

Claims

1. A polypeptide or a pharmaceutically acceptable salt thereof comprising the amino acid sequence:

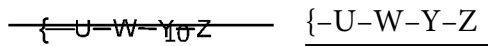
Y-X1-E-G-T-F-T-S-D-Y-S-I-X2-L-Xaa15-K-I-A-Xaa19-X3-Xaa21-F-V-Xaa24-W-L-X4-A-G-G-P-S-S-G-A-P-P-P-S-X5-X6-X7-X8-X9-X10-X11 (Seq. ID 1)

Wherein

X1 is Aib, Ser(OMe) or (D)Ser(OMe);

X2 is Tyr, Ser(OMe), (D)Ser(OMe) or Aib;

X3 is Gln or Lys; wherein, when X3 is Lys, the side chain amino (ϵ amino) group of Lys is acylated with a moiety:



wherein U is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-\}$ wherein $\}$ is the point of attachment with group W;

W is selected from a group consisting of $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_p-\text{NH}-]$, $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-]$ and $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-]$, wherein p is 3 or 4 and wherein $]$ is the point of attachment with group Y;

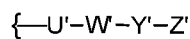
Y is $-\text{C}(\text{O})-(\text{CH}_2)_2-\text{CH}(\text{COOH})\text{NH--}$ and $--$ is the point of attachment with the group Z;

Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ or $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{CH}_3$ wherein n is an integer from 14 to 20;

and with a proviso that when X3 is Lys and X2 is Aib, then W is not $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-]$;

X4 is Leu, Ile or Glu;

X5 is absent, Arg or Lys; wherein, when X5 is Lys, the side chain amino (ϵ amino) group of Lys is acylated with a moiety:



wherein U' is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-\}$ wherein $\}$ is the point of attachment with group W' ;

W' is selected from a group consisting of $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_q-\text{NH}-]$, $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-]$ and $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-]$, wherein q is 3 or 4 and wherein] is the point of attachment with group Y';

Y' is $-\text{C}(\text{O})-(\text{CH}_2)_2-\text{CH}(\text{COOH})\text{NH}-$ and $-$ is the point of attachment with the group Z';

Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ or $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{CH}_3$ wherein m is an integer from 14 to 20;

X6 is absent or Lys;

X7 is absent or Lys;

X8 is absent or Lys;

X9 is absent or Lys;

X10 is absent or Lys;

X11 is absent or Lys;

Xaa15 is Asp or Glu;

Xaa19 is Gln or Ala;

Xaa21 is Ala or Glu;

Xaa24 is Gln or Asn;

wherein the acid group of the C terminal amino acid is a free carboxylic acid group or is amidated as a C-terminal primary amide;

and with a proviso at least one of X3 and X5 is Lys.

2. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X1 is Aib.

3. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X2 is Aib.

4. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X1 and X2 are both Aib.

5. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X1 is Aib and X2 is Ser(OMe) or (D)Ser(OMe).

6. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X1 is Ser(OMe) or (D)Ser(OMe) and X2 is Aib.

7. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-6, wherein X4 is Ile.

8. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein X5 is Arg.

9. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, wherein X1 is Aib and X2 is Tyr.

10. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1, 2 and 5, comprising an amino acid sequence:

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Ser(OMe)-L-D-K-I-A-Q-X3-A-F-V-Q-W-L-X4-A-G-G-P-S-S-G-A-P-P-P-S-X5-X6-X7-X8-X9-X10-X11 (Seq. ID 2).

11. The polypeptide or pharmaceutically acceptable salt thereof according to claim 10, wherein X4 is Ile.

12. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-2 comprising an amino acid sequence:

Y-X1-E-G-T-F-T-S-D-Y-S-I-X2-L-D-K-I-A-Q-X3-A-F-V-Q-W-L-X4-A-G-G-P-S-S-G-A-P-P-P-S (Seq. ID 3)

wherein X1 is Aib; X2 is Ser(OMe) or Aib; X4 is Ile or Glu.

13. The polypeptide or pharmaceutically acceptable salt thereof according to claim 12, wherein X2 is Aib and X4 is Ile.

14. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, comprising an amino acid sequence:

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-X3-A-F-V-Q-W-L-Ile-A-G-G-P-S-S-G-A-P-P-P-S (Seq. ID 4);

wherein, X3 is Lys and acetylated with the moiety $\{-U-W-Y-Z$ and W is selected from a group consisting of $-C(O)-NH-(CH_2)_p-NH-$ or $-C(O)-C(CH_3)_2-NH-$ wherein] is the point of attachment with group Y and p is 3 or 4.

15. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1, comprising an amino acid sequence selected from the group consisting of:

i) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ (SEQ ID NO 5);

ii) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile D-Ser-(OMe) Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ (SEQ ID NO 9);

iii) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Ser(OMe) Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ (SEQ ID NO 10);

iv) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Arg (SEQ ID NO 11);

v) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Tyr Leu Glu Lys Ile Ala Ala Gln Glu Phe Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Lys-NH₂ (SEQ ID NO 12);

vi) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Ser(OMe) Leu Glu Lys Ile Ala Ala Gln Glu Phe Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Lys-NH₂ (SEQ ID NO 13);

vii) Tyr D-Ser(OMe) Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ (SEQ ID NO 6); and

viii) Tyr Ser(OMe) Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂ (SEQ ID NO 7).

16. The polypeptide of any one of the claims 1-11, wherein X5, X6, X7, X8, X9, X10 and X11 are all absent.

17. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein W is -C(O)-C(CH₃)₂-NH-].

18. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein W is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_p-\text{NH}-$ and p is 3 or 4.
19. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein W is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_4-\text{NH}-$.
20. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-2, 5, 7-11 and 15-16, wherein W is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$.
21. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ and n is 16 or 18.
22. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein W is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_4-\text{NH}-$, Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ and n is 18.
23. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-16, wherein W is $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-$, Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ and n is 18.
24. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-2, 5-12 and 15-16, wherein W is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$, Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ and n is 16.
25. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-2, 5-12 and 15-16, wherein W is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$, Z is $-\text{C}(\text{O})-(\text{CH}_2)_n-\text{COOH}$ and n is 18.
26. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-$.
27. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_q-\text{NH}-$ and q is 3 or 4.
28. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_4-\text{NH}-$.
29. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$.
30. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ and m is 16 or 18.

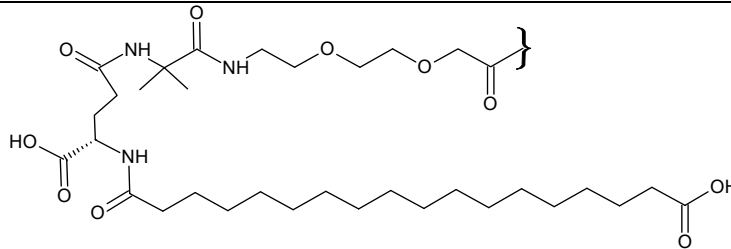
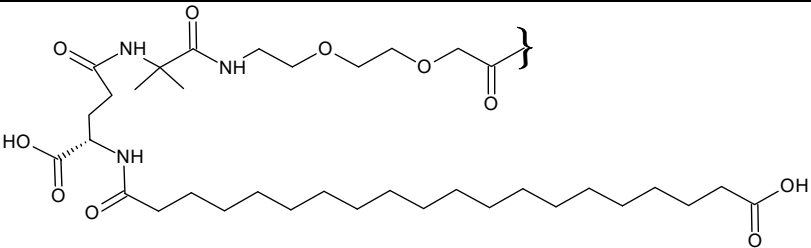
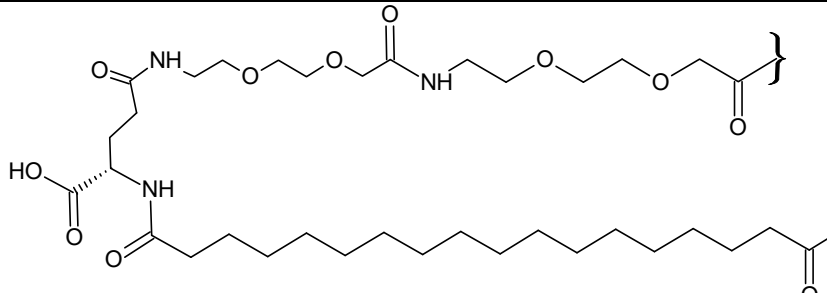
31. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_4-\text{NH}-$], Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ and m is 18.

32. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-$], Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ and m is 18.

33. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$], Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ and m is 16.

34. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{CH}_2-\text{O}-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-\text{NH}-$], Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$ and m is 18.

35. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-34, wherein -U-W-Y-Z and/or -U'-W'-Y'-Z' is selected from the group consisting of:

	Moiety A;
	Moiety B;
	Moiety C;

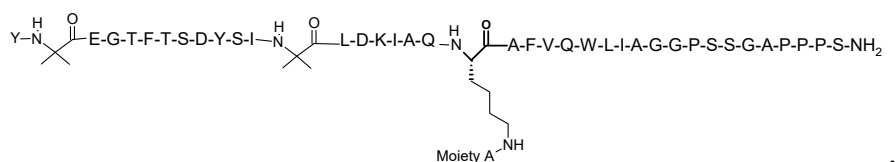
	Moiety D; and
	Moiety E

36. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1- 35 wherein the C terminal amino acid is amidated as a C-terminal primary amide.

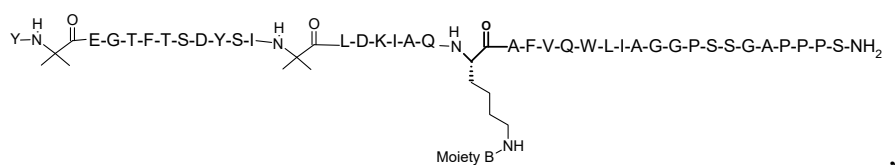
37. The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-35, wherein the acid group of the C terminal amino acid is a free carboxylic acid.

38. A polypeptide or pharmaceutically acceptable salt thereof, selected from the group consisting of:

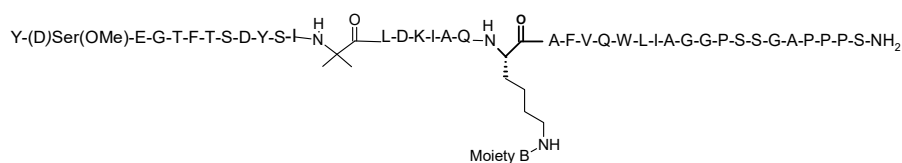
Compound 1:



