

suppressing appetite and reducing food intake, as well as increasing energy consumption and promoting the thermogenesis of brown adipose tissue. On the basis of maintaining the efficacy of a GLP-1 agonist, the introduction of GCG activity will have the medicinal effects of: helping to further promote the secretion of insulin from pancreatic β cells; promoting the metabolism of brown adipose tissue; enhancing the β -oxidation of the fatty acids in liver and reducing the generation of lipids and cholesterol; improving the survival rate of cardiomyocytes; accelerating the lipid metabolism of white adipose tissue and reducing the fat content. The GLP-1/GCG dual-target synergy is likely to have better effect in improving blood sugar and weight loss than a single-target action. Therefore, the research on the GLP-1/GCG dual-target drugs in the treatment of obesity and related diseases is of great significance.

SUMMARY

[0005] The present disclosure provides a polypeptide with a sequence represented by the following formulas,

His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-¹Lys-Lys-Ala-¹Lys-
Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-X₂
(I-1, SEQ ID NO: 1)

His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-¹Lys-Lys-Ala-Lys-
¹Lys-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-X₂
(I-2, SEQ ID NO: 2)

His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-¹Lys-Ala-Lys-
¹Lys-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-X₂
(I-3, SEQ ID NO: 3)

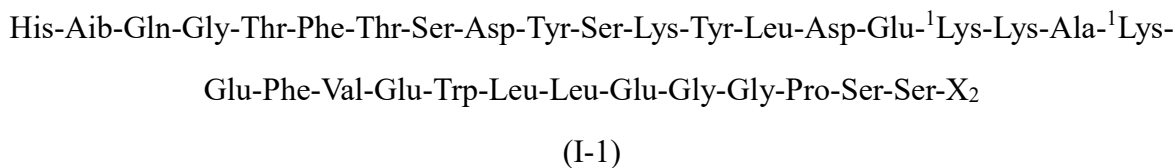
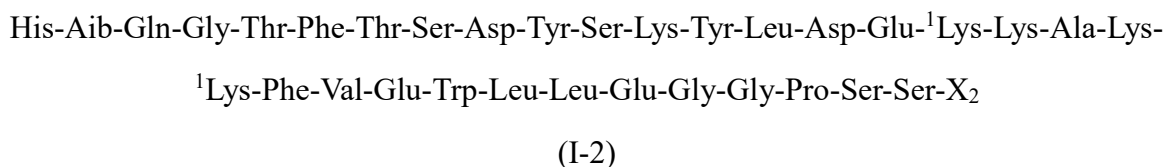
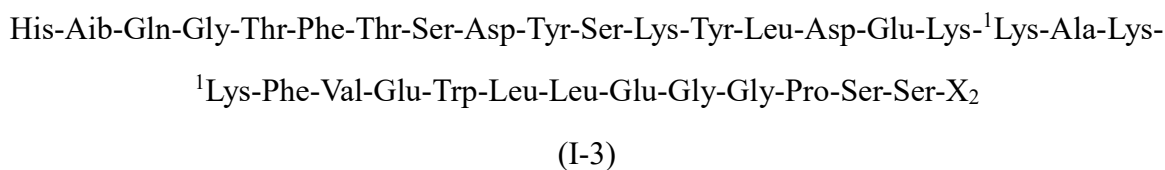
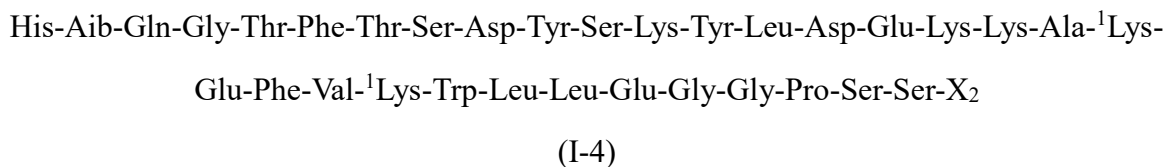
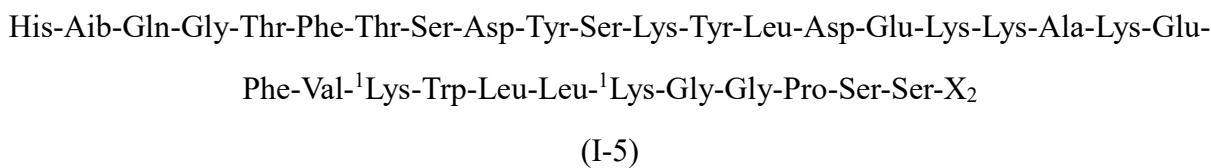
His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-¹Lys-
Glu-Phe-Val-¹Lys-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-X₂
(I-4, SEQ ID NO: 4)

