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(54) **Title**: GLP-1 RECEPTOR AGONIST COMPOUNDS WITH A MODIFIED N-TERMINUS

(57) **Abstract**: The invention relates to GLP-1 receptor agonist compounds with a modified N- terminus. The compounds are of the formula Chem. 1: Y-Z-P, wherein P represents a fragment of a GLP-1 receptor agonist peptide lacking the two N-terminal amino acid residues; and Y-Z represents novel His-Ala mimetics. Examples of GLP-1 receptor agonist compounds are derived from human GLP-1 (7-37), exendin-4(1-39), or GLP-1 A (1-37). The invention also relates to derivatives of these compounds, in particular compounds with one or more albumin binding side chains capable of protracting the duration of action in vivo of these compounds. The peptides and derivatives of the invention have a good potency, a protracted pharmacokinetic profile, are stable against degradation by gastro intestinal enzymes, and/or have a high oral bioavailability. These properties are of importance in the development of GLP-1 receptor agonist compounds for subcutaneous, intravenous, and/or in particular oral administration. The invention also relates to intermediate products for use in the preparation of the GLP-1 receptor agonist compounds of the inven-

# GLP-1 RECEPTOR AGONIST COMPOUNDS WITH A MODIFIED N-TERMINUS

## FIELD OF THE INVENTION

The present invention relates to analogues and derivatives of GLP-1 receptor agonist peptides, and their pharmaceutical use. In the GLP-1 receptor agonist peptides of the invention, such as Glucagon-Like Peptide-1 (GLP-1), exendins and analogues thereof, the two N-terminal amino acids have been replaced by N-terminal mimetics.

## INCORPORATION-BY-REFERENCE OF THE SEQUENCE LISTING

The Sequence Listing, entitled "SEQUENCE LISTING", is 1770 bytes, was created on 01-DEC-2010, and is incorporated herein by reference.

## BACKGROUND OF THE INVENTION

WO 2004/067548 A2 relates to chemically modified metabolites of regulatory peptides and methods of producing and using same.

Liraglutide, a GLP-1 derivative for once daily administration which is marketed by Novo Nordisk A/S, is disclosed in Example 37 of WO 98/08871.

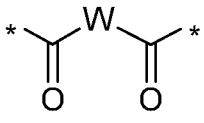
Semaglutide, a GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S, is disclosed in Example 4 of WO 06/097537.

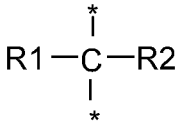
## SUMMARY OF THE INVENTION

The invention relates to GLP-1 receptor agonist compounds comprising a modified N-terminus.

Preferred compounds have the formula Chem. 1: Y-Z-P, wherein P represents a fragment of a GLP-1 receptor agonist peptide lacking the N-terminus; and Y-Z represents a group mimicing the N-terminus of the peptide. The new N-terminal is preferably a His-Ala, a His-Gly, and/or a His-Ser mimetic.

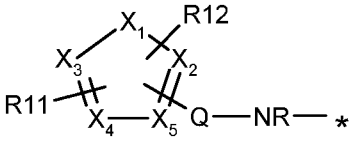
More in particular the invention relates to a GLP-1 receptor agonist peptide having the formula Chem. 1: Y-Z-P, wherein P represents a fragment of a GLP-1 receptor agonist peptide lacking the two N-terminal amino acid residues; Z represents a group of the formula

Chem. 2: 

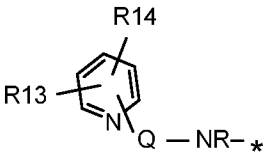
, wherein W represents a group of formula Chem. 3: 

, wherein R1 and R2 independently represent (i) hydrogen, alkyl, aryl, heterocyclyl, heteroaryl,

halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl, or R1 and R2 together form (ii) cyclo alkyl, heterocyclyl, or heteroaryl; and Y represents a group of formula Chem. 4:




, or Chem. 5:




, wherein $X_1$ is N, O, or S; $X_2$, $X_3$, $X_4$, and $X_5$ independently represent C, or N, with the proviso that at least one of $X_2$, $X_3$, $X_4$ and $X_5$ is C; R11, R12, R13, and R14 independently represent hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl; Q represents a bond, or a group of formula Chem. 6:*-$(C(R15)(R16))_q$-* , wherein q is 1-6, and R15 and R16 independently of each other and independently for each value of q represent hydrogen, alkyl, carboxyl, or hydroxyl; and R represents hydrogen, or alkyl; or a pharmaceutically acceptable salt, amide, or ester thereof.

The invention also relates to a derivative of this peptide, and a pharmaceutically acceptable salt, amide, or ester thereof.

