Arg Glu Phe Pro Glu Glu Lys  
 35 . . . . . 40

## (2) INFORMATION FOR SEQ ID NO:82:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val  
 1 . . . . . 5 . . . . . 10 . . . . . 15  
 Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu  
 20 . . . . . 25 . . . . . 30  
 Val Lys Gly Arg Gly Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:83:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val  
 1 . . . . . 5 . . . . . 10 . . . . . 15  
 Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu  
 20 . . . . . 25 . . . . . 30  
 Val Arg Gly Arg Gly Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:84:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 38 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val  
 1 . . . . . 5 . . . . . 10 . . . . . 15

64dd

Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu  
 20 25 30  
 Val Arg Gly Lys Gly Lys  
 35

## (2) INFORMATION FOR SEQ ID NO:85:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 32 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Lys  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:86:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 32 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Lys  
 20 25 30

## (2) INFORMATION FOR SEQ ID NO:87:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 32 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly  
 1 5 10 15  
 Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Lys  
 20 25 30

64ee

## (2) INFORMATION FOR SEQ ID NO:88:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly Lys			
20	25	30	

## (2) INFORMATION FOR SEQ ID NO:89:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val			
1	5	10	15
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu			
20	25	30	
Val Lys Gly Arg Gly Arg Lys			
35			

## (2) INFORMATION FOR SEQ ID NO:90:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:

His Asp Glu Phe Glu Arg His Ala Glu Gly Thr Phe Thr Ser Asp Val			
1	5	10	15
Ser Ser Tyr Leu Glu Gly Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu			
20	25	30	
Val Arg Gly Arg Gly Arg Lys			
35			

## (2) INFORMATION FOR SEQ ID NO:91:

64ff

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 39 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:

His	Asp	Glu	Phe	Glu	Arg	His	Ala	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Val
1				5					10					15	
Ser	Ser	Tyr	Leu	Glu	Gly	Gln	Ala	Ala	Arg	Glu	Phe	Ile	Ala	Trp	Leu
				20					25					30	
Val	Arg	Gly	Lys	Gly	Arg	Lys									
							35								

(2) INFORMATION FOR SEQ ID NO:92:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:

(2) INFORMATION FOR SEO ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:

64gg

## (2) INFORMATION FOR SEQ ID NO:94:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 33 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:

His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Arg			
20	25	30	
Lys			

## (2) INFORMATION FOR SEQ ID NO:95:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly Lys			
20	25	30	

## (2) INFORMATION FOR SEQ ID NO:96:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 32 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:

His Gly Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly			
1	5	10	15
Gln Ala Ala Arg Glu Phe Ile Ala Trp Leu Val Arg Gly Lys Gly Lys			
20	25	30	

## CLAIMS

1. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor; characterized in that the derivative has only one lipophilic substituent which is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue, and wherein the lipophilic substituent comprises from 8 to 25 carbon atoms and is selected from the group consisting of:
  - i) substituents comprising a partially or completely hydrogenated cyclopentanophenanthrene skeleton;
  - ii) straight-chain or branched alkyl;
  - iii) acyl of branched fatty acids;
  - iv) acyl of straight chain fatty acids selected from  $\text{CH}_3(\text{CH}_2)_{10}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{14}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{16}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{18}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{20}\text{CO}-$  and  $\text{CH}_3(\text{CH}_2)_{22}\text{CO}-$ ;
  - v) acyl of straight-chain or branched alkane  $\alpha,\omega$ -dicarboxylic acids;
  - vi) substituents of the formula  $\text{CH}_3(\text{CH}_2)_p((\text{CH}_2)_q\text{COOH})\text{CHNH-CO}(\text{CH}_2)_2\text{CO}-$ , wherein p and q are integers and p+q is an integer of from 8 to 33;
  - vii) substituents of the formula  $\text{CH}_3(\text{CH}_2)_r\text{CO-NHCH(COOH)(CH}_2)_2\text{CO}-$ , wherein r is an integer of from 10 to 24;
  - viii) substituents of the formula  $\text{CH}_3(\text{CH}_2)_s\text{CO-NHCH}((\text{CH}_2)_2\text{COOH})\text{CO}-$ , wherein s is an integer of from 8 to 24;
  - ix) substituents of the formula  $-\text{NHCH(COOH)(CH}_2)_4\text{NH-CO}(\text{CH}_2)_u\text{CH}_3$ , wherein u is an integer of from 8 to 18;
  - x) substituents of the formula  $-\text{NHCH(COOH)(CH}_2)_4\text{NH-COCH}((\text{CH}_2)_2\text{COOH})\text{NH-CO}(\text{CH}_2)_w\text{CH}_3$ , wherein w is an integer of from 10 to 16;
  - xi) substituents of the formula  $-\text{NHCH(COOH)(CH}_2)_4\text{NH-CO}(\text{CH}_2)_2\text{CH(COOH)NH-CO}(\text{CH}_2)_x\text{CH}_3$ , wherein x is an integer of from 10 to 16;
  - xii) substituents of the formula  $-\text{NHCH(COOH)(CH}_2)_4\text{NH-CO}(\text{CH}_2)_2\text{CH(COOH)NH-CO}(\text{CH}_2)_y\text{CH}_3$ , wherein y is zero or an integer of from 1 to 22; and
  - xiii) lithocholoyl.
2. A derivative of claim 1 vi), wherein p+q is an integer of from 12 to 28.

