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(54) **DOUBLE-ACYLATED GLP-1 DERIVATIVES**

(75) Inventors: **PATRICK WILLIAM GARIBAY**, HOLTE (DK); **JANE SPETZLER**, BRONSHOJ (DK); **JÁNOS TIBOR KODRA**, KOBENHAVN O (DK); **LARS LINDEROTH**, ALLEROD (DK); **JESPER LAU**, FARUM (DK); **PER SAUERBERG**, FARUM (DK)

(73) Assignee: **NOVO NORDISK A/S**, BAGSVAERD (DK)

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(57) **ABSTRACT**

The invention relates to a derivative of a GLP-1 analogue, which analogue comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1(7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}, which derivative comprises two albumin binding moieties attached to K^{26} and K^{37}, respectively, wherein the albumin binding moiety comprises a protracting moiety selected from:

$HOOC—(CH_2)_x—CO—*$ Chem. 1:

$HOOC—C_6H_4—O—(CH_2)_y—CO—*$ Chem. 2:

$R^1—C_6H_4—(CH_2)_z—CO—*$ Chem. 3:

$HOOC—C_4SH_2—(CH_2)_w—CO—*$ Chem. 4:

in which x is an integer in the range of 6-18, y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, and w is an integer in the range of 6-18; with the proviso that when the protracting moiety is Chem. 1, the albumin binding moiety further comprises a linker of formula Chem. 5: *—NH—$(CH_2)_2$—(O—$(CH_2)_2)_k$—O—$(CH_2)_n$—CO—*, wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5; or a pharmaceutically acceptable salt, amide, or ester thereof.

The invention also relates to the pharmaceutical use thereof, for example in the treatment and/or prevention of all forms of diabetes and related diseases, as well as to corresponding novel peptides and side chain intermediates. The derivatives are suitable for oral administration.

DOUBLE-ACYLATED GLP-1 DERIVATIVES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit under 35 U.S.C. 119 of Danish application EP09179390.1 filed Dec. 16, 2009, and of U.S. provisional application 61/288,601, filed Dec. 21, 2009, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to derivatives of Glucagon-Like Peptide 1 (GLP-1) and their pharmaceutical use, viz. to double-acylated GLP-1 derivatives acylated at position 26 and 37, and their pharmaceutical use.

INCORPORATION-BY-REFERENCE OF THE SEQUENCE LISTING

[0003] The Sequence Listing, entitled "SEQUENCE LISTING", is 1 kilobyte, was created on Dec. 16, 2010, and is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0004] Journal of Medicinal Chemistry (2000), vol. 43, no. 9, p. 1664-669 discloses derivatives of GLP-1(7-37) that are double-acylated at $K^{26,34}$—see Table 1.

[0005] WO 98/08871 discloses a number of GLP-1 derivatives including some that are double-acylated at $K^{26,34}$, see Examples 3, 7, 17, 24, 32, 33, and 36. Liraglutide, a mono-acylated GLP-1 derivative for once daily administration which is marketed as of 2009 by Novo Nordisk A/S, is also disclosed in WO 98/08871 (Example 37).

[0006] WO 99/43706 discloses a number of mono- and double-acylated GLP-1 derivatives including some $K^{26,37}$ derivatives (see p. 148-178).

[0007] WO 2005/027978 discloses a number of GLP-1 derivatives including a few that are double-acylated at one and the same residue, K^{37}, see Examples 8 and 9.

[0008] WO 2009/030738 discloses a number of GLP-1 derivatives including one double-acylated at K^{31}, Dap^{34}, see Example 37.

[0009] Journal of Controlled Release (2010), vol. 144, p. 10-16 relates to acylated exendin-4 analogs and discloses, among others, a double-acylated exendin-4 ($K^{12,27}$-diLUA-Exendin-4) is disclosed (LUA is lauric acid, C12).

[0010] WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S.

