The insulinotropic derivatives according to the present invention are not disclosed by former inventors, or are broadly disclosed without any specific amino acid sequences and their activities are never compared to those of the native exendon-4, other derivatives and variants. Therefore, it never be expected that exendin-4 derivatives whose alpha amino group or alpha carbon of N-terminus is substituted or deleted exert remarkably excellent activities. Accordingly, the excellent stability in serum and insulinotropic activity of the insulinotropic peptide derivatives according to the present invention maximize a therapeutic effect on type 2 diabetes.

[Mode for Invention]

Hereinafter, a better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as the limit of the present invention.

The insulinotropic derivatives according to the present invention are not disclosed by former inventors, or are broadly disclosed without any specific amino acid sequences and their activities are never compared to those of the native exendon-4, other derivatives and variants. Therefore, it never be expected that exendin-4 derivatives whose alpha amino group or alpha carbon of N-terminus is substituted or deleted exert remarkably excellent activities. Accordingly, the excellent stability in serum and insulinotropic activity of the insulinotropic peptide derivatives according to the present invention maximize a therapeutic effect on type 2 diabetes.

[Mode for Invention]

Hereinafter, a better understanding of the present invention may be obtained through the following examples which are set forth to illustrate, but are not to be construed as the limit of the present invention.

Example 1. Plasma stability of exendin-4 derivative

To measure plasma stability of exendin-4 derivatives, each

The present invention also provides any one of the embodiments disclosed below and indicated with the numbers 1 to 10.

【Claim 1】

An insulinotropic peptide derivative, wherein N-terminal histidine residue of the insulinotropic peptide is substituted by a material selected from a group consisting of desamino-histidyl, N-dimethyl-histidyl, beta-hydroxy imidazopropionyl, 4-imidazoacetyl and beta-carboxyimidazopropionyl.

【Claim 2】

The insulinotropic peptide derivative as set forth claim 1, wherein the insulinotropic peptide is selected from exendin-3, exendin-4 and the derivatives thereof.

【Claim 3】

The insulinotropic peptide derivetive as set forth claim 2, wherein the insulinotropic peptide is exendin-4 or its derivative.

【Claim 4】

The insulinotropic peptide derivative as set forth claim 1 or 2, wherein the insulinotropic peptide derivative consists of an amino acid of the following Formula 1:

R1-X-R2 <Formula 1>

wherein R1 is selected from the group consisting of desamino-histidyl, N-dimethyl-histidyl, beta-hydroxy imidazopropionyl, 4-imidazoacetyl and beta-carboxyimidazopropionyl;

R2 is selected from the group consisting of $-NH_2$ or -OH;

X is selected from the group consisting of

Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser,

Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly and

Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Y-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Z-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser;

Y is selected from the group consisting of Lys, Ser, and Arg; and

Z is selected from the group consisting of Lys, Ser, and Arg.

【Claim 5】

The insulinotropic peptide derivative as set forth claim 4, wherein R1 is desamino-histidyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

【Claim 6】

The insulinotropic peptide derivative as set forth claim 4, wherein R1 is N-dimethyl-histidyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

【Claim 7】

The insulinotropic peptide derivative as set forth claim 4, wherein R1 is 4-imidazoacetyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