3. A derivative of claim 1 v), wherein the alkane  $\alpha,\omega$ -dicarboxylic acids is selected from the group comprising HOOC(CH<sub>2</sub>)<sub>m</sub>CO-, wherein m is from 4 to 38.
4. A derivative of claim 3, wherein m is from 4 to 24.
5. A derivative of any one of claims 3-4, wherein the lipophilic substituent is selected from the group comprising HOOC(CH<sub>2</sub>)<sub>14</sub>CO-, HOOC(CH<sub>2</sub>)<sub>16</sub>CO-, HOOC(CH<sub>2</sub>)<sub>18</sub>CO-, HOOC(CH<sub>2</sub>)<sub>20</sub>CO- and HOOC(CH<sub>2</sub>)<sub>22</sub>CO-.
6. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor, and which has two lipophilic substituents, wherein
  - (i) one of the lipophilic substituents is attached to the C-terminal amino acid residue while the other is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue; or
  - (ii) both lipophilic substituents are attached to amino acid residues which are neither the N-terminal nor the C-terminal amino acid residue.
7. A derivative according to claim 6, characterised in that one of the lipophilic substituents is attached to the C-terminal amino acid residue while the other is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue.
8. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor; characterised in that the derivative has only two lipophilic substituents which are attached to amino acid residues which are not the N-terminal or C-terminal amino acid residue.
9. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor and wherein the peptide is GLP-1 (7-C) where C is from 38 to 45; characterized in that it has only one lipophilic substituent which is attached to the C-terminal amino acid residue.
10. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor, wherein

the peptide is GLP-1(A-B) wherein A is an integer from 1 to 7 and B is an integer from 38 to 45; characterized in that the derivative has one lipophilic substituent attached to the C-terminal amino acid residue and a second optional lipophilic substituent attached to one of the other amino acid residues.

11. A derivative of any one of claims 1-10, wherein the peptide is selected from the group consisting of :

$\text{Arg}^{26}\text{-GLP-1(7-37)}$ ;  $\text{Arg}^{34}\text{-GLP-1(7-37)}$ ;  $\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  $\text{Arg}^{26,34}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(7-38)}$ ;  $\text{Arg}^{26,34}\text{Lys}^{39}\text{-GLP-1(7-39)}$ ;  $\text{Arg}^{26,34}\text{Lys}^{40}\text{-GLP-1(7-40)}$ ;  $\text{Arg}^{26}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  
 $\text{Arg}^{34}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  $\text{Arg}^{26}\text{Lys}^{39}\text{-GLP-1(7-39)}$ ;  $\text{Arg}^{34}\text{Lys}^{40}\text{-GLP-1(7-40)}$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{36,39}\text{-GLP-1(7-39)}$ ;  $\text{Arg}^{26,34}\text{Lys}^{36,40}\text{-GLP-1(7-40)}$ ;  $\text{Gly}^8\text{Arg}^{26}\text{-GLP-1(7-37)}$ ;  
 $\text{Gly}^8\text{Arg}^{34}\text{-GLP-1(7-37)}$ ;  $\text{Gly}^8\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  $\text{Gly}^8\text{Arg}^{26,34}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  
 $\text{Gly}^8\text{Arg}^{26,34}\text{Lys}^{39}\text{-GLP-1(7-39)}$ ;  $\text{Gly}^8\text{Arg}^{26,34}\text{Lys}^{40}\text{-GLP-1(7-40)}$ ;  $\text{Gly}^8\text{Arg}^{26}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  
 $\text{Gly}^8\text{Arg}^{34}\text{Lys}^{36}\text{-GLP-1(7-37)}$ ;  $\text{Gly}^8\text{Arg}^{26}\text{Lys}^{39}\text{-GLP-1(7-39)}$ ;  $\text{Gly}^8\text{Arg}^{34}\text{Lys}^{40}\text{-GLP-1(7-40)}$ ;  
 $\text{Gly}^8\text{Arg}^{26,34}\text{Lys}^{36,39}\text{-GLP-1(7-39)}$  and  $\text{Gly}^8\text{Arg}^{26,34}\text{Lys}^{36,40}\text{-GLP-1(7-40)}$ .

