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- (54) **DERIVATIVES OF GLP-1 ANALOGS**
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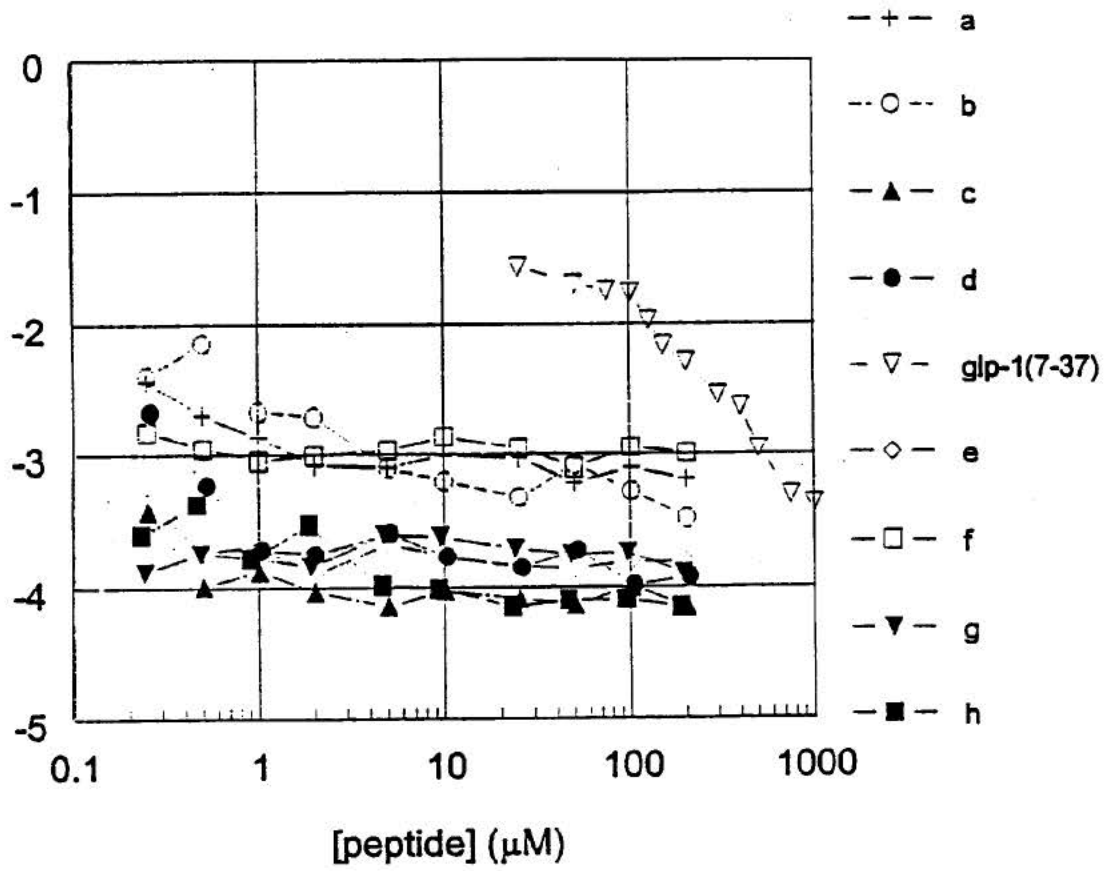
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(57) **ABSTRACT**

The present invention relates to GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making an using same. The GLP-1 derivatives of the present invention have a protracted profile of action.

40 Claims, 1 Drawing Sheet

Fig. 1



DERIVATIVES OF GLP-1 ANALOGS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Ser. No. 09/038,432 filed Mar. 11, 1998, now abandoned which is a continuation-in-part of Ser. No. 08/918,810 filed Aug. 26, 1997 now abandoned and of PCT application serial no. PCT/DK97/00340 filed Aug. 22, 1997, and claims priority of U.S. provisional application Ser. Nos. 60/035,904, 60/036,226, 60/036,255, 60/082,478, 60/082,480, 60/082,802, and 60/084,357 filed Jan. 24, 1997, Jan. 25, 1997, Jan. 24, 1997, Apr. 21, 1998, Apr. 21, 1998, Apr. 23, 1998, and May 5, 1998, respectively, and of Danish application serial nos. 0931/96, 1259/96, 1470/96, 0263/98, 0264/98, 0268/98, 0272/98, 0274/98, 0508/98, and 0509/98 filed Aug. 30, 1996, Nov. 8, 1996, Dec. 20, 1996, Feb. 27, 1998, Feb. 27, 1998, Feb. 27, 1998, Feb. 27, 1998, Apr. 8, 1998, and Apr. 8, 1998, respectively, the contents of each of which is fully incorporated herein by reference.

FIELD OF THE INVENTION

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

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.

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 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. 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 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.

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 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); 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 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 glycine-extended but equally bioactive GLP-1(7–37), (PG (78–108)) are also formed (14); 3) intervening peptide-2(PG (111–112)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.

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 (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.

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 β -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 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 β -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 β -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 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, 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).

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 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 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).

The amino acid sequence of GLP-1 is given i.a. by Schmidt et al. (*Diabetologia* 28 704-707 (1985)). Human GLP-1 is a 37 amino acid residue peptide originating from proglucagon which is synthesised, i.a. in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of proglucagon to GLP-1 (7-36)amide, GLP-1 (7-37) and GLP-2 occurs mainly in the L-cells. 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 have been described by Thornton 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 useful i.a. in the treatment of Type 1 and Type 2 diabetes and obesity.

WO 87/06941 discloses GLP-1 fragments, including GLP-1 (7-37), and functional derivatives thereof and to their use as an insulinotropic agent.

WO 90/11296 discloses GLP-1 fragments, including GLP-1 (7-36), and functional derivatives thereof which 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.

The amino acid sequence of GLP-1 (7-36) and GLP-1 (7-37) is (SEQ ID NO:1):

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7  8  9 10 11 12 13 14 15 16 17  (I)
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
18 19 20 21 22 23 24 25 26 27 28
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
29 30 31 32 33 34 35 36
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

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wherein X is H_2 for GLP-1 (7-36) and X is Gly for GLP-1 (7-37).

WO 91/11457 discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37 which can also be useful as GLP-1 moieties.

EP 0708179-A2 (Eli Lilly & Co.) discloses GLP-1 analogues and derivatives that include an N-terminal imidazole group and optionally an unbranched C_6-C_{10} acyl group in attached to the lysine residue in position 34.

EP 0699686-A2 (Eli Lilly & Co.) discloses certain N-terminal truncated fragments of GLP-1 that are reported to be biologically active.

Unfortunately, the high clearance limits the usefulness of these compounds. Thus there still is a need for improvements in this field.

Accordingly, it is an 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 composition with improved solubility and stability.

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SUMMARY OF THE INVENTION

The present invention relates to derivatives of GLP-1 (1–45) and analogs and/or fragments thereof. The GLP-1 derivatives of the present invention have interesting pharmacological properties, in particular they have a more protracted profile of action than the parent peptides. The GLP-1 derivatives of the present invention also have insulinotropic activity, ability to decrease glucagon, ability to suppress gastric motility, ability to restore glucose competency to beta-cells, and/or ability to suppress appetite/reduce weight.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the results of Circular Dichroism (CD) at 222 nm as a function of peptide concentration for native GLP-1 (7–37) and various GLP-1 derivatives of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A simple system is used to describe fragments and analogues of GLP-1. For example, Gly⁸—GLP-1(7–37) designates a peptide which relates to GLP-1 by the deletion of the amino acid residues at positions 1 to 6 and substituting the naturally occurring amino acid residue in position 8 (Ala) by Gly. Similarly, Lys³⁴(N^ε-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 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 proglucagon unless otherwise indicated.