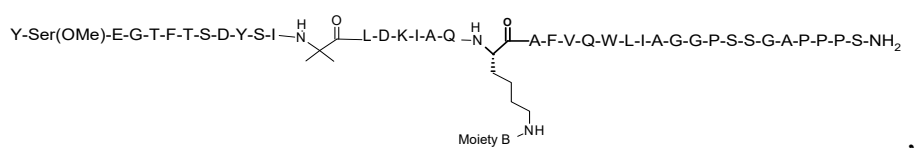
Compound 2



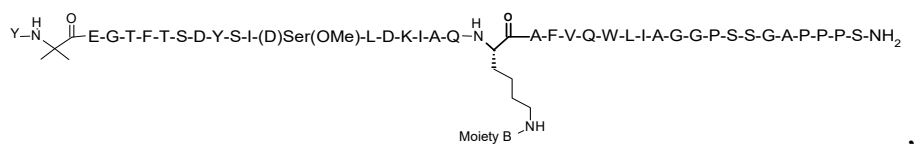
Compound 3



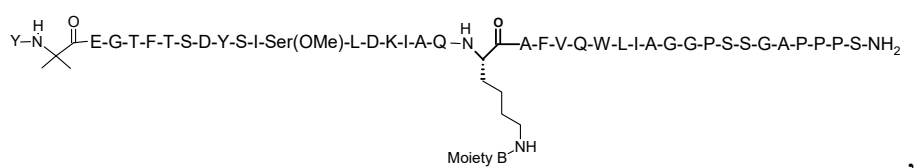
Compound 4



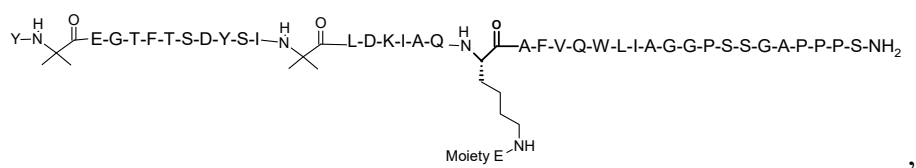
Compound 6



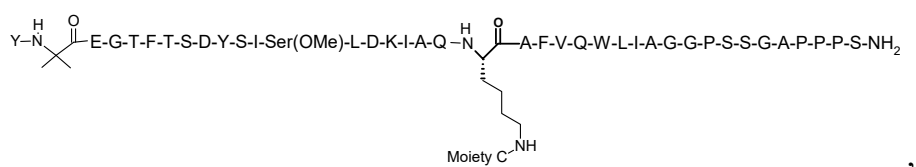
Compound 7



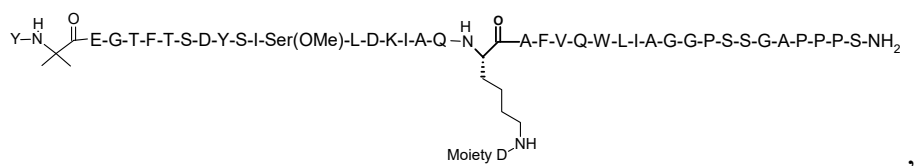
Compound 8



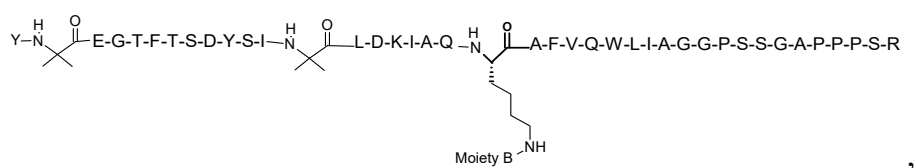
Compound 9



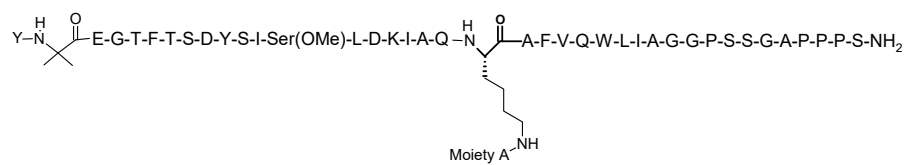
Compound 10



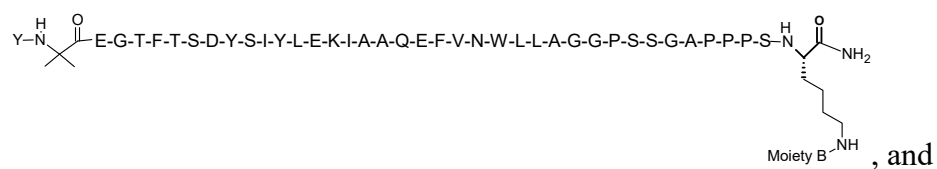
Compound 11



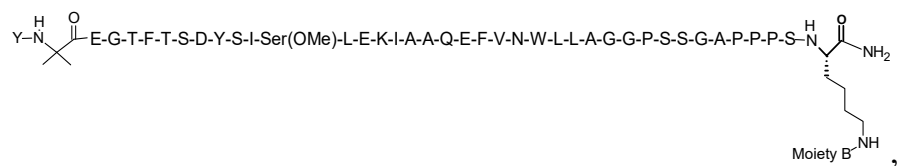
Compound 13



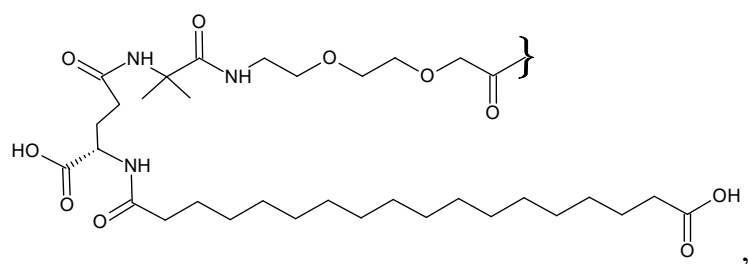
Compound 14



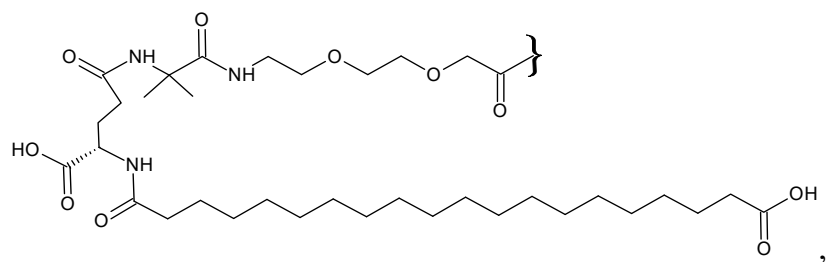
Compound 15



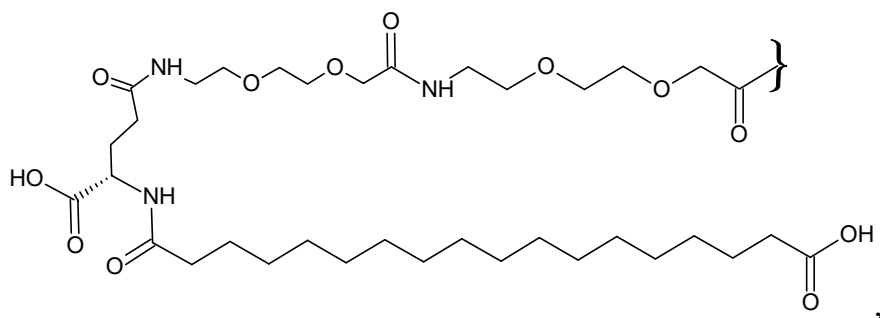
wherein, Moiety A is



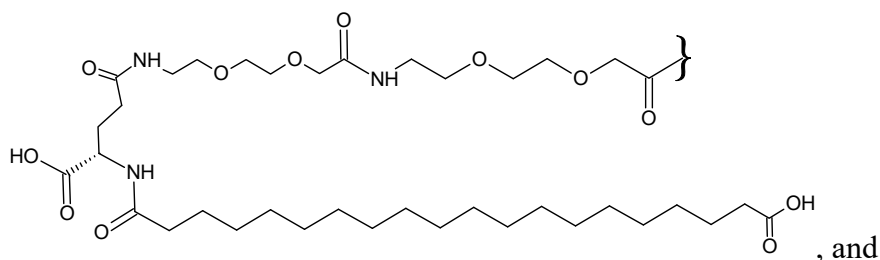
Moiety B is



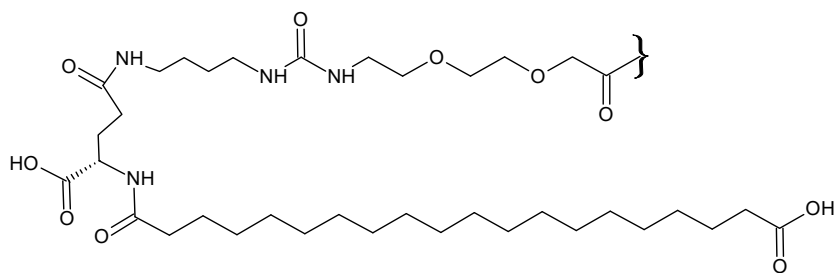
Moiety C is



Moiety D is



Moiety E is



- 39.** A pharmaceutical composition comprising a polypeptide or pharmaceutically acceptable salt thereof according to any one of the claims 1-38, and one or more of a carrier, diluent or pharmaceutically acceptable excipient.

- 40.** A polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-38 or a pharmaceutical composition according to claim 39 for use as a medicament.

- ~~41. A polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-38 or a pharmaceutical composition according to claim 39 for use in the treatment or prevention of a disease in a patient.~~

- 42.41.** Use of Aa polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-38 or a pharmaceutical composition according to claim 39 for use according to claim 41 in the preparation of a medicament for the treatment or prevention of a disease in a patient, wherein said disease is selected from the group consisting of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension,