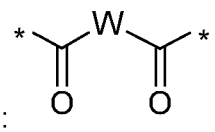
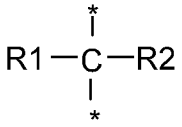
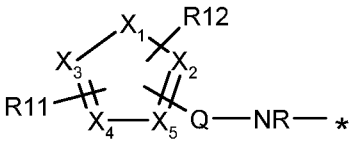
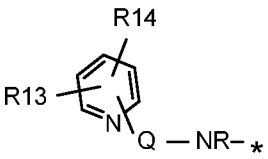
The invention also relates to the pharmaceutical use of these compounds, preferably for the treatment and/or prevention of all forms of diabetes and related diseases, such as eating disorders, cardiovascular diseases, gastrointestinal diseases, diabetic complications, critical illness, and/or polycystic ovary syndrome; and/or for improving lipid parameters, improving β-cell function, and/or for delaying or preventing diabetic disease progression.

Finally, the invention relates to intermediate products corresponding to the new N-terminus, as well as to the peptide fragments, i.e. before attachment of the new N-terminus, both relevant for the preparation of the peptides of the invention.

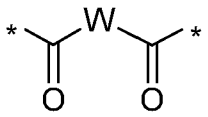
The peptides and derivatives of the invention are biologically active, preferably of a high potency. Also, or alternatively, they have a protracted pharmacokinetic profile. Also, or alternatively, they are stable against degradation by gastro intestinal enzymes. Also, or alternatively, they have a high oral bioavailability. These properties are of importance in the

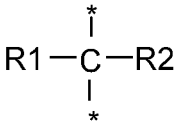
development of next generation GLP-1 compounds for subcutaneous, intravenous, and/or in particular oral administration.

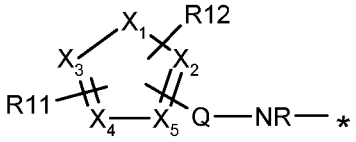
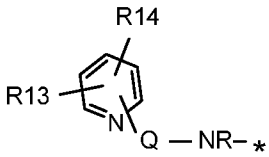
## DESCRIPTION OF THE INVENTION

The invention relates to a GLP-1 receptor agonist peptide having the formula Chem. 1: Y-Z-P, wherein P represents a fragment of a GLP-1 receptor agonist peptide lacking the two N-terminal amino acid residues; Z represents a group of the formula Chem. 2:  , wherein W represents a group of formula Chem. 3:  , wherein R1 and R2 independently represent (i) hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl, or R1 and R2 together form (ii) cyclo alkyl, heterocyclyl, or heteroaryl; and Y represents a group of formula Chem. 4:  , or Chem. 5:  , wherein $X_1$ is N, O, or S; $X_2$, $X_3$, $X_4$, and $X_5$ independently represent C, or N, with the proviso that at least one of $X_2$, $X_3$, $X_4$ and $X_5$ is C; R11, R12, R13, and R14 independently represent hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl; Q represents a bond, or a group of formula Chem. 6:*-(C(R15)(R16))$_q$-* , wherein q is 1-6, and R15 and R16 independently of each other and independently for each value of q represent hydrogen, alkyl, carboxyl, or hydroxyl; and R represents hydrogen, or alkyl; or a pharmaceutically acceptable salt, amide, or ester thereof.

In a first aspect, R1 and R2 do not both represent hydrogen, and the invention accordingly relates to a GLP-1 receptor agonist peptide having the formula Chem. 1: Y-Z-P, wherein P represents a fragment of a GLP-1 receptor agonist peptide lacking the two N-

terminal amino acid residues; Z represents a group of the formula Chem. 2:  ,



wherein W represents a group of formula Chem. 3: , wherein R1 and R2 independently represent (i) hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl, or R1 and R2 together form (ii) cyclo alkyl, heterocyclyl, or heteroaryl, with the proviso that (iii) R1 and R2 do not both represent hydrogen; and Y represents a group of formula Chem. 4:  , or Chem. 5:  , wherein $X_1$ is N, O, or S; $X_2$, $X_3$, $X_4$, and $X_5$ independently represent C, or N, with the proviso that at least one of $X_2$, $X_3$, $X_4$ and $X_5$ is C; R11, R12, R13, and R14 independently represent hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxylalkyl, cyano, amino, aminoalkyl, carboxyl, carboxylalkyl, alkoxy, aryloxy, carboxamide, substituted carboxamide, alkyl ester, aryl ester, alkyl sulfonyl, or aryl sulfonyl; Q represents a bond, or a group of formula Chem. 6:*-$(C(R15)(R16))_q$-* , wherein q is 1-6, and R15 and R16 independently of each other and independently for each value of q represent hydrogen, alkyl, carboxyl, or hydroxyl; and R represents hydrogen, or alkyl; or a pharmaceutically acceptable salt, amide, or ester thereof.

In a second aspect, R1 and R2 may both represent hydrogen, and Q-NR-* is not attached to a nitrogen atom of Chem. 4.

In a third aspect, R1 and R2 may both represent hydrogen, and Q-NR-* is attached to a carbon atom of Chem. 4.

The invention also relates to a derivative of each of these peptides, and to pharmaceutically acceptable salts, amides, or esters thereof.

The invention also relates to the pharmaceutical use of these compounds, preferably for 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

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