GLP-1 Analogs

The term “an analogue” is defined herein as a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue. In a preferred embodiment, the total number of different amino acids between the GLP-1 derivative and the corresponding native form of GLP-1 is up to fifteen, preferably up to ten amino acid residues, and most preferably up to six amino acid residues.

The total number of different amino acids between the derivative of the GLP-1 analog and the corresponding native form of GLP-1 preferably does not exceed six. Preferably, the number of different amino acids is five. More preferably, the number of different amino acids is four. Even more preferably, the number of different amino acids is three.

Even more preferably, the number of different amino acids is two. Most preferably, the number of different amino acids is one. In order to determine the number of different amino acids, one should compare the amino acid sequence of the GLP-1 derivative of the present invention with the corresponding native GLP-1. For example, there are two different amino acids between the derivative Gly⁸Arg²⁶Lys³⁴(N^ε-(7-deoxychoyl)-GLP-1(7-40)) and the corresponding native GLP-1 (i.e., GLP-1(7-40)). The differences are located at positions 8 and 26. Similarly, there is only one different amino acid between the derivative Lys²⁶(N^ε-(7-deoxychoyl))Arg³⁴-GLP-1(7-40) and the corresponding native GLP-1. The difference is located at position 34.

In a preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is GLP-1(1-45) or an analogue thereof. In a further preferred embodiment, the parent peptide is 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), GLP-1(1-41) or an analogue thereof.

In a preferred embodiment, the present invention relates to derivatives of GLP-1 analogues of formula I (SEQ ID NO:2):



wherein

Xaa at position 7 is His, a modified amino acid or is deleted,

Xaa at position 8 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 9 is Glu, Asp, or Lys, or is deleted,

Xaa at position 10 is Gly or is deleted,

Xaa at position 11 is Thr, Ala, Gly, Ser, Leu, Ile, Val, Glu, Asp, or Lys or is deleted,

Xaa at position 12 is Phe or is deleted,

Xaa at position 13 is Thr or is deleted,

Xaa at position 14 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys or is deleted,

Xaa at position 15 is Asp or is deleted,

Xaa at position 16 is Val, Ala, Gly, Ser, Thr, Leu, Ile, Glu, Asp, or Lys or is deleted,

Xaa at position 17 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 18 is Ser, Ala, Gly, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 19 is Tyr, Phe, Trp, Glu, Asp, or Lys,

Xaa at position 20 is Leu, Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 21 is Glu, Asp, or Lys,

Xaa at position 22 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 23 is Gln, Asn, Arg, Glu, Asp, or Lys,

Xaa at position 24 is Ala, Gly, Ser, Tr, Leu, Ile, Val, Arg, Glu, Asp, or Lys,

Xaa at position 25 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 26 is Lys, Arg, Gln, Glu, Asp, or His,

Xaa at position 27 is Glu, Asp, or Lys,

Xaa at position 30 is Ala, Gly, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 31 is Trp, Phe, Tyr, Glu, Asp, or Lys,

Xaa at position 32 is Leu, Gly, Ala, Ser, Thr, Ile, Val, Glu, Asp, or Lys,

Xaa at position 33 is Val, Gly, Ala, Ser, Thr, Leu, Ile, Glu, Asp, or Lys,

Xaa at position 34 is Lys, Arg, Glu, Asp, or His,

Xaa at position 35 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys,

Xaa at position 36 is Arg, Lys, Glu, Asp, or His,

Xaa at position 37 is Gly, Ala, Ser, Thr, Leu, Ile, Val, Glu, Asp, or Lys, or is deleted,

Xaa at position 38 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 39 is Arg, Lys, Glu, Asp, or His, or is deleted,

Xaa at position 40 is Asp, Glu, or Lys, or is deleted,

Xaa at position 41 is Phe, Trp, Tyr, Glu, Asp, or Lys, or is deleted,

Xaa at position 42 is Pro, Lys, Glu, or Asp, or is deleted,

Xaa at position 43 is Glu, Asp, or Lys, or is deleted,

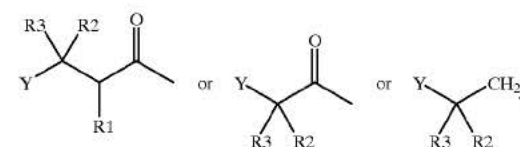
Xaa at position 44 is Glu, Asp, or Lys, or is deleted, and

Xaa at position 45 is Val, Glu, Asp, or Lys, or is deleted, or

(a) a C-1-6-ester thereof, (b) amide, C-1-6-alkylamide, or C-1-6-dialkylamide thereof and/or (c) a pharmaceutically acceptable salt thereof,

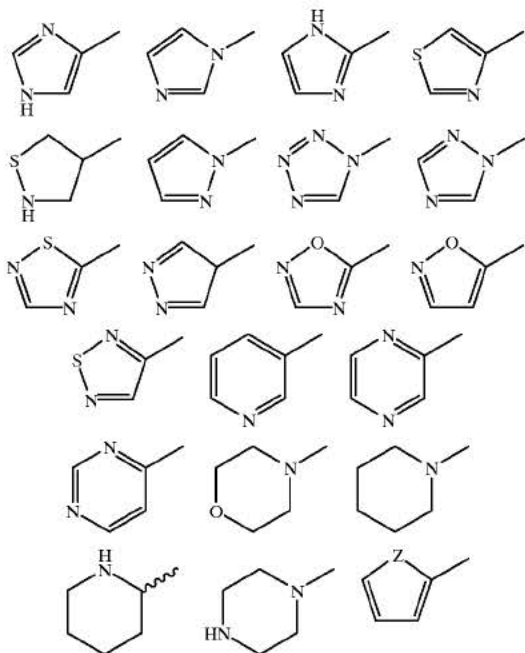
provided that when the amino acid at position 37, 38, 39, 41, 42, 43 or 44 is deleted, then each amino acid downstream of the amino acid is also deleted and when the amino acid at position 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 is deleted then each amino acid upstream of the amino acid is also deleted.

The term "modified amino acid" is defined herein as



wherein R¹, R² and R³ are independently H, lower alkyl, optionally substituted phenyl, NH₂, NH-CO-(lower alkyl), -OH, lower alkoxy, halogen, SO₂-(lower alkyl) or CF₃, wherein said phenyl is optionally substituted with at least one group selected from NH₂, -OH, lower alkyl or lower alkoxy having 1-6 carbon atoms, halogen, SO₂-(lower alkyl), NH-CO-(lower alkyl) or CF₃, or R¹ and R² may together form a bond; and Y is a five or six membered ring system selected from the group consisting of:

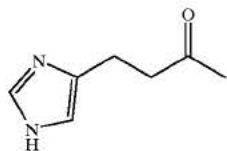
11



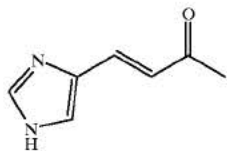
wherein Z is N, O or S, and said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH₂, NO₂, OH, lower alkyl, lower alkoxy, halogen, CF₃ and aryl (i.e., optionally substituted phenyl, as define above), provided that A is not histidine;

The terms "lower alkyl" and "lower alkoxy" refer to an alkyl or alkoxy group, respectively, having 1-6 carbon atoms.

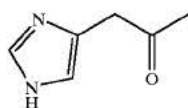
In a preferred embodiment, A is



In another preferred embodiment, A is:

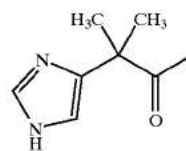


In another preferred embodiment, A is:

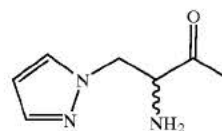


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In another preferred embodiment, A is:



In another preferred embodiment, A is:



In another preferred embodiment, A is 4-imidazopropionyl.