12. A derivative of any of claims 1-10, wherein the peptide is selected from the group consisting of:

$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(7-38)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(7-39)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(7-40)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(7-41)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(7-42)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1(7-43)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1(7-44)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1(7-45)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(1-38)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(1-39)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(1-40)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(1-41)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(1-42)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1(1-43)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1(1-44)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1(1-45)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(2-38)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(2-39)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(2-40)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(2-41)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(2-42)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1(2-43)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1(2-44)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1(2-45)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(3-38)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(3-39)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(3-40)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(3-41)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(3-42)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1(3-43)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1(3-44)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1(3-45)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(4-38)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(4-39)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(4-40)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(4-41)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(4-42)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1(4-43)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1(4-44)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1(4-45)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1(5-38)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1(5-39)}$ ;
$\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1(5-40)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1(5-41)}$ ;	$\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1(5-42)}$ ;

$\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1}(5\text{-}43)$ ;  $\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1}(5\text{-}44)$ ;  $\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1}(5\text{-}45)$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1}(6\text{-}38)$ ;  $\text{Arg}^{26,34}\text{Lys}^{39}\text{GLP-1}(6\text{-}39)$ ;  $\text{Arg}^{26,34}\text{Lys}^{40}\text{GLP-1}(6\text{-}40)$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{41}\text{GLP-1}(6\text{-}41)$ ;  $\text{Arg}^{26,34}\text{Lys}^{42}\text{GLP-1}(6\text{-}42)$ ;  $\text{Arg}^{26,34}\text{Lys}^{43}\text{GLP-1}(6\text{-}43)$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{44}\text{GLP-1}(6\text{-}44)$ ;  $\text{Arg}^{26,34}\text{Lys}^{45}\text{GLP-1}(6\text{-}45)$ ;  $\text{Arg}^{26}\text{Lys}^{38}\text{GLP-1}(1\text{-}38)$ ;  $\text{Arg}^{34}\text{Lys}^{38}\text{GLP-1}(1\text{-}38)$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{36,38}\text{GLP-1}(1\text{-}38)$ ;  $\text{Arg}^{26}\text{Lys}^{38}\text{GLP-1}(7\text{-}38)$ ;  $\text{Arg}^{34}\text{Lys}^{38}\text{GLP-1}(7\text{-}38)$ ;  
 $\text{Arg}^{26,34}\text{Lys}^{36,38}\text{GLP-1}(7\text{-}38)$ ;  $\text{Arg}^{26,34}\text{Lys}^{38}\text{GLP-1}(7\text{-}38)$ ;  $\text{Arg}^{26}\text{Lys}^{39}\text{GLP-1}(1\text{-}39)$ ;  
 $\text{Arg}^{34}\text{Lys}^{39}\text{GLP-1}(1\text{-}39)$ ;  $\text{Arg}^{26,34}\text{Lys}^{36,39}\text{GLP-1}(1\text{-}39)$ ;  $\text{Arg}^{26}\text{Lys}^{39}\text{GLP-1}(7\text{-}39)$ ;  $\text{Arg}^{34}\text{Lys}^{39}\text{GLP-1}(7\text{-}39)$  and  $\text{Arg}^{26,34}\text{Lys}^{36,39}\text{GLP-1}(7\text{-}39)$ .

