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(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK–2880 Bagsvaerd (DK).

(72) Inventors: KNUDSEN, Liselotte, Bjerre; Valby Langgade 49A, 1. tv., DK–2500 Valby (DK). HUUSFELDT, Per, Olaf; Applebys Plads 27,5. mf., DK–1411 Copenhagen K (DK). NIELSEN, Per, Franklin; Dalsø Park 59, DK–3500 Værløse (DK). MADSEN, Kjeld; Nyvestergårdsvej 3, DK–3500 Værløse (DK).

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(54) Title: N–TERMINALLY MODIFIED GLP–1 DERIVATIVES

(57) Abstract

The present invention relates to N–terminally modified derivatives of human glucagon–like peptide–1 (GLP–1) and analogues thereof having a protracted profile of action, as well as the use of such derivatives in pharmaceutical compositions for the treatment of obesity, insulin dependent or non–insulin dependent diabetes mellitus. The GLP–1 derivatives have a lipophilic substituent attached to at least one amino acid residue and are substituted at the N–terminal end with a substituent comprising an optionally substituted 5– or 6–membered ring system, e.g. an imidazole.

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N-TERMINALLY MODIFIED GLP-1 DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments and analogues thereof having a protracted profile of action and to the use of such derivatives in pharmaceutical compositions.

BACKGROUND OF THE INVENTION

GLP-1 (Glucacon-Like-Peptide-1) is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism. Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised *i.a.* in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1(7-36)amide, GLP-1(7-37) and GLP-2 occurs mainly in the L-cells.

WO 87/06941 (The General Hospital Corporation) disclose peptide fragments which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulinotropic agent.

WO 90/11296 (The General Hospital Corporation) disclose peptide fragments which comprise GLP-1(7-36) and functional derivatives thereof and have an insulinotropic activity which exceeds the insulinotropic activity of GLP-1(1-36) or GLP-1(1-37) and to their use as insulinotropic agents.