In another preferred embodiment, A is 4-imidazoacetyl.

In another preferred embodiment, A is 4-imidazo- α , α -dimethyl-acetyl,

The GLP-1 derivatives of the present invention preferably have only one or two Lys wherein the ϵ -amino group of one or both Lys is substituted with a lipophilic substituent. Preferably, the GLP-1 derivatives of the present invention have only one Lys. In a more preferred embodiment, there is only one Lys which is located at the carboxy terminus of the derivative of the GLP-1 analogs. In an even more preferred embodiment, the GLP-1 derivatives of the present invention have only one Lys and Glu or Asp is adjacent to Lys.

In a preferred environment, the amino acids at positions 37-45 are absent.

In a another preferred environment, the amino acids at positions 38-45 are absent.

In a another preferred environment, the amino acids at positions 39-45 are absent.

In a another preferred environment, the amino acids at position 7 is deleted.

In a another preferred environment, the amino acids at position 7 and 8 are deleted.

In a another preferred environment, the amino acids at position 7-9 are deleted.

In a another preferred environment, the amino acids at position 7-10 are deleted.

In a another preferred environment, the amino acids at position 7-11 are deleted.

In a another preferred environment, the amino acids at position 7-12 are deleted.

In a another preferred environment, the amino acids at position 7-13 are deleted.

In a another preferred environment, the amino acids at position 7-14 are deleted.

In a another preferred environment, the amino acids at position 7-15 are deleted.

In a another preferred environment, the amino acids at position 7-16 are deleted.

In a another preferred environment, the amino acids at position 7-17 are deleted.

In another preferred environment, Xaa at position 7 is His.

In another preferred environment, Xaa at position 8 is Ala, Gly, Ser, Thr, or Val.

In another preferred environment, Xaa at position 9 is Glu.

In another preferred environment, Xaa at position 10 is Gly.

In another preferred embodiment, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at positions 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-36).

In another preferred embodiment, Xaa at positions 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-37).

In another preferred embodiment, Xaa at positions 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(7-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 26 is Arg, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-36).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 26 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 26 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 34 is Arg, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-36).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 34 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 34 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-36).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(1-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at positions 26 and 34 is Arg, Xaa at position 36 is Lys, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at positions 26 and 34 is Arg, Xaa at position 38 is Lys, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 36 is Lys, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 37 is Glu, Xaa at position 38 is Lys, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-36).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 18, 23 or 27 is Lys, and Xaa at positions 26 and 34 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 37–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-36).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 38–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-37).

In another preferred embodiment, Xaa at position 7 is a modified amino acid or is deleted, Xaa at position 8 is Thr, Ser, Gly or Val, Xaa at position 18, 23 or 27 is Lys, and Xaa at position 26 and 34 is Arg, each of Xaa at positions 39–45 is deleted, and each of the other Xaa is the amino acid in native GLP-1(8-38).

Derivatives

The term “derivative” is defined as a modification of one or more amino acid residues of a peptide by chemical means, either with or without an enzyme, e.g., by alkylation, acylation, ester formation, or amide formation.

Lipophilic Substituents

To obtain a satisfactory protracted profile of action of the GLP-1 derivative, one or more lipophilic substituents are attached to a GLP-1 moiety. The lipophilic substituents preferably comprises 4–40 carbon atoms, in particular 8–25 carbon atoms. The lipophilic substituent may be attached to an amino group 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. Preferably, the GLP-1 derivatives have three, more preferably two, and most preferably one lipophilic substituent.

In a preferred embodiment, 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 peptide then this substituent is an alkyl group or a group which has an ω -carboxylic acid group.

In another preferred embodiment, 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 ω -carboxylic acid group and is attached to the N-terminal amino acid residue of the parent peptide.

In another preferred embodiment, 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 ω -carboxylic acid group and is attached to the C-terminal amino acid residue of the parent peptide.

In another preferred embodiment, the present invention relates to a GLP-1 derivative having only one lipophilic substituent which substituent can be attached to any on amino acid residue which is no the N-terminal or C-terminal amino acid residue of the parent peptide.

In another preferred embodiment, 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.

In another preferred embodiment, 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 an amino acid residue which is not N-terminal or the C-terminal amino acid residue.

In another preferred embodiment, 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 the an amino acid residue which is not the N-terminal or the C-terminal amino acid residue.

A lipophilic substituent may be 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. Alternatively, a lipophilic substituent may be 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.

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. For example, the lipophilic substituent may be 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.

In a most preferred embodiment, the lipophilic substituent is attached—optionally via a spacer—to the ϵ -amino group of a Lys residue contained in the parent peptide.

In a preferred embodiment, the spacer is an α,ω -amino acid. Examples of suitable spacers are succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys. When the spacer is succinic 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 substituent. When Lys is used as the spacer, a further spacer may in some instances be inserted between the ϵ -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 ϵ -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 the ϵ -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. Other preferred spacers are N $^{\epsilon}$ -(γ -L-glutamyl), N $^{\epsilon}$ -(β -L-asparagyl), N $^{\epsilon}$ -glycyl, and N $^{\epsilon}$ -(α -(γ -aminobutanoyl)).

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

In a further preferred embodiment, the lipophilic substituent is attached to the parent peptide by means of a spacer which is an unbranched alkane, α , Ω -dicarboxylic acid group having from 1 to 7 methylene groups, 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 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. The expression "a dipeptide such as Gly-Lys" is defined herein as 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, Ile, Leu, Val, Phe and Pro.

In a further preferred embodiment, the 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 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.

In a further preferred embodiment, the 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 space, and an amino group of the amino acid residue or dipeptide spacer forms an amide bond with a carboxyl group of the lipophilic substituent.

In a further preferred embodiment, the 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 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.

In a further embodiment, the 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 embodiment, the lipophilic substituent is a partially or completely hydrogenated cyclopentanophenathrene skeleton.

In a further embodiment, the lipophilic substituent is a straight-chain or branched alkyl group.

In a further embodiment, the lipophilic substituent is the acyl group of a straight-chain or branched fatty acid.

In a further embodiment, the lipophilic substituent is an acyl group of the formula $\text{CH}_3(\text{CH}_2)_n\text{CO}-$, wherein n is an integer from 4 to 38, preferably an integer from 4 to 24, more preferably $\text{CH}_3(\text{CH}_2)_6\text{CO}-$, $\text{CH}_3(\text{CH}_2)_8\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{10}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{12}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{14}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{16}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{18}\text{CO}-$, $\text{CH}_3(\text{CH}_2)_{20}\text{CO}-$ or $\text{CH}_3(\text{CH}_2)_{22}\text{CO}-$.

In a further preferred embodiment, the lipophilic substituent is an acyl group of a straight-chain or branched alkane, α, ω -dicarboxylic acid.

In a further preferred embodiment, the lipophilic substituent is an acyl group of the formula $\text{HOOC}(\text{CH}_2)_m\text{CO}-$, wherein m is an integer from 4 to 38, preferably an integer from 4 to 24, more preferably $\text{HOOC}(\text{CH}_2)_4\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{16}\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{18}\text{CO}-$, $\text{HOOC}(\text{CH}_2)_{20}\text{CO}-$ or $\text{HOOC}(\text{CH}_2)_{22}\text{CO}-$.

In a further preferred embodiment, the lipophilic substituent is a group of the formula $\text{CH}_3(\text{CH}_2)_p(\text{CH}_2)_q\text{COOH}$ $\text{CHNH}-\text{CO}(\text{CH}_2)_2\text{CO}-$, wherein p and q are integers and +q is an integer of from 8 to 33, preferably from 12 to 28.

