

Claims

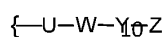
1. A polypeptide or a pharmaceutically acceptable salt thereof comprising the amino acid sequence:
 Y-X1-E-G-T-F-T-S-D-Y-S-I-X2-L-Xaa15-K-I-A-Xaa19-X3-Xaa21-F-V-Xaa24-W-L-X4-A-G-G-P-S-S-G-A-P-P-P-S-X5-X6-X7-X8-X9-X10-X11 (Seq. ID 1)

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 $-C(O)-CH_2-O-(CH_2)_2-O-(CH_2)_2-NH-$ wherein } is the point of attachment with group W;

W is selected from a group consisting of $-C(O)-NH-(CH_2)_p-NH-$, $-C(O)-C(CH_3)_2-NH-$ and $-C(O)-CH_2-O-(CH_2)_2-O-(CH_2)_2-NH-$, wherein p is 3 or 4 and wherein] is the point of attachment with group Y;

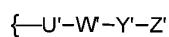
Y is $-C(O)-(CH_2)_2-CH(COOH)NH-$ and -- is the point of attachment with the group Z;

Z is $-C(O)-(CH_2)_n-COOH$ or $-C(O)-(CH_2)_n-CH_3$ 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 $-C(O)-CH_2-O-(CH_2)_2-O-(CH_2)_2-NH-$;

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 $-C(O)-CH_2-O-(CH_2)_2-O-(CH_2)_2-NH-$ wherein } is the point of attachment with group W';

- 26 W' is selected from a group consisting of $-\text{C}(\text{O})-\text{NH}-(\text{CH}_2)_q-\text{NH}-$, $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-$
27 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
28 attachment with group Y';
- 29 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';
- 30 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;
- 31 X6 is absent or Lys;
- 32 X7 is absent or Lys;
- 33 X8 is absent or Lys;
- 34 X9 is absent or Lys;
- 35 X10 is absent or Lys;
- 36 X11 is absent or Lys;
- 37 Xaa15 is Asp or Glu;
- 38 Xaa19 is Gln or Ala;
- 39 Xaa21 is Ala or Glu;
- 40 Xaa24 is Gln or Asn;
- 41 wherein the acid group of the C terminal amino acid is a free carboxylic acid group or is
42 amidated as a C-terminal primary amide;
- 43 and with a proviso at least one of X3 and X5 is Lys.
- 1 2. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1,
2 wherein X1 is Aib.
- 1 3. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1,
2 wherein X2 is Aib.
- 1 4. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1,
2 wherein X1 and X2 are both Aib.
- 1 5. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1,
2 wherein X1 is Aib and X2 is Ser(OMe) or (D)Ser(OMe).
- 1 6. The polypeptide or pharmaceutically acceptable salt thereof according to claim 1,
2 wherein X1 is Ser(OMe) or (D)Ser(OMe) and X2 is Aib.

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

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

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

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

3 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-
4 G-P-S-S-G-A-P-P-P-S-X5-X6-X7-X8-X9-X10-X11 (Seq. ID 2).

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

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

3 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-
4 G-A-P-P-P-S (Seq. ID 3)

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

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

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

3 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-
4 S-G-A-P-P-P-S (Seq. ID 4);

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

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

- 3 i) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys
4 Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH₂
5 (SEQ ID NO 5);
- 6 ii) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile D-Ser-(OMe) Leu Asp Lys Ile Ala
7 Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-
8 NH₂ (SEQ ID NO 9);
- 9 iii) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Ser(OMe) Leu Asp Lys Ile Ala
10 Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-
11 NH₂ (SEQ ID NO 10);
- 12 iv) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala Gln Lys
13 Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Arg (SEQ
14 ID NO 11);
- 15 v) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Tyr Leu Glu Lys Ile Ala Ala Gln
16 Glu Phe Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser Lys-
17 NH₂ (SEQ ID NO 12);
- 18 vi) Tyr Aib Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Ser(OMe) Leu Glu Lys Ile Ala
19 Ala Gln Glu Phe Val Asn Trp Leu Leu Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro
20 Ser Lys-NH₂ (SEQ ID NO 13);
- 21 vii) Tyr D-Ser(OMe) Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala
22 Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-
23 NH₂ (SEQ ID NO 6); and
- 24 viii) Tyr Ser(OMe) Glu Gly Thr Phe Thr Ser Asp Tyr Ser Ile Aib Leu Asp Lys Ile Ala
25 Gln Lys Ala Phe Val Gln Trp Leu Ile Ala Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-
26 NH₂ (SEQ ID NO 7).