13. A glucagon-like peptide-1 (GLP-1) derivative which is an agonist of the human GLP-1 receptor, wherein at least one amino acid residue has a lipophilic substituent attached and the peptide is selected from the group consisting of:

Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(7-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(7-40);  
Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(7-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(7-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(7-43);  
Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(7-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(7-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(1-38);  
Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(1-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(1-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(1-41);  
Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(1-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(1-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(1-44);  
Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(1-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(2-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(2-39);  
Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(2-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(2-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(2-42);  
Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(2-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(2-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(2-45);  
Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(3-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(3-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(3-40);  
Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(3-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(3-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(3-43);  
Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(3-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(3-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(4-38);  
Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(4-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(4-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(4-41);  
Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(4-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(4-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(4-44);  
Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(4-45); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(5-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(5-39);  
Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(5-40); Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(5-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(5-42);  
Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(5-43); Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(5-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(5-45);  
Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(6-38); Arg<sup>26,34</sup>Lys<sup>39</sup>GLP-1(6-39); Arg<sup>26,34</sup>Lys<sup>40</sup>GLP-1(6-40);  
Arg<sup>26,34</sup>Lys<sup>41</sup>GLP-1(6-41); Arg<sup>26,34</sup>Lys<sup>42</sup>GLP-1(6-42); Arg<sup>26,34</sup>Lys<sup>43</sup>GLP-1(6-43);  
Arg<sup>26,34</sup>Lys<sup>44</sup>GLP-1(6-44); Arg<sup>26,34</sup>Lys<sup>45</sup>GLP-1(6-45); Arg<sup>26</sup>Lys<sup>38</sup>GLP-1(1-38); Arg<sup>34</sup>Lys<sup>38</sup>GLP-1(1-38);  
Arg<sup>26,34</sup>Lys<sup>36,38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>34</sup>Lys<sup>38</sup>GLP-1(7-38);  
Arg<sup>26,34</sup>Lys<sup>36,38</sup>GLP-1(7-38); Arg<sup>26,34</sup>Lys<sup>38</sup>GLP-1(7-38); Arg<sup>26</sup>Lys<sup>39</sup>GLP-1(1-39);

Arg<sup>34</sup>Lys<sup>39</sup>GLP-1(1-39); Arg<sup>26,34</sup>Lys<sup>36,39</sup>GLP-1(1-39); Arg<sup>26</sup>Lys<sup>39</sup>GLP-1(7-39); Arg<sup>34</sup>Lys<sup>39</sup>GLP-1(7-39) and Arg<sup>26,34</sup>Lys<sup>36,39</sup>GLP-1(7-39),

with the proviso that if only one lipophilic substituent is present and this substituent is attached to the N-terminal or to the C-terminal amino acid residue, then this substituent is an alkyl group or a group which has an  $\omega$ -carboxylic group.

14. A derivative of any one of claims 1-13, wherein the lipophilic substituent comprises from 4 to 40 carbon atoms.

15. A derivative of claim 14, wherein the lipophilic substituent comprises from 8 to 25 carbon atoms.

16. A derivative of any one of claims 1-15, wherein a lipophilic substituent is attached to an amino acid residue via an amide bond formed by a carboxyl group of the lipophilic substituent and an amino group of the amino acid residue.

17. A derivative of any one of the claims 1-14, wherein a lipophilic substituent is attached to an amino acid residue in such a way that an amino group of the lipophilic substituent forms an amide bond with a carboxyl group of the amino acid residue.

18. A derivative of any one of claims 1-17, wherein the lipophilic substituent is attached to the amino acid residue by means of a spacer.

19. A derivative of claim 18, wherein the spacer is an unbranched alkane  $\alpha,\omega$ -dicarboxylic acid group having from 1 to 7 methylene groups, which forms a bridge between an amino group of the peptide and an amino group of the lipophilic substituent.