In a further preferred embodiment, the lipophilic substituent 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.

In a further preferred embodiment, the lipophilic substituent 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.

In a further preferred embodiment, the lipophilic substituent is a group of the formula $\text{COOH}(\text{CH}_2)_t\text{CO}-$ wherein t is an integer of from 8 to 24.

In a further preferred embodiment, the lipophilic substituent 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 lipophilic substituent is a group of the formula $\text{CH}_3(\text{CH}_2)_v\text{CO}-\text{NH}-(\text{CH}_2)_z-\text{CO}$, wherein n is an integer of from 8 to 24 and z is an integer of from 1 to 6.

In a further preferred embodiment, the lipophilic substituent 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.

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

In a further preferred embodiment, the lipophilic substituent 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.

In a further preferred embodiment, the lipophilic substituent contains a group that can be negatively charged. Such a lipophilic substituent can for example be a substituent which has a carboxyl group.

Other Derivatives

The derivatives of GLP-1 analogues of the present invention may be in the form of one or more of (a) a C-1-6-ester, (b) an amide, C-1-6-alkylamide, or C-1-6-dialkylamide, and (c) a pharmaceutical salt. In a preferred embodiment, the derivatives of GLP-1 analogues are in the form of an acid addition salt or a carboxylate salt, most preferably in the form of an acid addition salt.

Preferred Derivatives of GLP-1 Analogues of the Present Invention

In a preferred embodiment, a parent peptide for a derivative of the invention is

5 Arg²⁶-GLP-1(7-37); Arg³⁴-GLP-1(7-37); Lys³⁶-GLP-1(7-37); Arg^{26,34}Lys³⁶-GLP-1(7-37); Arg^{26,34}Lys³⁸GLP-1(7-38); Arg^{26,34}Lys³⁹-GLP-1(7-39); Arg^{26,34}Lys⁴⁰-GLP-1(7-40); Arg²⁶Lys³⁶-GLP-1(7-37); Arg³⁴Lys³⁶-GLP-1(7-37); Arg²⁶Lys³⁹-GLP-1(7-39); Arg³⁴Lys³⁶-GLP-1(7-40); Arg^{26,34}Lys^{36,39}-GLP-1(7-39); Arg^{26,34}Lys³⁹-GLP-1(7-40); Gly⁸Arg²⁶-GLP-1(7-37); Gly⁸Arg³⁴-GLP-1(7-37); Gly⁸Lys³⁶-GLP-1(7-37); Gly⁸Arg^{26,34}-Lys³⁶-GLP-1(7-37); Gly⁸Arg^{26,34}-Lys³⁹GLP-1(7-39); Gly⁸Lys^{26,34}-Lys⁴⁰GLP-1(7-40); Gly⁸Arg²⁶-Lys³⁶-GLP-1(7-37); Gly⁸Arg³⁴-Lys³⁶GLP-1(7-37); Gly⁸Lys³⁶Lys²⁶-Lys³⁹GLP-1(7-39); Gly⁸Arg^{26,34}Lys⁴⁰-GLP-1(7-40); Gly⁸Arg^{26,34}Lys^{37,39}-GLP-1(7-39); or Gly⁸Arg^{26,34}Lys^{36,40}-GLP-1(7-40).

In a further preferred embodiment, the parent peptide is 20 Arg^{26,34}Lys³⁸GLP-1(7-38); Arg^{26,34}Lys³⁹GLP-1(7-39); Arg^{26,34}Lys⁴⁰GLP-1(7-40); Arg^{26,34}Lys⁴¹GLP-1(7-41); Arg^{26,34}Lys⁴²GLP-1(7-42); Arg^{26,34}Lys⁴³GLP-1(7-43); Arg^{26,34}Lys⁴⁴GLP-1(7-44); Arg^{26,34}Lys⁴⁵GLP-1(7-45); Arg^{26,34}Lys³⁸GLP-1(1-38); Arg^{26,34}Lys³⁹GLP-1(1-39); Arg^{26,34}Lys⁴⁰GLP-1(1-40); Arg^{26,34}Lys⁴¹GLP-1(1-41); Arg^{26,34}Lys⁴²GLP-1(1-42); Arg^{26,34}Lys⁴³GLP-1(1-43); Arg^{26,34}Lys⁴⁴GLP-1(1-44); Arg^{26,34}Lys⁴⁵GLP-1(1-45); Arg^{26,34}Lys³⁸GLP-1(2-38); Arg^{26,34}Lys³⁹GLP-1(2-39); Arg^{26,34}Lys⁴⁰GLP-1(2-40); Arg^{26,34}Lys⁴¹GLP-1(2-41); Arg^{26,34}Lys⁴²GLP-1(2-42); Arg^{26,34}Lys⁴³GLP-1(2-43); Arg^{26,34}Lys⁴⁴GLP-1(2-44); Arg^{26,34}Lys⁴⁵GLP-1(2-45); Arg^{26,34}Lys³⁸GLP-1(3-38); Arg^{26,34}Lys³⁹GLP-1(3-39); Arg^{26,34}Lys⁴⁰GLP-1(3-40); Arg^{26,34}Lys⁴¹GLP-1(3-41); Arg^{26,34}Lys⁴²GLP-1(3-42); Arg^{26,34}Lys⁴³GLP-1(3-43); Arg^{26,34}Lys⁴⁴GLP-1(3-44); Arg^{26,34}Lys⁴⁵GLP-1(3-45); Arg^{26,34}Lys³⁸GLP-1(4-38); Arg^{26,34}Lys³⁹GLP-1(4-39); Arg^{26,34}Lys⁴⁰GLP-1(4-40); Arg^{26,34}Lys⁴¹GLP-1(4-41); Arg^{26,34}Lys⁴²GLP-1(4-42); Arg^{26,34}Lys⁴³GLP-1(4-43); Arg^{26,34}Lys⁴⁴GLP-1(4-44); Arg^{26,34}Lys⁴⁵GLP-1(4-45); Arg^{26,34}Lys³⁸GLP-1(5-38); Arg^{26,34}Lys³⁹GLP-1(5-39); Arg^{26,34}Lys⁴⁰GLP-1(5-40); Arg^{26,34}Lys⁴¹GLP-1(5-41); Arg^{26,34}Lys⁴²GLP-1(5-42); Arg^{26,34}Lys⁴³GLP-1(5-43); Arg^{26,34}Lys⁴⁴GLP-1(5-44); Arg^{26,34}Lys⁴⁵GLP-1(5-45); Arg^{26,34}Lys³⁸GLP-1(6-39); Arg^{26,34}Lys³⁹GLP-1(6-39); Arg^{26,34}Lys⁴⁰GLP-1(6-40); Arg^{26,34}Lys⁴¹GLP-1(6-41); Arg^{26,34}Lys⁴²GLP-1(6-42); Arg^{26,34}Lys⁴³GLP-1(6-43); Arg^{26,34}Lys⁴⁴GLP-1(6-44); Arg^{26,34}Lys⁴⁵GLP-1(6-45); Arg²⁶Lys³⁸GLP-1(1-38); Arg³⁴Lys³⁸GLP-1(1-38); Arg^{26,34}Lys^{36,38}GLP-1(1-38); Arg²⁶Lys³⁸GLP-1(7-38); Arg³⁴Lys³⁸GLP-1(7-38); Arg^{26,34}Lys^{36,38}GLP-1(7-38); Arg^{26,34}Lys³⁹GLP-1(1-39); Arg³⁴Lys³⁹GLP-1(1-39); Arg^{26,34}Lys^{36,39}GLP-1(1-39); Arg²⁶Lys³⁹GLP-1(7-39); Arg³⁴Lys³⁹GLP-1(7-39) or Arg^{26,34}Lys^{36,39}GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is Arg²⁶-GLP-1(7-37), Arg³⁴-GLP-1(7-37), Lys³⁶-GLP-1(7-37), Arg^{26,34}Lys³⁶-GLP-1(7-37), Arg²⁶Lys³⁶-GLP-1(7-37), Arg³⁴Lys³⁶-GLP-1(7-37), Gly⁸Arg²⁶-GLP-1(7-37), Gly⁸Arg³⁴-GLP-1(7-37), Gly⁸Lys³⁶-GLP-1(7-37), Gly⁸Arg^{26,34}Lys³⁶-GLP-1(7-37), Gly⁸Arg²⁶Lys³⁶-GLP-1(7-37) or Gly⁸Arg³⁴Lys³⁶-GLP-1(7-37).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is Arg²⁶Lys³⁸-GLP-1(7-38), Arg^{26,34}Lys³⁸-GLP-1(7-38), Arg^{26,34}Lys^{36,38}-GLP-1(7-38), Gly⁸Arg²⁶Lys³⁸-GLP-1(7-38) or Gly⁸Arg^{26,34}Lys^{36,38}-GLP-1(7-38).

