INTERMEDIATE FOR PREPARING GLUCAGON AND GLP-1 DUAL AGONIST AND PREPARATION METHOD THEREFOR

CROSS REFERENCE TO RELATED APPLICATION

The application claims priority to Chinese application No. 202311494392.7, filed November 10, 2023, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

The present invention relates to an intermediate or a pharmaceutically acceptable salt thereof for preparing a compound that agonizes both a glucagon (Gcg) receptor and a glucagon-like peptide-1 (GLP-1) receptor, and a preparation method therefor, and specifically relates to an intermediate or a pharmaceutically acceptable salt thereof for preparing an oxyntomodulin/glucagon analog mazdutide, and a preparation method therefor.

BACKGROUND

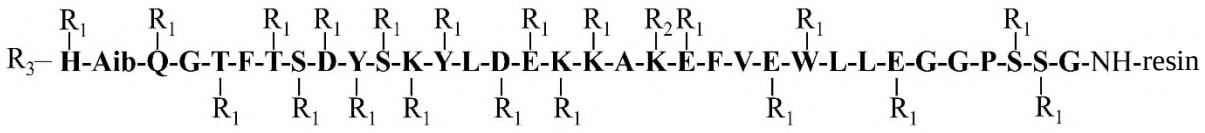
Mazdutide is a Gcg and GLP-1 dual agonist peptide that can be used for treating T2D and obesity, and is an oxyntomodulin/glucagon analog, which consists of a main peptide chain containing 34 amino acids and a side chain, wherein 2-aminoisobutyric acid (Aib) at position 2 is a non-natural amino acid, and the C-terminus is an amide; the side chain consists of two 2-(2-(2-aminoethoxy)ethoxy)acetic acid (AEEA) residues, one γ-Glu residue, one eicosanedioic acid residue; the side chain is connected to the Lys20 site of the main peptide chain via two 2-(2-(2-aminoethoxy)ethoxy)acetic acid (AEEA) residues. Methods for preparing such Gcg and GLP-1 dual agonist peptides are described in the prior art.

However, there is still a need for improved methods for preparing Gcg and GLP-1 dual agonist peptides that are more cost-effective, allowing for the generation of peptides with a variety of advantages including commercially desirable purity. At the same time, there is a need for faster and more stable methods, including stable compounds, to provide Gcg and GLP-1 dual agonist peptides with fewer or simpler preparation and/or purification steps. It is well known that there are a number of technical challenges in the preparation of such Gcg and GLP-1 dual agonist peptides that may affect overall yield and purity.

SUMMARY

In the present disclosure, a coupling of Fmoc-Gly-Gly-OH is used instead of a one-by-one coupling of Fmoc-Gly-OH in solid phase synthesis of peptides, and an OSU activated ester of a side chain synthesized by DIC/HOSu is directly coupled with a peptide chain, such that the reaction period is shortened, and possible racemization and impurities are reduced, resulting in fewer steps, while maintaining and improving quality and purity.

In one aspect, the present disclosure provides a method for preparing a compound of the following formula (SEQ ID NO: 1):



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the method comprising solid phase synthesis of the compound,

wherein, Fmoc-Gly-Gly-OH is used for the solid phase synthesis,

R_1 and R_3 are base-stable side-chain protecting groups, and

R_2 is an ivDde side-chain protecting group.

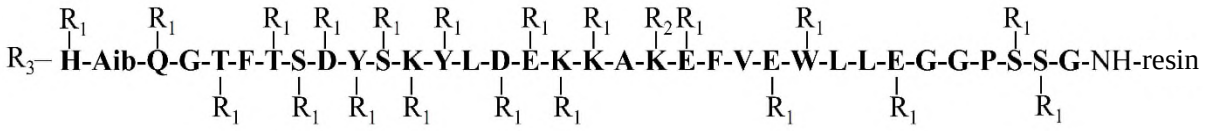
In one aspect, the present disclosure provides a method for preparing a compound of the following formula (SEQ ID NO: 2):

H-Aib-Q-G-T-F-T-S-D-Y-S-K-Y-L-D-E-K-K-A-K-E-F-V-E-W-L-L-E-G-G-P-S-S-G-NH_2

wherein, Lys at position 20 is chemically modified by conjugating an ε-amino group of a side chain of Lys at position 20 to ([2-(2-aminoethoxy)-ethoxy]-acetyl)-2-(γ-Glu)-CO-$(CH_2)_{18}CO_2H$,

the method comprising:

(i) solid phase synthesis of a compound of the following formula (SEQ ID NO: 1):



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wherein, Fmoc-Gly-Gly-OH is used for the solid phase synthesis,

R_1 and R_3 are base-stable side-chain protecting groups, and

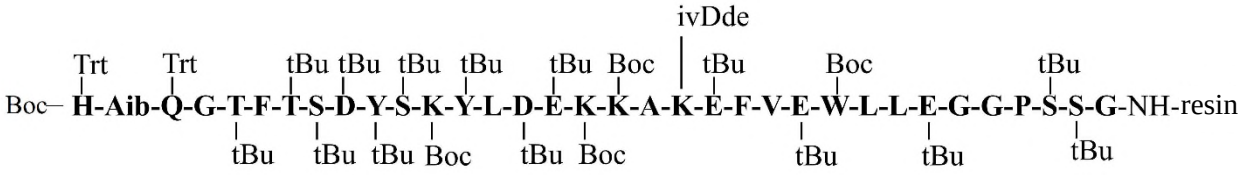
R_2 is an ivDde side-chain protecting group;

(ii) selective deprotection of Lys at position 20 and direct coupling of tBuO-C_{20}-γGlu(tBu)-AEEA-AEEA-OSu activated ester obtained via DIC/HOSu to an ε-amino group of a side chain of Lys at position 20;

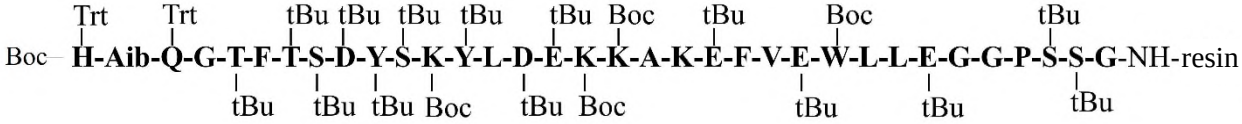
(iii) cleavage of the compound from a solid support and removal of the base-stable side-chain protecting groups; and

(iv) purification of the compound.

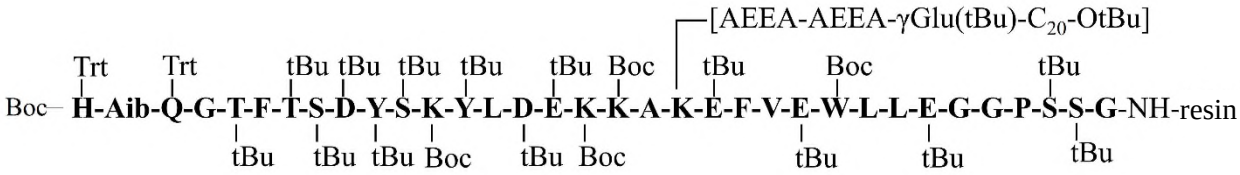
In another aspect, the present disclosure provides a compound of the following formula (I) (SEQ ID NO: 3) or a pharmaceutically acceptable salt thereof, a compound of the following formula (II) (SEQ ID NO: 4) or a pharmaceutically acceptable salt thereof, or a compound of the following formula (III) (SEQ ID NO: 5) or a pharmaceutically acceptable salt thereof:



formula (I)

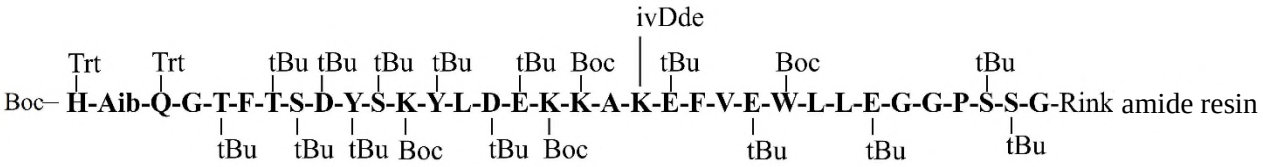


formula (II)

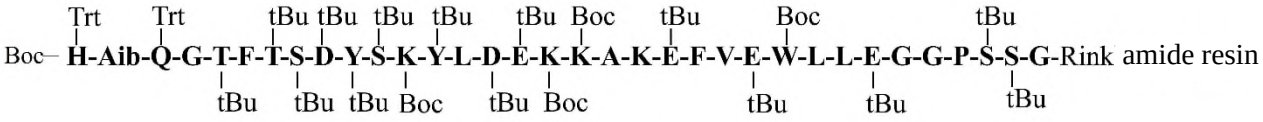


formula (III).