[0011] Angewandte Chemie International Edition 2008, vol. 47, p. 3196-3201 reports the discovery and characterisation of a class of 4-(p-iodophenyl)butyric acid derivatives which purportedly display a stable noncovalent binding interaction with both mouse serum albumin (MSA) and human serum albumin (HSA).

SUMMARY OF THE INVENTION

[0012] The invention relates to derivatives of GLP-1 peptides.

[0013] The derivatives are acylated at the native lysine at [illegible] moieties. They comprise a protracting moiety, preferably selected from fatty diacids, and fatty acids with a distal phenyl, phenoxy, or thiophene group, all optionally substituted. A carboxy group of the fatty acid or fatty diacid is acylated, optionally via a linker, to a lysine residue of the GLP-1 peptide, preferably at the epsilon-amino group thereof. The GLP-1 peptide may be an analogue of GLP-1(7-37) (SEQ ID NO: 1) having a total of up to ten amino acid differences as compared to GLP-1(7-37), for example one or more additions, one or more deletions, and/or one or more substitutions.

[0014] More in particular, the invention relates to a derivative of a GLP-1 analogue, which analogue comprises a first K residue at a position corresponding to position 37 of GLP-1 (7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1(7-37), and a maximum of ten amino acid modifications as compared to GLP-1 (7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}; which derivative comprises two albumin binding moieties attached to K^{26} and K^{37}, respectively, wherein each albumin binding moiety comprises a protracting moiety selected from Chem. 1, Chem. 2, Chem. 3, and Chem. 4:

HOOC—$(CH_2)_x$—CO—* Chem. 1:

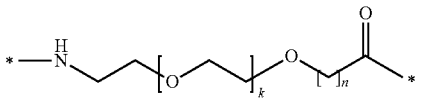
HOOC—C_6H_4—O—$(CH_2)_y$—CO—* Chem. 2:

R^1—C_6H_4—$(CH_2)_z$—CO—* Chem. 3:

HOOC—C_4SH_2—$(CH_2)_w$—CO—*, Chem. 4:

in which x is an integer in the range of 6-18, y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, and w is an integer in the range of 6-18; with the proviso that when the protracting moiety is Chem. 1, the albumin binding moiety further comprises a linker of formula Chem. 5:

Chem. 5:



wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5; or a pharmaceutically acceptable salt, amide, or ester thereof.

[0015] The invention also relates to such derivative for use as a medicament, in particular for use in the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, cardiovascular diseases, gastrointestinal diseases, diabetic complications, critical illness, and/or polycystic ovary syndrome; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

[0016] The invention furthermore relates to intermediate products in the form of GLP-1 peptides and side chains, which are relevant for the preparation of certain GLP-1 peptides and derivatives of the invention.

[0017] The derivatives of the invention are biologically active. Also, or alternatively, they have a protracted pharmacokinetic profile. Also, or alternatively, they are stable against [illegible]

are of importance in the development of next generation GLP-1 compounds for subcutaneous, intravenous, and/or in particular oral administration.

DESCRIPTION OF THE INVENTION

[0018] The invention relates to derivatives of GLP-1 peptides. The derivatives are acylated at the native lysine at position 26, as well as at a lysine substituted for the native glycine at position 37. The side chains are albumin binding moieties. They comprise a protracting moiety, preferably selected from fatty diacids, and fatty acids with a distal, or terminal, phenyl, thiophene, or phenoxy group, all optionally substituted. A carboxy group of the fatty acid or fatty diacid is acylated, optionally via a linker, to a lysine residue of the GLP-1 peptide, preferably at the epsilon-amino group thereof. The GLP-1 peptide may be an analogue of GLP-1(7-37) (SEQ ID NO: 1) having a total of up to ten amino acid differences as compared to GLP-1(7-37), for example one or more additions, one or more deletions, and/or one or more substitutions.