20. A derivative of claim 19, wherein the  $\alpha,\omega$ -dicarboxylic acid group has two methylene groups.

21. A derivative of claim 18, wherein the spacer is an amino acid residue except Cys, or a dipeptide.

22. A derivative of claim 21, wherein the dipeptide is Gly-Lys.
23. A derivative of claim 21, wherein a carboxyl group of the parent peptide forms an amide bond with an amino group of a Lys spacer or a dipeptide spacer containing a Lys residue, and the other amino group of the Lys spacer or the dipeptide spacer containing a Lys residue forms an amide bond with a carboxyl group of the lipophilic substituent.
24. A derivative of claim 21, wherein an amino group of the peptide forms an amide bond with a carboxylic group of the amino acid residue or dipeptide spacer, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.
25. A derivative of claim 21, wherein a carboxyl group of the peptide forms an amide bond with an amino group of the amino acid residue spacer or dipeptide spacer, and a carboxyl group of the amino acid residue spacer or dipeptide spacer forms an amide bond with an amino group of the lipophilic substituent.
26. A derivative of claim 21, wherein a carboxyl group of the peptide forms an amide bond with an amino group of a spacer which is Asp or Glu, or a dipeptide spacer containing an Asp or Glu residue, and a carboxyl group of the spacer forms an amide bond with an amino group of the lipophilic substituent.
27. A derivative of any one of the claims 6-26, wherein the lipophilic substituent comprises a partially or completely hydrogenated cyclopantanophenathrene skeleton.
28. A derivative of any one of the claims 6-26, wherein the lipophilic substituent is a straight-chain or branched alkyl group.
29. A derivative of any one of the claims 6-26, wherein the lipophilic substituent is an acyl group of a straight-chain or branched fatty acid.
30. A derivative of claim 29, wherein the acyl group is selected from the group comprising  $\text{CH}_3(\text{CH}_2)_n\text{CO}-$ , wherein n is 4 to 38.

31. A derivative of claim 30, wherein the acyl group is selected from  $\text{CH}_3(\text{CH}_2)_6\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_8\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{10}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{14}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{16}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{18}\text{CO}-$ ,  $\text{CH}_3(\text{CH}_2)_{20}\text{CO}-$  and  $\text{CH}_3(\text{CH}_2)_{22}\text{CO}-$ .
32. A derivative of any one of the claims 6-26, wherein the lipophilic substituent is an acyl group of a straight-chain or branched alkane  $\alpha,\omega$ -dicarboxylic acid.
33. A derivative of claim 32, wherein the acyl group is selected from the group comprising  $\text{HOOC}(\text{CH}_2)_m\text{CO}-$ , wherein m is from 4 to 38.
34. A derivative of claim 33, wherein m is from 4 to 24.
35. A derivative of claim 34, wherein the acyl group is selected from the group comprising  $\text{HOOC}(\text{CH}_2)_{14}\text{CO}-$ ,  $\text{HOOC}(\text{CH}_2)_{16}\text{CO}-$ ,  $\text{HOOC}(\text{CH}_2)_{18}\text{CO}-$ ,  $\text{HOOC}(\text{CH}_2)_{20}\text{CO}-$  and  $\text{HOOC}(\text{CH}_2)_{22}\text{CO}-$ .
36. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula  $\text{CH}_3(\text{CH}_2)_p((\text{CH}_2)_q\text{COOH})\text{CHNH-CO}(\text{CH}_2)_2\text{CO}-$ , wherein p and q are integers and p+q is an integer of from 8 to 33.
37. A derivative of claim 36, where p+q is an integer of from 12 to 28.
38. A derivative of any of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula  $\text{CH}_3(\text{CH}_2)_r\text{CO-NHCH(COOH)(CH}_2)_2\text{CO}-$ , wherein r is an integer of from 10 to 24.
39. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula  $\text{CH}_3(\text{CH}_2)_s\text{CO-NHCH}((\text{CH}_2)_2\text{COOH})\text{CO}-$ , wherein s is an integer of from 8 to 24.

40. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula -NHCH(COOH)(CH<sub>2</sub>)<sub>4</sub>NH-CO(CH<sub>2</sub>)<sub>u</sub>CH<sub>3</sub>, wherein u is an integer of from 8 to 18.

41. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula -NHCH(COOH)(CH<sub>2</sub>)<sub>4</sub>NH-COCH((CH<sub>2</sub>)<sub>2</sub>COOH)NH-CO(CH<sub>2</sub>)<sub>w</sub>CH<sub>3</sub>, wherein w is an integer of from 10 to 16.

42. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula -NHCH(COOH)(CH<sub>2</sub>)<sub>4</sub>NH-CO(CH<sub>2</sub>)<sub>2</sub>CH(COOH)NH-CO(CH<sub>2</sub>)<sub>x</sub>CH<sub>3</sub>, wherein x is an integer of from 10 to 16.

43. A derivative of any one of the claims 6-26, wherein the lipophilic substituent with the spacer is a group of the formula -NHCH(COOH)(CH<sub>2</sub>)<sub>4</sub>NH-CO(CH<sub>2</sub>)<sub>2</sub>CH(COOH)NH-CO(CH<sub>2</sub>)<sub>y</sub>CH<sub>3</sub>, wherein y is zero or an integer of from 1 to 22.