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GLP-1(7-36); Gly⁸Arg³⁴Lys²⁷-GLP-1(7-36); Gly⁸Arg²⁶Lys²⁷GLP-1(7-37); Gly⁸Arg³⁴Lys²⁷GLP-1(7-37); Gly⁸Arg²⁶Lys²⁷GLP-1(7-38); Gly⁸Arg³⁴Lys²⁷GLP-1(7-38); Gly⁸Arg²⁶Lys²⁷GLP-1(7-39); Gly⁸Arg³⁴Lys²⁷GLP-1(7-39); Gly⁸Arg^{26,34}Lys^{18,36}-GLP-1(7-36); Gly⁸Arg^{26,34}Lys¹⁸GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{18,37}GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{23,38}GLP-1(7-38); Gly⁸Arg^{26,34}Lys^{18,39}GLP-1(7-39); Gly⁸Arg^{26,34}Lys^{23,36}-GLP-1(7-36); Gly⁸Arg^{26,34}Lys²³GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{23,37}GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{23,38}GLP-1(7-38); Gly⁸Arg^{26,34}Lys^{27,36}-GLP-1(7-36); Gly⁸Arg^{26,34}Lys²⁷GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{27,37}GLP-1(7-37); Gly⁸Arg^{26,34}Lys^{27,38}GLP-1(7-38); Gly⁸Arg^{26,34}Lys^{27,39}GLP-1(7-39); Val⁸GLP-1(7-36); Val⁸GLP-1(7-37); Val⁸GLP-1(7-38); Val⁸GLP-1(7-39); Val⁸Arg²⁶Lys³⁶-GLP-1(7-36); Val⁸Arg³⁴Lys³⁶-GLP-1(7-36); Val⁸Arg²⁶Lys³⁶-GLP-1(7-37); Val⁸Arg³⁴Lys³⁶-GLP-1(7-37); Val⁸Arg²⁶Lys³⁷-GLP-1(7-37); Val⁸Arg³⁴Lys³⁹-GLP-1(7-39); Val⁸Arg³⁴Lys³⁹-GLP-1(7-39); Val⁸Arg^{26,34}Lys^{36,39}-GLP-1(7-39); Val⁸Arg²⁶Lys¹⁸-GLP-1(7-36); Val⁸Arg³⁴Lys¹⁸-GLP-1(7-36); Val⁸Arg²⁶Lys¹⁸GLP-1(7-37); Val⁸Arg³⁴Lys¹⁸GLP-1(7-37); Val⁸Arg²⁶Lys¹⁸GLP-1(7-38); Val⁸Arg³⁴Lys¹⁸GLP-1(7-38); Val⁸Arg²⁶Lys¹⁸GLP-1(7-39); Val⁸Arg³⁴Lys¹⁸GLP-1(7-39); Val⁸Arg²⁶Lys²³-GLP-1(7-36); Val⁸Arg³⁴Lys²³-GLP-1(7-36); Val⁸Arg²⁶Lys²³GLP-1(7-37); Val⁸Arg³⁴Lys²³GLP-1(7-37); Val⁸Arg²⁶Lys²³GLP-1(7-38); Val⁸Arg³⁴Lys²³GLP-1(7-38); Val⁸Arg²⁶Lys²³GLP-1(7-39); Val⁸Arg³⁴Lys²³GLP-1(7-39); Val⁸Arg²⁶Lys²⁷-GLP-1(7-36); Val⁸Arg³⁴Lys²⁷-GLP-1(7-36); Val⁸Arg²⁶Lys²⁷GLP-1(7-37); Val⁸Arg³⁴Lys²⁷GLP-1(7-37); Val⁸Arg²⁶Lys²⁷GLP-1(7-38); Val⁸Arg³⁴Lys²⁷GLP-1(7-38); Val⁸Arg²⁶Lys²⁷GLP-1(7-39); Val⁸Arg³⁴Lys²⁷GLP-1(7-39); Val⁸Arg^{26,34}Lys^{18,36}GLP-1(7-36); Val⁸Arg^{26,34}Lys¹⁸GLP-1(7-37); Val⁸Arg^{26,34}Lys^{18,37}GLP-1(7-37); Val⁸Arg^{26,34}Lys^{18,38}GLP-1(7-38); Val⁸Arg^{26,34}Lys^{18,39}GLP-1(7-39); Val⁸Arg^{26,34}Lys^{23,36}-GLP-1(7-36); Val⁸Arg^{26,34}Lys²³GLP-1(7-37); Val⁸Arg^{26,34}Lys^{23,37}GLP-1(7-37); Val⁸Arg^{26,34}Lys^{23,38}GLP-1(7-38); Val⁸Arg^{26,34}Lys^{23,39}GLP-1(7-39); Val⁸Arg^{26,34}Lys^{27,36}-GLP-1(7-36); Val⁸Arg^{26,34}Lys²⁷GLP-1(7-37); Val⁸Arg^{26,34}Lys^{27,37}GLP-1(7-37); Val⁸Arg^{26,34}Lys^{27,38}GLP-1(7-38); Val⁸Arg^{26,34}Lys^{27,39}GLP-1(7-39); or Val⁸Arg^{26,34}Lys^{27,39}GLP-1(7-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

Arg²⁶-GLP-1(8-37); Arg³⁴-GLP-1(8-37); Lys³⁶-GLP-1(8-37); Arg^{26,34}Lys³⁶-GLP-1(8-37); Arg^{26,34}Lys³⁸GLP-1(8-38); Arg^{26,34}Lys³⁹-GLP-1(8-39); Arg^{26,34}Lys⁴⁰-GLP-1(8-40); Arg²⁶Lys³⁶-GLP-1(8-37); Arg³⁴Lys³⁶-GLP-1(8-37); Arg²⁶Lys³⁹-GLP-1(8-39); Arg³⁴Lys⁴⁰-GLP-1(8-40); Arg^{26,34}Lys^{36,39}-GLP-1(8-39); Arg^{26,34}Lys^{36,40}-GLP-1(8-40); Gly⁸Arg²⁶-GLP-1(8-37); Gly⁸Arg³⁴-GLP-1(8-37); Gly⁸Lys³⁶-GLP-1(8-37); Gly⁸Arg^{26,34}Lys³⁶-GLP-1(8-37); Gly⁸Arg^{26,34}Lys³⁹-GLP-1(8-39); Gly⁸Arg^{26,34}Lys⁴⁰-GLP-1(8-40); Gly⁸Arg²⁶Lys³⁶-GLP-1(8-37); Gly⁸Arg³⁴-GLP-1(8-37); Gly⁸Arg²⁶Lys³⁹-GLP-1(8-39); Gly⁸Arg³⁴Lys⁴⁰-GLP-1(8-40); Gly⁸Arg^{26,34}Lys^{36,39}-GLP-1(8-39); or Gly⁸Arg^{26,34}Lys^{36,40}-GLP-1(8-40).