[0019] More in particular, in a first aspect, the invention relates to a derivative of a GLP-1 analogue, which analogue comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1 (7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}, which derivative comprises two albumin binding moieties attached to K^{26} and K^{37}, respectively, wherein the albumin binding moiety comprises a protracting moiety selected from Chem. 1, Chem. 2, Chem. 3, and Chem. 4:

$HOOC—(CH_2)_x—CO—*$ Chem. 1:

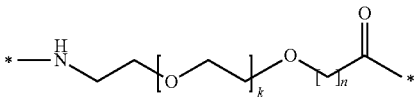
$HOOC—C_6H_4—O—(CH_2)_y—CO—*$ Chem. 2:

$R^1—C_6H_4—(CH_2)_z—CO—*$ Chem. 3:

$HOOC—C_4SH_2—(CH_2)_w—CO—*$ Chem. 4:

in which x is an integer in the range of 6-18, y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, and w is an integer in the range of 6-18; with the proviso that when the protracting moiety is Chem. 1, the albumin binding moiety further comprises a linker of formula Chem. 5:

Chem. 5:



wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5; or a pharmaceutically acceptable salt, amide, or ester thereof.

[0020] Thus, in a first aspect, the invention relates to a derivative of a GLP-1 analogue, wherein the GLP-1 analogue comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1 (7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}, which derivative comprises two albumin binding moieties attached to K^{26} and K^{37}, respectively, wherein the albumin binding moiety comprises a protracting moiety selected from Chem. 2, Chem. 3, and Chem. 4:

$HOOC—C_6H_4—O—(CH_2)_y—CO—*$ Chem. 2:

$R^1—C_6H_4—(CH_2)_z—CO—*$ Chem. 3:

$HOOC—C_4SH_2—(CH_2)_w—CO—*$ Chem. 4:

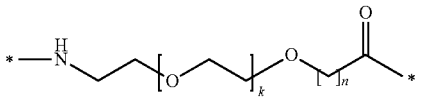
in which y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, and w is an integer in the range of 6-18; or a pharmaceutically acceptable salt, amide, or ester thereof.

[0021] In a second aspect, the invention relates to a derivative of a GLP-1 analogue, wherein the GLP-1 analogue comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1(7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}, which derivative comprises two albumin binding moieties attached to K^{26} and K^{37}, respectively, wherein the albumin binding moiety comprises i) a protracting moiety of formula Chem. 1:

$HOOC—(CH_2)_x—CO—*$ Chem. 1:

in which x is an integer in the range of 6-18; and ii) a linker of formula Chem. 5:

Chem. 5:



wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5;

or a pharmaceutically acceptable salt, amide, or ester thereof.

[0022] In a third aspect, the invention relates to a derivative of a GLP-1 analogue, wherein the GLP-1 analogue comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1(7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}; which derivative comprises two protracting moieties attached to K^{26} and K^{37}, respectively, via a linker, wherein the protracting moiety is selected from Chem. 1, Chem. 2, Chem. 3, and Chem. 4:

$HOOC—(CH_2)_x—CO—*$ Chem. 1:

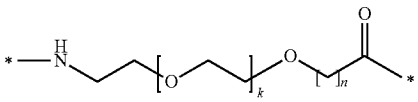
$HOOC—C_6H_4—O—(CH_2)_y—CO—*$ Chem. 2:

$R^1—C_6H_4—(CH_2)_z—CO—*$ Chem. 3:

$HOOC—C_4SH_2—(CH_2)_w—CO—*$ Chem. 4:

in which x is an integer in the range of 6-18, y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, and w is

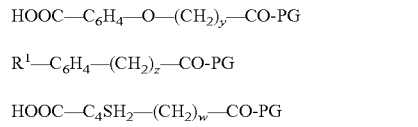
Chem. 5:



wherein k is an integer in the range of 1-5, and n is an integer in the range of 1-5; or a pharmaceutically acceptable salt, amide, or ester thereof.