44. A derivative of claim 1 which is Lys<sup>26</sup>(N<sup>e</sup>-tetradecanoyl)-GLP-1(7-37).

45. A derivative of claim 1 which is Lys<sup>34</sup>(N<sup>e</sup>-tetradecanoyl)-GLP-1(7-37).

46. A derivative of claim 8 which is Lys<sup>26,34</sup>-bis(N<sup>e</sup>-tetradecanoyl)-GLP-1(7-37).

47. A derivative of claim 1 which is Lys<sup>26</sup>(N<sup>e</sup>-tetradecanoyl)Arg<sup>34</sup>-GLP-1(7-37).

48. A derivative of claim 1 which is Gly<sup>8</sup>Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>e</sup>-tetradecanoyl)-GLP-1(7-37).

49. A derivative of claim 1 which is Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>e</sup>-tetradecanoyl)-GLP-1(7-37).

50. A derivative of claim 8 which is Lys<sup>26,34</sup>bis(N<sup>e</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-37).

51. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-( $\omega$ -carboxynonadecanoyl))-GLP-1(7-38).

52. A derivative of claim 1 which is Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-37).
53. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyheptadecanoyl))-GLP-1(7-38).
54. A derivative of claim 1 which is Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-37).
55. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-38).
56. A derivative of claim 8 which is Lys<sup>26,34</sup>bis(N<sup>ε</sup>-(ω-carboxyundecanoyl))-GLP-1(7-37).
57. A derivative of claim 1 which is Arg<sup>34</sup>Lys<sup>26</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37).
58. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-38).
59. A derivative of claim 1 which is Arg<sup>26,34</sup>Lys<sup>36</sup>(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37).
60. A derivative of claim 8 which is Lys<sup>26,34</sup>bis(N<sup>ε</sup>-(ω-carboxyheptanoyl))-GLP-1(7-37).
61. A derivative of claim 9 which is Glu<sup>22,23,30</sup>Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-tetradecanoyl)))-GLP-1(7-38).
62. A derivative of claim 9 which is Glu<sup>23,26</sup>Arg<sup>34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-tetradecanoyl)))-GLP-1(7-38).
63. A derivative of claim 8 which is Lys<sup>26,34</sup>-bis(N<sup>ε</sup>-(ω-carboxytridecanoyl))-GLP-1(7-37).
64. A derivative of claim 8 which is Lys<sup>26,34</sup>-bis(N<sup>ε</sup>-(γ-glutamyl(N<sup>α</sup>-tetradecanoyl)))-GLP-1(7-37).
65. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>ε</sup>-(ω-carboxypentadecanoyl))-GLP-1(7-38).

66. A derivative of claim 8 which is Lys<sup>26,34</sup>-bis(N<sup>e</sup>-(γ-glutamyl(N<sup>α</sup>-hexadecanoyl)))-GLP-1(7-37).
67. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-(γ-glutamyl(N<sup>α</sup>-tetradecanoyl)))-GLP-1(7-38).
68. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-(ω-carboxypentadecanoyl))-GLP-1(7-38).
69. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-(γ-glutamyl(N<sup>α</sup>-hexadecanoyl)))-GLP-1(7-38).
70. A derivative of claim 9 which is Arg<sup>18,23,26,30,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-hexadecanoyl)-GLP-1(7-38).
71. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-(ω-carboxytridecanoyl))-GLP-1(7-38).
72. A derivative of claim 9 which is Arg<sup>26,34</sup>Lys<sup>38</sup>(N<sup>e</sup>-(γ-glutamyl(N<sup>α</sup>-octadecanoyl)))-GLP-1(7-38).
73. A pharmaceutical composition comprising a derivative of any one of claims 1-72 and a pharmaceutically acceptable vehicle or carrier.
74. Use of a derivative of any one of claims 1-72 for the preparation of a medicament which has a protracted profile of action relative to GLP-1(7-37).
75. Use of a derivative of any one of claims 1-72 for the preparation of a medicament for the treatment of non-insulin dependent diabetes mellitus.
76. Use of a derivative of any one of claims 1-72 for the preparation of a medicament for the treatment of insulin dependent diabetes mellitus.

77. Use of a derivative of any one of claims 1-72 for the preparation of a medicament for the treatment of obesity.
  
78. Use of a derivative of any one of claims 1-72 for the preparation of a medicament for the treatment of one or more conditions selected from non-insulin dependent diabetes mellitus, insulin dependent diabetes mellitus and obesity.