His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-
Phe-Val-¹Lys-Trp-Leu-Leu-¹Lys-Gly-Gly-Pro-Ser-Ser-X₂
(I-5, SEQ ID NO: 5)

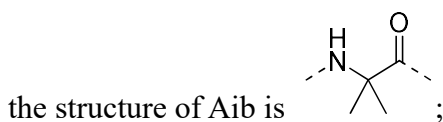
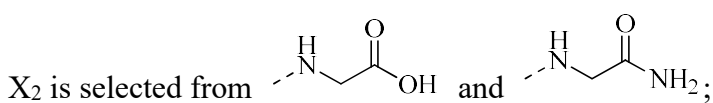
[0006] wherein

CLAIMS

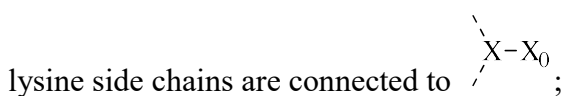
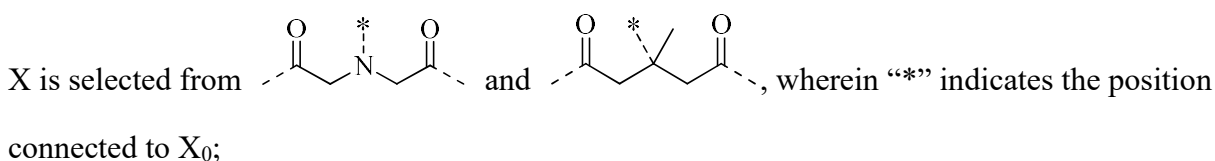
1. A polypeptide represented by a sequence shown below,

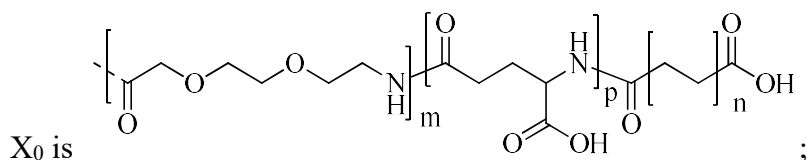


wherein



¹Lys represents a modified lysine, and the modification is that the amino groups on the two





m is selected from 2 and 3;

n is selected from 8, 9 and 10;

p is selected from 1 and 2.

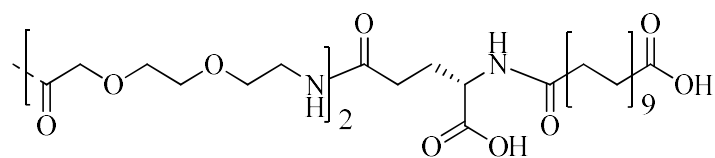
2. The polypeptide according to claim 1, wherein m is 2.

3. The polypeptide according to any one of claims 1 to 2, wherein n is 9.

4. The polypeptide according to any one of claims 1 to 3, wherein p is 1.

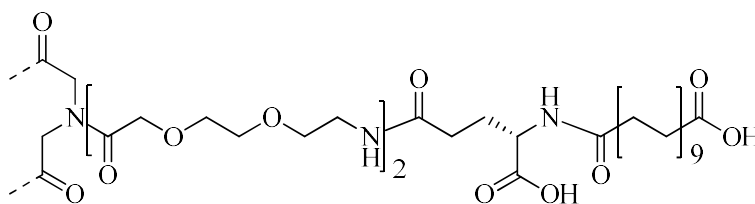
5. The polypeptide according to any one of claims 1 to 4, wherein X₂ is $\text{NH}-\text{CH}_2-\text{C}(=\text{O})\text{NH}_2$.