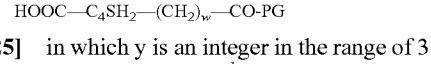
[0023] The invention also relates to an intermediate product in the form of a GLP-1 analogue which comprises the following modifications as compared to GLP-1(7-37) (SEQ ID NO: 1): (i) (8Aib, 31H, 34Q, 37K); (ii) (des7-8, 34R, 37K, 38E); (iii) (des7-8, 34R, 37K); (iv) (8Aib, 9G, 34R, 37K); (v) (8Aib, 23R, 34R, 37K); (vi) (31H, 34Q, 37K); (vii) (9Q, 34R, 37K); (iix) (30E, 34R, 37K); (ix) (34R, 37K, 38G); (x) (34R, 36G, 37K); or (xi) (34R, 37K, 38E); or a pharmaceutically acceptable salt, amide, or ester of any of the analogues thereof.

[0024] The invention also relates to an intermediate product comprising a protracting moiety selected from Chem. 2c, Chem. 3b, and Chem. 4b:



Chem. 2c:

Chem. 3b:



Chem. 4b:

[0025] in which y is an integer in the range of 3-17, z is an integer in the range of 1-5, R^1 is a group having a molar mass not higher than 150 Da, w is an integer in the range of 6-18, and *—CO-PG is an activated ester; wherein, optionally, the distal *—COOH group of the protracting moiety, if present, is functionalised as a non-reactive ester; or a pharmaceutically acceptable salt, amide, or ester thereof.

[0026] And finally the invention also relates to the pharmaceutical use of the analogues and derivatives of the invention, in particular for use in the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, cardiovascular diseases, gastrointestinal diseases, diabetic complications, critical illness, and/or polycystic ovary syndrome; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

[0027] In what follows, Greek letters may be represented by their symbol or the corresponding written name, for example: α=alpha; β=beta; ϵ=epsilon; γ=gamma; ω=omega; etc. Also, the Greek letter of μ my be represented by "u", e.g. in μl=ul, or in μM=uM.

[0028] An asterisk (*) in a chemical formula designates i) a point of attachment, ii) a radical, and/or iii) an unshared electron.

GLP-1 Analogues

[0029] The term "GLP-1 analogue" or "analogue of GLP-1" as used herein refers to a peptide, or a compound, which is a variant of the human Glucagon-Like Peptide-1 (GLP-1(7-37)), the sequence of which is included in the sequence listing as SEQ ID NO: 1. The peptide having the sequence of SEQ ID NO: 1 may also be designated "native" GLP-1.

[0030] In the sequence listing, the first amino acid residue of SEQ ID NO: 1 (histidine) is assigned number 1. However, in this description, this histidine residue is referred to as no. 7, and subsequent amino acid residues are numbered accordingly, ending with glycine no. 37. Therefore, generally, any reference herein to an amino acid residue number or a position number of the GLP-1(7-37) sequence is to the sequence starting with His at position 7 and ending with Gly at position 37.

[0031] GLP-1 analogues of the derivatives of the invention may be described by reference to i) the number of the amino acid residue in native GLP-1(7-37) which corresponds to the amino acid residue which is modified (i.e., the corresponding position in native GLP-1), and to ii) the actual modification. The following are non-limiting examples of suitable analogue nomenclature.

[0032] A non-limiting example of a GLP-1 analogue of the derivative of the invention is an analogue that only is modified so as to comprise a first lysine residue at a position corresponding to position 37 of GLP-1(7-37). The amino acid sequence of this analogue is otherwise identical to that of native GLP-1, and this analogue may be designated K^{37}-GLP-1(7-37). This designation represents the amino acid sequence of native GLP-1 where glycine at position 37 has been substituted with lysine.

[0033] This GLP-1 analogue of the derivative of the invention furthermore comprises a second lysine residue at a position corresponding to position 26 of GLP-1(7-37). As the amino acid sequence of this analogue is otherwise identical to that of native GLP-1, such analogue is, still, designated K^{37}-GLP-1(7-37), as K^{26} is implied by the reference to native GLP-1(7-37), SEQ ID NO: 1.

[0034] Accordingly, K^{37}-GLP-1(7-37) designates a GLP-1 (7-37) analogue wherein the naturally occurring glycine at position 37 has been substituted with lysine.