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In a further preferred embodiment, the parent peptide is: Arg^{26,34}Lys³⁸GLP-1(8-38); Arg^{26,34}Lys³⁹GLP-1(8-39); Arg^{26,34}Lys⁴⁰GLP-1(8-40); Arg^{26,34}Lys⁴¹GLP-1(8-41); Arg^{26,34}Lys⁴²GLP-1(8-42); Arg^{26,34}Lys⁴³GLP-1(8-43); Arg^{26,34}Lys⁴⁴GLP-1(8-44); Arg^{26,34}Lys⁴⁵GLP-1(8-45); Arg²⁶Lys³⁸GLP-1(8-38); Arg³⁴Lys³⁸GLP-1(8-38); Arg^{26,34}Lys^{36,38}GLP-1(8-38); Arg^{26,34}Lys³⁸GLP-1(8-38); Arg²⁶Lys³⁹GLP-1(8-39); Arg³⁴Lys³⁹GLP-1(8-39); or Arg^{26,34}Lys^{36,39}GLP-1(8-39).

In a further preferred embodiment, the parent peptide is Arg²⁶-GLP-1(8-37), Arg³⁴-GLP-1(8-37), Lys³⁶-GLP-1(8-37), Arg^{26,34}Lys³⁶-GLP-1(8-37), Arg²⁶Lys³⁶-GLP-1(8-37), Arg³⁴Lys³⁶-GLP-1(8-37), Gly⁸Arg²⁶-GLP-1(8-37), Gly⁸Arg³⁴-GLP-1(8-37), Gly⁸Lys³⁶-GLP-1(8-37), Gly⁸Arg^{26,34}Lys³⁶-GLP-1(8-37), Gly⁸Arg²⁶Lys³⁶-GLP-1(8-37), or Gly⁸Arg³⁴Lys³⁶-GLP-1(8-37).

In a further preferred embodiment, the parent peptide is Arg²⁶Lys³⁸-GLP-1(8-38), Arg^{26,34}Lys³⁸-GLP-1(8-38), Arg^{26,34}Lys^{36,38}-GLP-1(8-38), Gly⁸Arg²⁶Lys³⁸-GLP-1(8-38) or Gly⁸Arg^{26,34}Lys^{36,38}-GLP-1(8-38).

In a further preferred embodiment, the parent peptide is Arg²⁶Lys³⁹-GLP-1(8-39), Arg^{26,34}Lys^{36,39}-GLP-1(8-39), Gly⁸Arg²⁶Lys³⁹-GLP-1(8-39), or Gly⁸Arg^{26,34}Lys^{36,39}-GLP-1(8-39).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is Arg³⁴Lys⁴⁰-GLP-1(8-40), Arg^{26,34}Lys^{36,40}-GLP-1(8-40), Gly⁸Arg³⁴Lys⁴⁰-GLP-1(8-40) or Gly⁸Arg^{26,34}Lys^{36,40}-GLP-1(8-40).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

Arg²⁶-GLP-1(8-36); Arg³⁴-GLP-1(8-36); Arg^{26,34}Lys³⁶-GLP-1(8-36); Arg²⁶-GLP-1(8-36)amide; Arg³⁴-GLP-1(8-36)amide; Arg^{26,34}Lys³⁶-GLP-1(8-36)amide; Arg²⁶-GLP-1(8-37); Arg³⁴-GLP-1(8-37); Arg^{26,34}Lys³⁶-GLP-1(8-37); Arg²⁶-GLP-1(8-38); Arg³⁴-GLP-1(8-38); Arg^{26,34}Lys³⁶GLP-1(8-38); Arg²⁶-GLP-1(8-39); Arg³⁴-GLP-1(8-39); Arg^{26,34}Lys³⁹-GLP-1(8-39); Gly⁸Arg²⁶-GLP-1(8-36); Gly⁸Arg³⁴-GLP-1(8-36); Gly⁸Arg^{26,34}Lys³⁶-GLP-1(8-36); Gly⁸Arg²⁶-GLP-1(8-36)amide; Gly⁸Arg³⁴-GLP-1(8-36)amide; Gly⁸Arg^{26,34}Lys³⁶-GLP-1(8-36); Gly⁸Arg²⁶-GLP-1(8-37); Gly⁸Arg³⁴-GLP-1(8-37); Gly⁸Arg^{26,34}Lys³⁶-GLP-1(8-37); Gly⁸Arg²⁶-GLP-1(8-38); Gly⁸Arg³⁴-GLP-1(8-38); Gly⁸Arg^{26,34}Lys³⁸GLP-1(8-38); Gly⁸Arg²⁶-GLP-1(8-39);

Gly⁸Arg³⁴-GLP-1(8-39); Gly⁸Arg^{26,34}Lys³⁹-GLP-1(8-39); Val⁸Arg²⁶-GLP-1(8-36); Val⁸Arg³⁴-GLP-1(8-36); Val⁸Arg^{26,34}Lys³⁶-GLP-1(8-36); Val⁸Arg²⁶-GLP-1(8-36)amide; Val⁸Arg³⁴-GLP-1(8-36)amide; Val⁸Arg^{26,34}Lys³⁶-GLP-1(8-36)amide; Val⁸Arg²⁶-GLP-1(8-37); Val⁸Arg³⁴-GLP-1(8-37); Val⁸Arg^{26,34}Lys³⁶-GLP-1(8-37); Val⁸Arg²⁶-GLP-1(8-38); Val⁸Arg³⁴-GLP-1(8-38); Val⁸Arg^{26,34}Lys³⁸GLP-1(8-39); Val⁸Arg³⁴-GLP-1(8-39); Val⁸Arg^{26,34}Lys³⁹-GLP-1(8-39); Ser⁸Arg²⁶-GLP-1(8-36); Ser⁸Arg³⁴-GLP-1(8-36); Ser⁸Arg^{26,34}Lys³⁶-GLP-1(8-36); Ser⁸Arg²⁶-GLP-1(8-36)amide; Ser⁸Arg³⁴-GLP-1(8-36)amide; Ser⁸Arg^{26,34}Lys³⁶-GLP-1(8-36)amide; Ser⁸Arg²⁶-GLP-1(8-37); Ser⁸Arg³⁴-GLP-1(8-37); Ser⁸Arg^{26,34}Lys³⁶-GLP-1(8-37); Ser⁸Arg²⁶-GLP-1(8-38); Ser⁸Arg³⁴-GLP-1(8-38); Ser⁸Arg^{26,34}Lys³⁸GLP-1(8-38); Ser⁸Arg²⁶-GLP-1(8-39); Ser⁸Arg³⁴-GLP-1(8-39); Ser⁸Arg^{26,34}Lys³⁹-GLP-1(8-39); Thr⁸Arg²⁶-GLP-1