6. The polypeptide according to any one of claims 1 to 5, wherein X₀ is

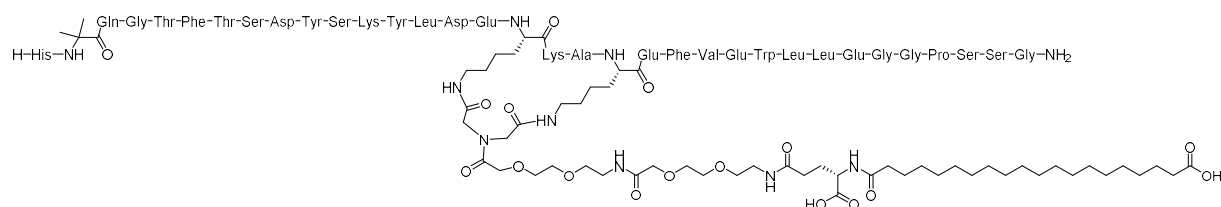


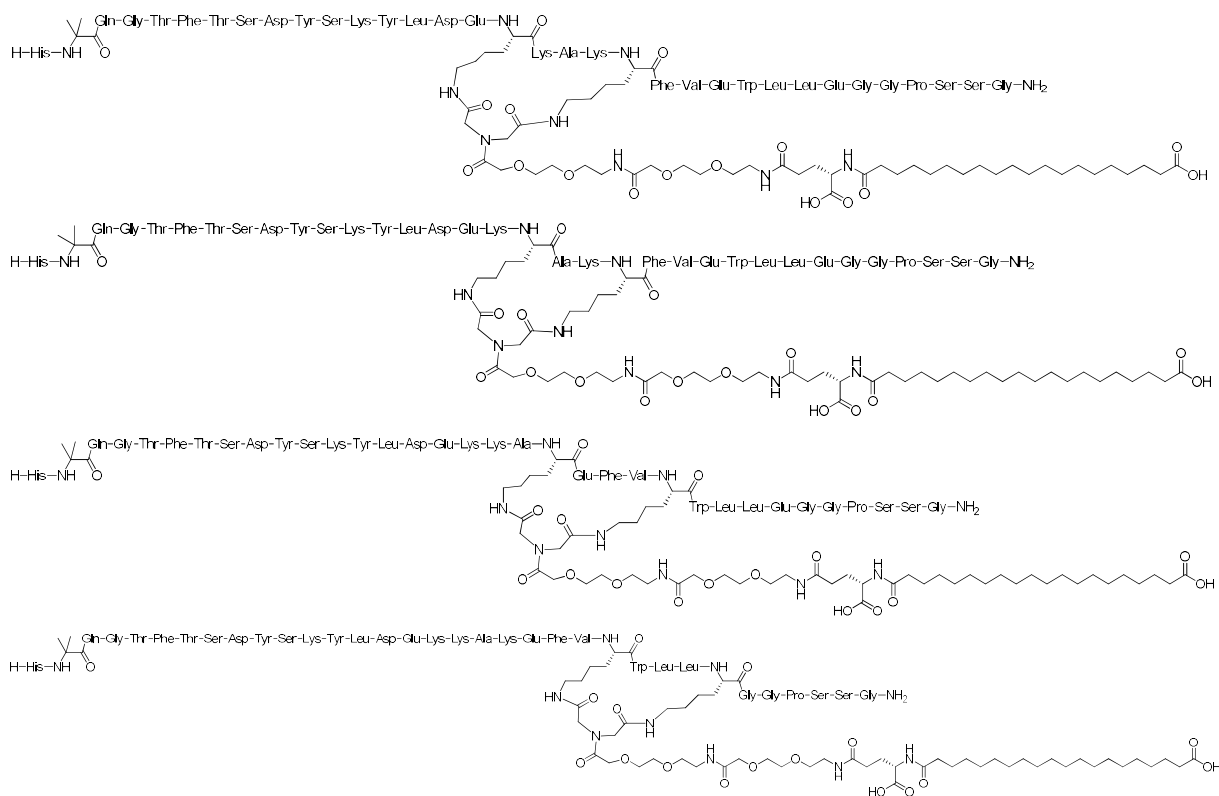
7. The polypeptide according to any one of claims 1 to 6, wherein X is $\text{C}(=\text{O})\text{CH}_2\text{N}^*\text{CH}_2\text{C}(=\text{O})$.

8. The polypeptide according to any one of claims 1 to 7, wherein the structural unit $\text{X}-\text{X}_0$ is



9. A polypeptide represented by the following formulas,





10. Use of the polypeptide compound according to any one of claims 1 to 9 in the manufacture of a medicament for the treatment of a GLP-1R/GCGR-related disease.

11. The use according to claim 10, wherein the GLP-1R/GCGR-related disease is obesity or nonalcoholic steatohepatitis.

12. A polypeptide compound according to any one of claims 1 to 9 for use in therapy.

13. The polypeptide for use according to claim 12, for use in the treatment of a GLP-1R/GCGR-related disease.

14. The polypeptide for use according to claim 13, wherein the GLP-1R/GCGR-related disease is obesity or nonalcoholic steatohepatitis.

15. A medicament, comprising the polypeptide according to any one of claims 1 to 9.

16. A medicament according to claim 15, for use in the treatment of a GLP-1R/GCGR-related disease.

17. The medicament for use according to claim 16, wherein the GLP-1R/GCGR-related disease is obesity or nonalcoholic steatohepatitis.