[0035] The term "analogue of K^{37}-GLP-1(7-37)" refers to an analogue of GLP-1(7-37) which comprises the modification K^{37} and at least one additional modification, as compared to GLP-1(7-37).

[0036] The GLP-1 analogue forming part of the derivative of the invention comprises a first K residue at a position corresponding to position 37 of GLP-1(7-37) (SEQ ID NO: 1), a second K residue at a position corresponding to position 26 of GLP-1(7-37), and a maximum of ten amino acid modifications as compared to GLP-1(7-37), wherein the first K residue is designated K^{37}, and the second K residue is designated K^{26}. In other words, it is a modified GLP-1(7-37) peptide in which a number of amino acid residues have been changed when compared to native GLP-1(7-37) (SEQ ID NO: 1). These changes, or modifications, may represent, independently, one or more amino acid substitutions, additions, and/or deletions.

[0037] Another non-limiting example of an analogue of a derivative of the invention is [Aib^8,Arg^{34},Lys^{37}]GLP-1(7-37), which designates a GLP-1(7-37) analogue, in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the lysine at position 34 has been substituted with arginine, and the glycine at position 37 has been substituted with lysine. This analogue may also be designated (8Aib, R34, K37) GLP-1(7-37).

[0038] An additional non-limiting example of an analogue of a derivative of the invention is an analogue "which comprises 34E, 34Q, or 34R" which refers to a GLP-1 analogue which has either a glutamic acid (E), a glutamine (Q), or an arginine (R) at a position corresponding to position 34 of

[0039] A still further non-limiting example of an analogue of a derivative of the invention is the analogue of GLP-1(7-37) (SEQ ID NO: 1) which is simply designated "(8Aib, 31H, 34Q, 37K)". This designation refers to an analogue which is identical to SEQ ID NO: 1 except for these four substitutions, i.e. an analogue in which the alanine at position 8 has been substituted with α-aminoisobutyric acid (Aib), the tryptophan at position 31 has been substituted with histidine, the lysine at position 34 has been substituted with glutamine, and the glycine at position 37 has been substituted with lysine. This analogue does not comprise further modifications as compared to SEQ ID NO: 1.

[0040] A still further non-limiting example of an analogue of a derivative of the invention is an analogue comprising des7 (or Des^7), which refers to an analogue of GLP-1(7-37) in which the N-terminal amino acid, histidine, has been deleted. This analogue may also be designated GLP-1(8-37).

[0041] Similarly, (des7+des8); (des7, des8); (des7-8); or (Des^7, Des^8) in relation to an analogue of GLP-1(7-37), where the reference to GLP-1(7-37) may be implied, refers to an analogue in which the amino acids corresponding to the two N-terminal amino acids of native GLP-1, histidine and alanine, have been deleted. This analogue may also be designated GLP-1(9-37).

[0042] A still further non-limiting example of an analogue of a derivative of the invention is an analogue comprising Imp^7, and/or (Aib^8 or S^8), which refers to a GLP-1(7-37) analogue, which, when compared to native GLP-1, comprises a substitution of histidine at position 7 with imidazopropionic acid (Imp); and/or a substitution of alanine at position 8 with α-aminoisobutyric acid (Aib), or with serine.

[0043] Analogues "comprising" certain specified modifications may comprise further modifications, when compared to SEQ ID NO: 1. Two examples, non-limiting, of analogues comprising Imp', and/or (Aib^8 or S^8), and forming part of derivatives of the invention are the peptide parts of Chem. 47 and Chem. 58.

[0044] Non-limiting examples of an analogue of GLP-1(7-37) comprising (des7+des8), Arg34, Lys37, and Glu38 are the following: [Des^7, Des^8,Arg^{34},Lys^{37}]GLP-1(7-37)-Glu^{38} peptide; and N^9-{2-[2-(1H-Imidazol-4-yl)-ethylcarbamoyl]-2-methyl-propionyl}[Arg^{34}, Lys^{37}]GLP-1(9-37)Glu^{38}-peptide. In the latter compound a dipeptide mimetic of the N-terminus of native GLP-1 (His-Ala) is attached to the new N-terminus, Glu 9, via an amide bond.