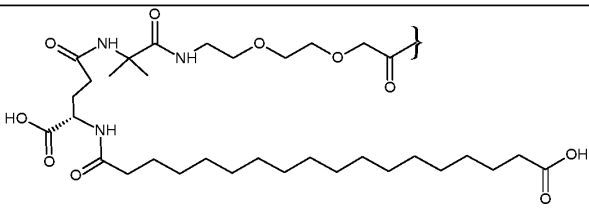
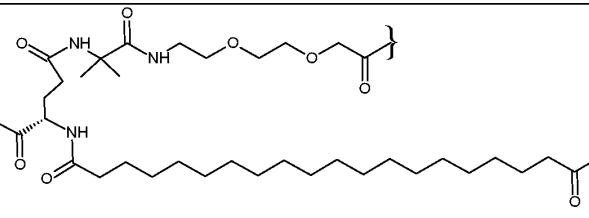
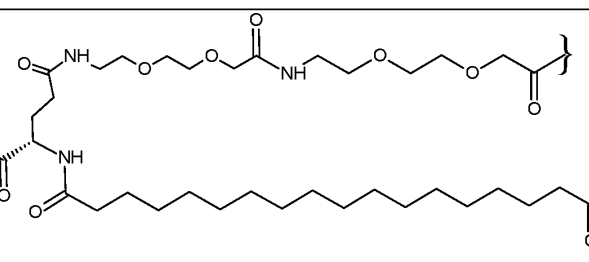
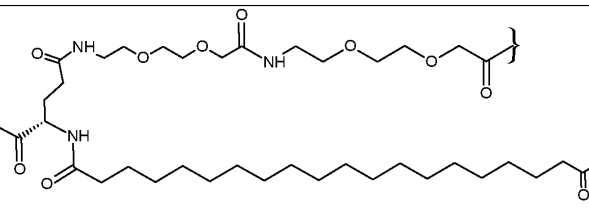
1 **16.** The polypeptide of any one of the claims 1-11, wherein X5, X6, X7, X8, X9, X10
2 and X11 are all absent.

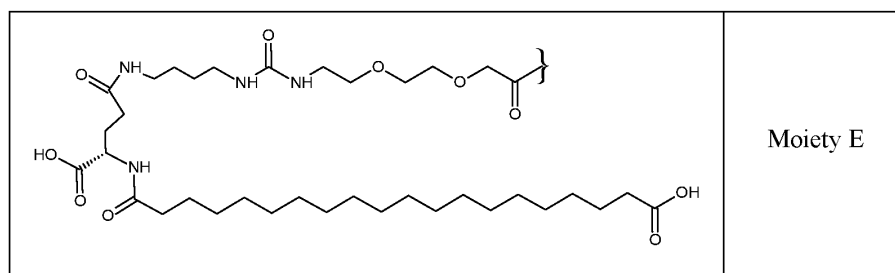
1 **17.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
2 claims 1-16, wherein W is -C(O)-C(CH₃)₂-NH-].

1 **18.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
2 claims 1-16, wherein W is -C(O)-NH-(CH₂)_p-NH-] and p is 3 or 4.

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

- 1 **32.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
 2 claims 1-7, 9-11 and 15, wherein W' is $-\text{C}(\text{O})-\text{C}(\text{CH}_3)_2-\text{NH}-$, Z' is $-\text{C}(\text{O})-(\text{CH}_2)_m-\text{COOH}$
 3 and m is 18.
- 1 **33.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
 2 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 $-\text{C}(\text{O})-$
 3 $(\text{CH}_2)_m-\text{COOH}$ and m is 16.
- 1 **34.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
 2 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 $-\text{C}(\text{O})-$
 3 $(\text{CH}_2)_m-\text{COOH}$ and m is 18.
- 1 **35.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
 2 claims 1-34, wherein $-\text{U}-\text{W}-\text{Y}-\text{Z}$ and/or $-\text{U}'-\text{W}'-\text{Y}'-\text{Z}'$ is selected from the group consisting
 3 of:

	Moieté A;
	Moieté B;
	Moieté C;
	Moieté D; and



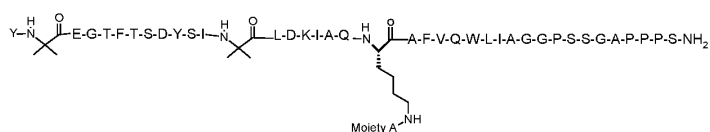
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1 **36.** The polypeptide or pharmaceutically acceptable salt thereof according to any one of
2 claims 1- 35 wherein the C terminal amino acid is amidated as a C-terminal primary amide.