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(8-38); Val⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36);
 Val⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36);
 Val⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Val⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Val⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-37); 5
 Val⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-38);
 Val⁸ Asp²⁶ Arg^{26,34} Lys²⁷ GLP-1(8-38); Arg^{26,34} Lys¹⁸-
 GLP-1(8-36); Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Arg^{26,34} Lys¹⁸ GLP-1(8-37); Arg^{26,34} Lys¹⁸ GLP-1
 (8-38); Ser⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸-GLP-1(8-36); 10
 Ser⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸-GLP-1(8-36);
 Ser⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Ser⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Ser⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸ GLP-1(8-37);
 Ser⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸ GLP-1(8-38); Arg^{26,34} Lys²³-
 GLP-1(8-36); Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Arg^{26,34} Lys²³ GLP-1(8-37); Arg^{26,34} Lys²³ GLP-1
 (8-38); Ser⁸ Asp²⁴ Arg^{26,34} Lys²³-GLP-1(8-36);
 Ser⁸ Asp²² Arg^{26,34} Lys²³-GLP-1(8-36); 20
 Ser⁸ Asp²⁴ Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Ser⁸ Asp²² Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Ser⁸ Asp²⁴ Arg^{26,34} Lys²³ GLP-1(8-37);
 Ser⁸ Asp²⁴ Arg^{26,34} Lys²³ GLP-1(8-38);
 Ser⁸ Asp²² Arg^{26,34} Lys²³ GLP-1(8-38); Arg^{26,34} Lys²⁷-
 GLP-1(8-36); Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Arg^{26,34} Lys²⁷ GLP-1(8-37); Arg^{26,34} Lys²⁷ GLP-1
 (8-38); Ser⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36);
 Ser⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36); 30
 Ser⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Ser⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Ser⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-37);
 Ser⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-38);
 Ser⁸ Asp²⁶ Arg^{26,34} Lys²⁷ GLP-1(8-38); Arg^{26,34} Lys¹⁸-
 GLP-1(8-36); Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Arg^{26,34} Lys¹⁸ GLP-1(8-37); Arg^{26,34} Lys¹⁸ GLP-1
 (8-38); Thr⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸-GLP-1(8-36);
 Thr⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸-GLP-1(8-36);
 Thr⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Thr⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸-GLP-1(8-36)amide;
 Thr⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸ GLP-1(8-37);
 Thr⁸ Asp¹⁹ Arg^{26,34} Lys¹⁸ GLP-1(8-38);
 Thr⁸ Asp¹⁷ Arg^{26,34} Lys¹⁸ GLP-1(8-38); Arg^{26,34} Lys²³-
 GLP-1(8-36); Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Arg^{26,34} Lys²³ GLP-1(8-37); Arg^{26,34} Lys²³ GLP-1
 (8-38); Thr⁸ Asp²⁴ Arg^{26,34} Lys²³-GLP-1(8-36);
 Thr⁸ Asp²² Arg^{26,34} Lys²³-GLP-1(8-36); 45
 Thr⁸ Asp²⁴ Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Thr⁸ Asp²² Arg^{26,34} Lys²³-GLP-1(8-36)amide;
 Thr⁸ Asp²⁴ Arg^{26,34} Lys²³ GLP-1(8-37);
 Thr⁸ Asp²⁴ Arg^{26,34} Lys²³ GLP-1(8-38); 50
 Thr⁸ Asp²² Arg^{26,34} Lys²³ GLP-1(8-38); Arg^{26,34} Lys²⁷-
 GLP-1(8-36); Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Arg^{26,34} Lys²⁷ GLP-1(8-37); Arg^{26,34} Lys²⁷ GLP-1
 (8-38); Thr⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36); 55
 Thr⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36);
 Thr⁸ Asp²⁸ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Thr⁸ Asp²⁶ Arg^{26,34} Lys²⁷-GLP-1(8-36)amide;
 Thr⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-37);
 Thr⁸ Asp²⁸ Arg^{26,34} Lys²⁷ GLP-1(8-38); or 60
 Thr⁸ Asp²⁶ Arg^{26,34} Lys²⁷ GLP-1(8-38).

In a further preferred embodiment, the present invention relates to a GLP-1 derivative wherein the parent peptide is:

Arg²⁶ Lys³⁶-GLP-1(8-36); Arg³⁴ Lys³⁶-GLP-1(8-36);
 Arg²⁶ Lys³⁶-GLP-1(8-37); Arg³⁴ Lys³⁶-GLP-1(8-37); 65
 Arg²⁶ Lys³⁷-GLP-1(8-37); Arg³⁴ Lys³⁷-GLP-1(8-37);
 Arg²⁶ Lys³⁹-GLP-1(8-39); Arg³⁴ Lys³⁹-GLP-1(8-39);