hyperlipidemia, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease, stroke, inflammatory bowel syndrome, dyspepsia, alcoholism and gastric ulcers.

~~43.42.~~ The polypeptide or pharmaceutically acceptable salt thereof or a pharmaceutical composition for use according to claims ~~40-42~~41 wherein said polypeptide or pharmaceutically acceptable salt thereof or said pharmaceutical composition is medicament is adapted to be provided simultaneously, separately, or sequentially in combination with an effective amount of one or more additional therapeutic agents.

~~44.~~ — A method of treating or preventing hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, hyperlipidemia, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease, stroke, inflammatory bowel syndrome, dyspepsia, alcoholism and gastric ulcers in a patient, comprising administering to a patient in need thereof, an effective amount of the polypeptide or pharmaceutically acceptable salt thereof according to any one of claims ~~1-38~~.

~~45.~~ — A method of treating or preventing hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, hyperlipidemia, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease, stroke, inflammatory bowel syndrome, dyspepsia, alcoholism and gastric ulcers in a patient, wherein said method comprising administering to a patient in need thereof, an effective amount of a pharmaceutical composition according to claim ~~39~~.

~~46.~~ — The method according to any one of claims ~~44-45~~, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more therapeutic agents.

~~47.~~ — The polypeptide or pharmaceutically acceptable salt thereof according to any one of claims ~~1-38~~, or composition according to claim ~~39~~ for use in the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, hypertension, syndrome X, dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart disease, stroke, inflammatory bowel syndrome, dyspepsia, alcoholism and gastric ulcers.