[0045] Suitable His- or His-Ala mimetics that may be used as a kind of a substitute for the deleted N-terminal amino acids, if any, comprise a heterocyclic, nitrogen-containing, aromatic ring structure, e.g. pyridine or imidazole. Preferred His- or His-Ala mimetics are derivatives of an imidazole or a pyridine, other than His and His-Ala, in one embodiment having a substituent with a free carboylic acid group, which can form an amide bond with an amino group of the N-terminal amino acid of the peptide. The term imidazole refers to imidazoles as a class of heterocycles with similar ring structure but varying substituents, and vice-versa for pyridine.

[0046] As is apparent from the above examples, amino acid residues may be identified by their full name, their one-letter code, and/or their three-letter code. These three ways are fully equivalent.

[0047] The expressions "a position equivalent to" or "corresponding position" may be used to characterise the site of modification in a modified GLP-1(7-37) sequence of

corresponding positions, as well as the number of modifications, are easily deduced, e.g. by simple handwriting and eyeballing; and/or a standard protein or peptide alignment program may be used, such as "align" which is a Needleman-Wunsch alignment. The algorithm is described in Needleman, S. B. and Wunsch, C. D., (1970), Journal of Molecular Biology, 48: 443-453, and the align program by Myers and W. Miller in "Optimal Alignments in Linear Space" CABIOS (computer applications in the biosciences) (1988) 4:11-17. For the alignment, the default scoring matrix BLOSUM50 and the default identity matrix may be used, and the penalty for the first residue in a gap may be set at −12, or preferably at −10, and the penalties for additional residues in a gap at −2, or preferably at −0.5.

[0048] An example of such alignment is inserted hereinbelow, in which sequence no. 1 is SEQ ID NO: 1, and sequence no. 2 is the analogue (des7-8, 34R, 37K, 38E) thereof:

```
# 1: GLP-1 (7-37)
# 2: GLP-1 (7-37)_Analogue
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
# Length: 32
# Identity: 27/32 (84.4%)
# Similarity: 28/32 (87.5%)
# Gaps: 3/32 (9.4%)
# Score: 138.0


1     1 HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG- 31
            |||||||||||||||||||||||||:||.
2     1 --EGTFTSDVSSYLEGQAAKEFIAWLVRGRKE 30
```

[0049] In case of non-natural amino acids such as Imp and/or Aib being included in the sequence, or in case of His-Ala mimetics, these may, for alignment purposes, be replaced with X. If desired, X can later be manually corrected.

[0050] The term "peptide", as e.g. used in the context of the GLP-1 analogues of the derivatives of the invention, refers to a compound which comprises a series of amino acids interconnected by amide (or peptide) bonds.

[0051] In a particular embodiment the peptide is to a large extent, or predominantly, composed of amino acids interconnected by amide bonds (e.g., at least 50%, 60%, 70%, 80%, or at least 90%, by molar mass). In another particular embodiment the peptide consists of amino acids interconnected by peptide bonds.

[0052] The peptides of the invention comprise at least five constituent amino acids connected by peptide bonds. In particular embodiments the peptide comprises at least 10, preferably at least 15, more preferably at least 20, even more preferably at least 25, or most preferably at least 28 amino acids.

[0053] In particular embodiments, the peptide is composed of at least five constituent amino acids, preferably composed of at least 10, at least 15, at least 20, at least 25, or most preferably composed of at least 28 amino acids.

[0054] In additional particular embodiments, the peptide is a) composed of, or b) consists of, i) 29, ii) 30, iii) 31, or iv) 32 amino acids.

[0055] In a still further particular embodiment the peptide consists of amino acids interconnected by peptide bonds.

[0056] Amino acids are molecules containing an amine

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