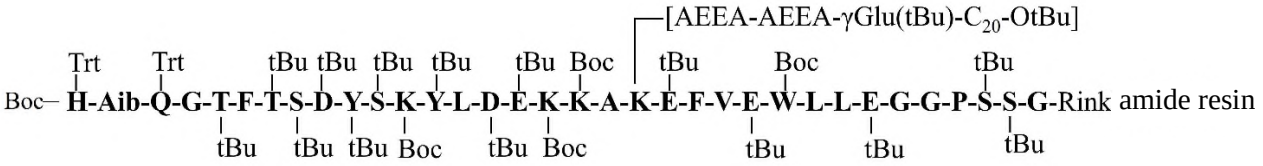
In some examples, the compound of formula (I) or the pharmaceutically acceptable salt thereof, the compound of formula (II) or the pharmaceutically acceptable salt thereof, or the compound of formula (III) or the pharmaceutically acceptable salt thereof is selected from the following compounds or pharmaceutically acceptable salts thereof:



(compound 2) (SEQ ID NO: 6),

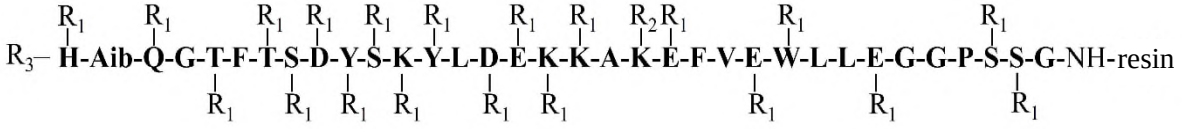


(compound 3) (SEQ ID NO: 7),



(compound 4) (SEQ ID NO: 8).

In another aspect, the present disclosure provides a compound of the following formula (SEQ ID NO: 1):



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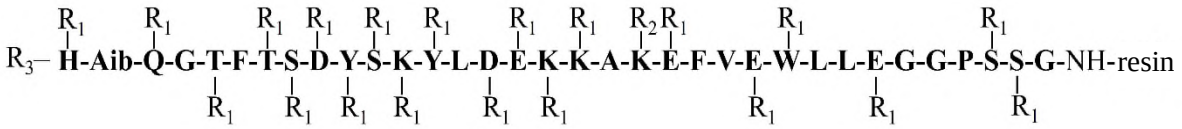
made by the method as described herein.

In another example, the present disclosure provides a compound of the following formula (SEQ ID NO: 1):



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made by a method comprising solid phase synthesis of the compound,

wherein, Fmoc-Gly-Gly-OH is used for the solid phase synthesis,

R_1 and R_3 are base-stable side-chain protecting groups, and

R_2 is an ivDde side-chain protecting group.

In another aspect, the present disclosure provides a compound of the following formula (SEQ ID NO: 2):

H-Aib-Q-G-T-F-T-S-D-Y-S-K-Y-L-D-E-K-K-A-K-E-F-V-E-W-L-L-E-G-G-P-S-S-G-NH_2

wherein, Lys at position 20 is chemically modified by conjugating an ε-amino group of a side chain of Lys at position 20 to ([2-(2-aminoethoxy)-ethoxy]-acetyl)-2-(γ-Glu)-CO-$(CH_2)_{18}CO_2H$,

made by the method as described herein.

In another example, the present disclosure provides a compound of the following formula (SEQ ID NO: 2):

H-Aib-Q-G-T-F-T-S-D-Y-S-K-Y-L-D-E-K-K-A-K-E-F-V-E-W-L-L-E-G-G-P-S-S-G-NH_2

wherein, Lys at position 20 is chemically modified by conjugating an ε-amino group of a side chain of Lys at position 20 to ([2-(2-aminoethoxy)-ethoxy]-acetyl)-2-(γ-Glu)-CO-$(CH_2)_{18}CO_2H$,