【Claim 8】

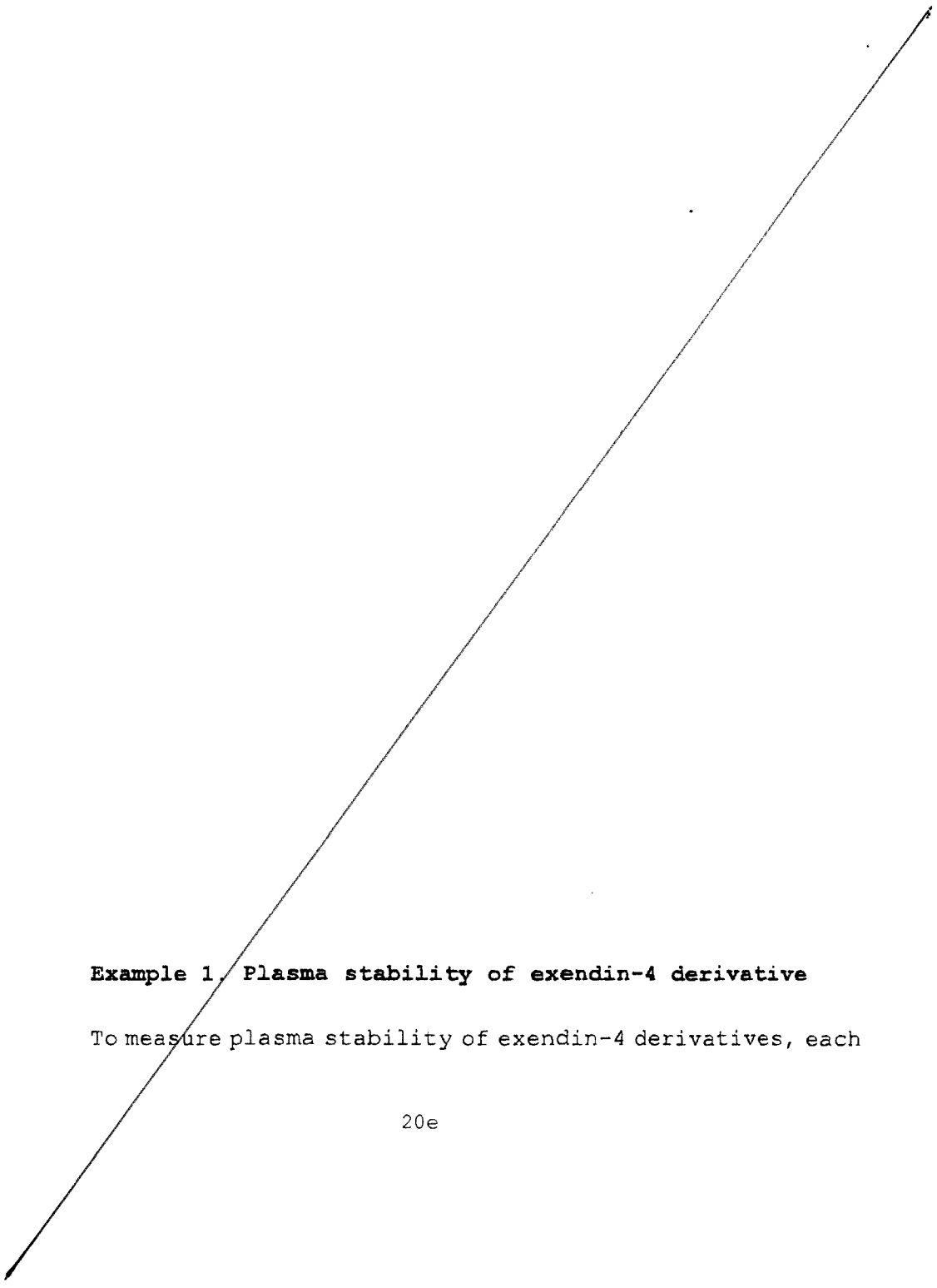
The insulinotropic peptide derivative as set forth claim 4, wherein R1 is beta-hydroxy-imidazopropionyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

【Claim 9】

The insulinotropic peptide derivative as set forth claim 4, wherein R1 is beta-carboxy-imidazopropionyl, Y is Lys or Ser, Z is Lys, and R2 is $-NH_2$.

【Claim 10】

A pharmaceutical composition for the treatment of diabetes, comprising the insulinotropic peptide derivative of claim 1.



Example 1. Plasma stability of exendin-4 derivative

To measure plasma stability of exendin-4 derivatives, each