The amino acid sequence of GLP-1(7-36)amide and GLP-1(7-37) is:

```
  7   8   9  10  11  12  13  14  15  16  17  18  19  20  21  22  23
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-

 24  25  26  27  28  29  30  31  32  33  34  35  36                (I)
Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X
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wherein X is NH_2 for GLP-1(7-36)amide and X is Gly-OH for GLP-1(7-37).

WO 91/11457 (Buckley *et al.*) discloses analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37.

WO 98/08871 discloses GLP-1 derivatives in which a lipophilic substituent is attached to at least one amino acid residue. The lipophilic substituents are in particular long-chain groups containing e.g. 12-24 carbon atoms.

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.

It is an object of the present invention to provide improved GLP-1 derivatives.

SUMMARY OF THE INVENTION

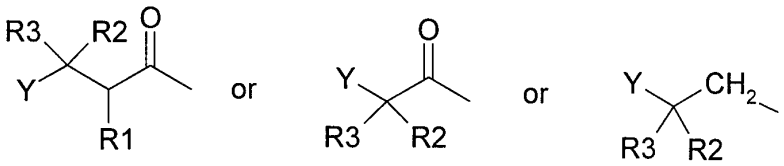
In its broadest aspect, the present invention relates to derivatives of GLP-1(7-B) and analogues thereof. The derivatives according to the invention have interesting pharmacological properties, including a protracted profile of action. The derivatives also are more metabolically and physically stable, and more soluble.

The GLP-1 derivatives and analogues of the present invention comprise a lipophilic substituent (optionally via a spacer) attached to at least one amino acid residue and the N-terminal amino acid, i.e., the histidine residue at position 7 is modified. The lipophilic substituent is in particular a long-chain group of the type described in WO 98/08871 (Novo Nordisk A/S), and the N-terminal substituent comprises an optionally substituted 5- or 6-membered ring system, e.g. an imidazole.

Accordingly, the invention relates to a GLP-1 derivative comprising a parent peptide of formula II

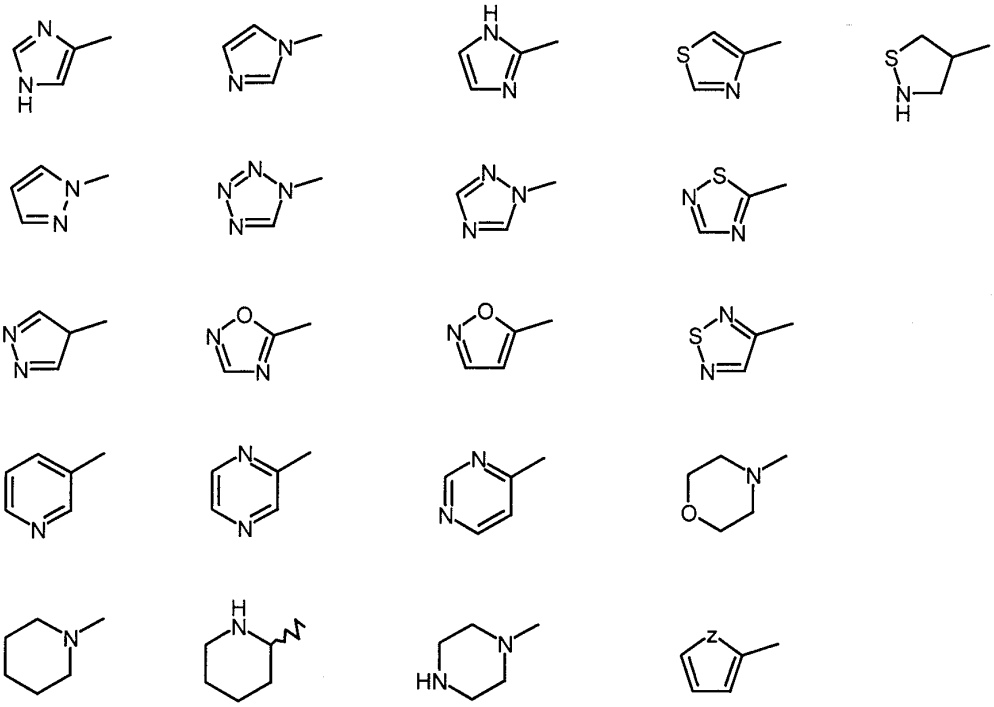
A–HN-GLP-1(8-B)-X (II)

wherein

A is: 

wherein R^1, R^2 and R^3 are independently H, lower alkyl having 1 to 6 carbon atoms, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy having 1 to 6 carbon atoms, halogen, SO_2-(lower alkyl) or CF_3, said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl or lower alkoxy having 1-6 carbon atoms, halogen, SO_2-(lower alkyl), NH-CO-(lower alkyl) or CF_3, or R^1 and R^2 may together form a bond;

Y is a five or six membered ring system selected from the group consisting of:



wherein Z is N, O or S, said ring system is optionally substituted with one or more functional groups selected from the group consisting of NH_2, NO_2, OH, lower alkyl, lower alkoxy, halogen, CF_3 and aryl;

B is an integer in the range of 35-45; and

X is –OH, –NH_2, or a C_{1-6} alkyl amide or C_{1-6} dialkyl amide group;

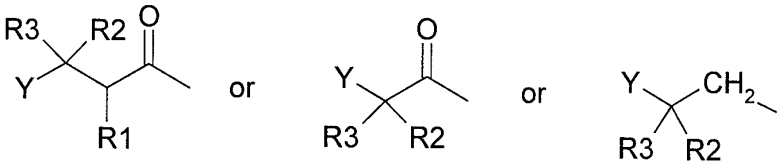
or an analogue thereof;

said GLP-1 derivative or analogue comprising a lipophilic substituent attached to at least one amino acid residue thereof.

In particular, the invention relates to GLP-1 derivatives of formula II

A–HN-GLP-1(8-B)-X (II)

wherein

A is: 

wherein R^1, R^2 and R^3 are independently H, lower alkyl, optionally substituted phenyl, NH_2, NH-CO-(lower alkyl), -OH, lower alkoxy, halogen, SO_2-(lower alkyl) or CF_3, wherein said phenyl is optionally substituted with at least one group selected from NH_2, -OH, lower alkyl or lower alkoxy

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