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Arg^{26,34} Lys^{36,39}-GLP-1(8-39); Arg²⁶ Lys¹⁸-GLP-1
 (8-36); Arg³⁴ Lys¹⁸-GLP-1(8-36); Arg²⁶ Lys¹⁸ GLP-1
 (8-37); Arg³⁴ Lys¹⁸ GLP-1(8-37); Arg²⁶ Lys¹⁸ GLP-1
 (8-38); Arg³⁴ Lys¹⁸ GLP-1(8-38); Arg²⁶ Lys¹⁸ GLP-1
 (8-39); Arg³⁴ Lys¹⁸ GLP-1(8-39); Arg²⁶ Lys²³-GLP-1
 (8-36); Arg³⁴ Lys²³ GLP-1(8-36); Arg²⁶ Lys²³ GLP-1
 (8-37); Arg³⁴ Lys²³ GLP-1(8-37); Arg²⁶ Lys²³ GLP-1
 (8-38); Arg³⁴ Lys²³ GLP-1(8-38); Arg²⁶ Lys²³ GLP-1
 (8-39); Arg³⁴ Lys²³ GLP-1(8-39); Arg²⁶ Lys²⁷-GLP-1
 (8-36); Arg³⁴ Lys²⁷-GLP-1(8-36); Arg²⁶ Lys²⁷-GLP-1
 (8-37); Arg³⁴ Lys²⁷-GLP-1(8-37); Arg²⁶ Lys²⁷-GLP-1
 (8-38); Arg³⁴ Lys²⁷-GLP-1(8-38); Arg²⁶ Lys²⁷-GLP-1
 (8-39); Arg³⁴ Lys²⁷ GLP-1(8-39);
 Arg^{26,34} Lys^{18,36} GLP-1(8-36); Arg^{26,34} Lys¹⁸ GLP-1
 (8-37); Arg^{26,34} Lys^{18,37} GLP-1(8-37);
 Arg^{26,34} Lys^{18,38} GLP-1(8-38); Arg^{26,34} Lys^{18,39} GLP-1
 (8-39); Arg^{26,34} Lys^{23,36}-GLP-1(8-36); Arg^{26,34}
 Lys²³ GLP-1(8-37); Arg^{26,34} Lys^{23,37} GLP-1(8-37);
 Arg^{26,34} Lys^{23,38} GLP-1(8-38); Arg^{26,34} Lys^{23,39} GLP-1
 (8-39); Arg^{26,34} Lys^{27,36}-GLP-1(8-36); Arg^{26,34}
 Lys²⁷ GLP-1(8-37); Arg^{26,34} Lys^{27,37} GLP-1(8-37);
 Arg^{26,34} Lys^{27,38} GLP-1(8-38); Arg^{26,34} Lys^{27,39} GLP-1
 (8-39); Gly⁸ GLP-1(8-36); Gly⁸ GLP-1(8-37);
 Gly⁸ GLP-1(8-38); Gly⁸ GLP-1(8-39);
 Gly⁸ Arg²⁶ Lys³⁶-GLP-1(8-36); Gly⁸ Arg³⁴ Lys³⁶-GLP-
 1(8-36); Gly⁸ Arg²⁶ Lys³⁶-GLP-1(8-37);
 Gly⁸ Arg³⁴ Lys³⁶-GLP-1(8-37); Gly⁸ Arg²⁶ Lys³⁷-GLP-
 1(8-37); Gly⁸ Arg³⁴ Lys³⁷-GLP-1(8-37);
 Gly⁸ Arg²⁶ Lys³⁹-GLP-1(8-39); Gly⁸ Arg³⁴ Lys³⁹-GLP-
 1(8-39); Gly⁸ Arg^{26,34} Lys^{36,39}-GLP-1(8-39);
 Gly⁸ Arg²⁶ Lys¹⁸-GLP-1(8-36); Gly⁸ Arg³⁴ Lys¹⁸-GLP-
 1(8-36); Gly⁸ Arg²⁶ Lys³⁶-GLP-1(8-37);
 Gly⁸ Arg³⁴ Lys³⁶-GLP-1(8-37); Gly⁸ Arg²⁶ Lys³⁷-GLP-
 1(8-37); Gly⁸ Arg³⁴ Lys³⁷-GLP-1(8-37);
 Gly⁸ Arg²⁶ Lys³⁹-GLP-1(8-39); Gly⁸ Arg³⁴ Lys³⁹-GLP-
 1(8-39); Gly⁸ Arg^{26,34} Lys^{36,39}-GLP-1(8-39);
 Gly⁸ Arg²⁶ Lys¹⁸-GLP-1(8-36); Gly⁸ Arg³⁴ Lys¹⁸-GLP-
 1(8-36); Gly⁸ Arg²⁶ Lys¹⁸ GLP-1(8-37);
 Gly⁸ Arg³⁴ Lys¹⁸ GLP-1(8-37); Gly⁸ Arg²⁶ Lys¹⁸ GLP-1
 (8-38); Gly⁸ Arg³⁴ Lys¹⁸ GLP-1(8-38);
 Gly⁸ Arg²⁶ Lys¹⁸ GLP-1(8-39); Gly⁸ Arg³⁴ Lys¹⁸ GLP-1
 (8-39); Gly⁸ Arg²⁶ Lys²³-GLP-1(8-36);
 Gly⁸ Arg²⁶ Lys²³ GLP-1(8-37); Gly⁸ Arg³⁴ Lys²³ GLP-1
 (8-37); Gly⁸ Arg³⁴ Lys²³ GLP-1(8-37);
 Gly⁸ Arg²⁶ Lys²³ GLP-1(8-38); Gly⁸ Arg³⁴ Lys²³ GLP-1
 (8-38); Gly⁸ Arg²⁶ Lys²³ GLP-1(8-39);
 Gly⁸ Arg³⁴ Lys²³ GLP-1(8-39); Gly⁸ Arg²⁶ Lys²⁷-GLP-1
 (8-36); Gly⁸ Arg³⁴ Lys²⁷-GLP-1(8-36);
 Gly⁸ Arg²⁶ Lys²⁷ GLP-1(8-37); Gly⁸ Arg³⁴ Lys²⁷ GLP-1
 (8-37); Gly⁸ Arg²⁶ Lys²⁷ GLP-1(8-38);
 Gly⁸ Arg³⁴ Lys²⁷ GLP-1(8-38); Gly⁸ Arg²⁶ Lys²⁷ GLP-1
 (8-39); Gly⁸ Arg³⁴ Lys²⁷ GLP-1(8-39);
 Gly⁸ Arg^{26,34} Lys^{18,36}-GLP-1(8-36);
 Gly⁸ Arg^{26,34} Lys¹⁸ GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{18,37} GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{18,38} GLP-1(8-38);
 Gly⁸ Arg^{26,34} Lys^{18,39} GLP-1(8-39);
 Gly⁸ Arg^{26,34} Lys^{23,36}-GLP-1(8-36);
 Gly⁸ Arg^{26,34} Lys²³ GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{23,37} GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{23,38} GLP-1(8-38);
 Gly⁸ Arg^{26,34} Lys^{23,39} GLP-1(8-39);
 Gly⁸ Arg^{26,34} Lys^{27,36}-GLP-1(8-36);
 Gly⁸ Arg^{26,34} Lys²⁷ GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{27,37} GLP-1(8-37);
 Gly⁸ Arg^{26,34} Lys^{27,38} GLP-1(8-38);
 Gly⁸ Arg^{26,34} Lys^{27,39} GLP-1(8-39);
 Val⁸ GLP-1(8-36); Val⁸ GLP-1(8-37);
 Val⁸ GLP-1(8-38); Val⁸ GLP-1(8-39);
 Val⁸ Arg²⁶ Lys³⁶-GLP-1(8-36); Val⁸ Arg²⁶ Lys³⁶-GLP-1
 (8-37); Val⁸ Arg³⁴ Lys³⁶-GLP-1(8-37);
 Val⁸ Arg²⁶ Lys³⁷-GLP-1(8-37); Val⁸ Arg³⁴ Lys³⁷-GLP-1
 (8-37); Val⁸ Arg²⁶ Lys³⁹-GLP-1(8-39);
 Val⁸ Arg³⁴ Lys³⁹-GLP-1(8-39);

In a further preferred embodiment, the GLP-1 derivative is Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-35).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys^{26,34}-bis(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-36)amide.

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁸(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg^{26,34}Lys³⁸(N^ε-lithocholoyl)-GLP-1(7-37).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-38).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-38).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-38).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁸(N^ε-lithocholoyl)-GLP-1(7-38).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-38).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-39).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-39).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-39).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-39).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-39).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg²⁶Lys³⁴(N^ε-lithocholoyl)-GLP-1(7-40).

In a further preferred embodiment, the GLP-1 derivative is Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-40).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Lys²⁶(N^ε-lithocholoyl)Arg³⁴-GLP-1(7-40).

In a further preferred embodiment, the GLP-1 derivative is Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-40).

In a further preferred embodiment, the GLP-1 derivative is Gly⁸Arg^{26,34}Lys³⁶(N^ε-lithocholoyl)-GLP-1(7-40).

Other preferred embodiments will be described using the following abbreviations:

Glut=N^ε-(γ-L-glutamyl)

Aspa=N^ε-(β-L-asparagyl)

Glyc=N^ε-glycyl

GAB=N^ε-(α-(γ-aminobutanoyl)

ADod=N^α-dodecanoyl

ATet=N^α-tetradecanoyl

AHex=N^α-hexadecanoyl

AOct=N^α-octadecanoyl

ALit=N^α-lithocholyl

GDod=N^γ-dodecanoyl

GTet=N^γ-tetradecanoyl

GHex=N^γ-hexadecanoyl

GOct=N^γ-octadecanoyl

GLit=N^γ-lithocholyl

Other preferred GLP-1 derivatives of the present invention are:

Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-36); Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-36); Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-36)amide; Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-36)amide; Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-36)amide; Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-37); Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-37); Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-37); Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-38); Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-38); Arg^{26,34}Lys³⁸-(Glut-ADod)-GLP-1(7-38); Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-39); Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-39); Arg^{26,34}Lys³⁹-(Glut-ADod)-GLP-1(7-39);

Gly⁸Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-36); Gly⁸Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-36); Gly⁸Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-36); Gly⁸Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-36)amide; Gly⁸Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-36)amide; Gly⁸Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-36)amide; Gly⁸Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-37); Gly⁸Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-37); Gly⁸Arg^{26,34}Lys³⁶-(Glut-ADod)-GLP-1(7-37); Gly⁸Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-38); Gly⁸Arg³⁴Lys²⁶-(Glut-ADod)-GLP-1(7-38); Gly⁸Arg^{26,34}Lys³⁸-(Glut-ADod)-GLP-1(7-38); Gly⁸Arg²⁶Lys³⁴-(Glut-ADod)-GLP-1(7-39);