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

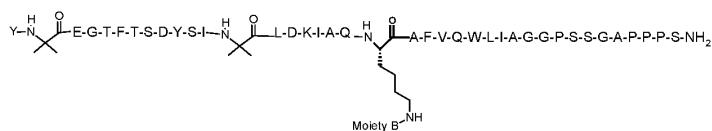
1 **38.** A polypeptide or pharmaceutically acceptable salt thereof, selected from the group
2 consisting of:

3 **Compound 1:**



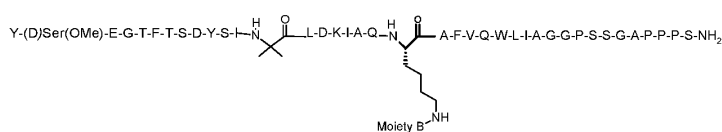
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5 **Compound 2**



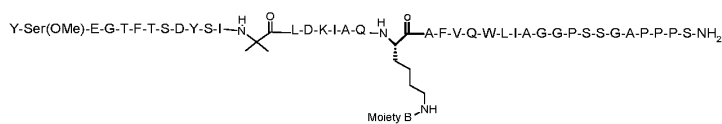
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7 **Compound 3**



8

9 **Compound 4**



10



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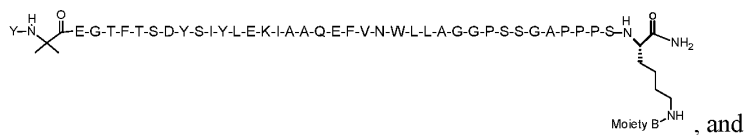
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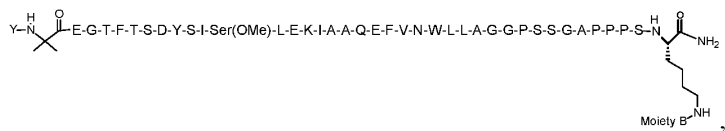
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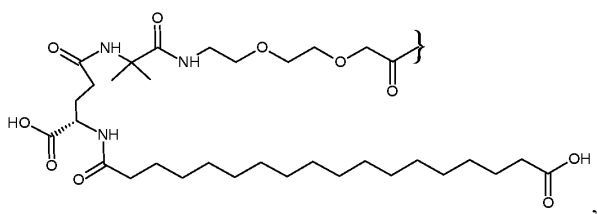
25 Compound 14



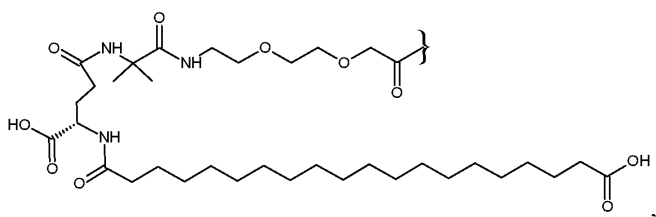
27 Compound 15



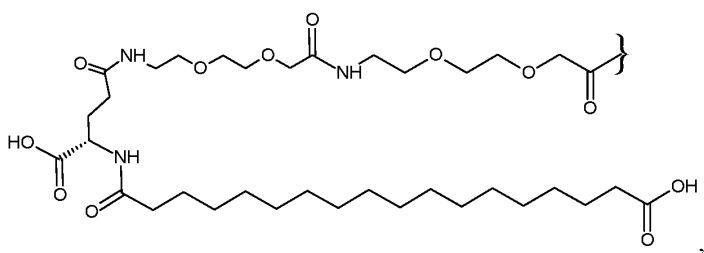
29 wherein, Moiety A is



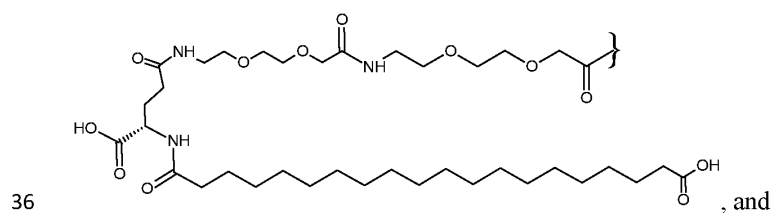
31 Moiety B is



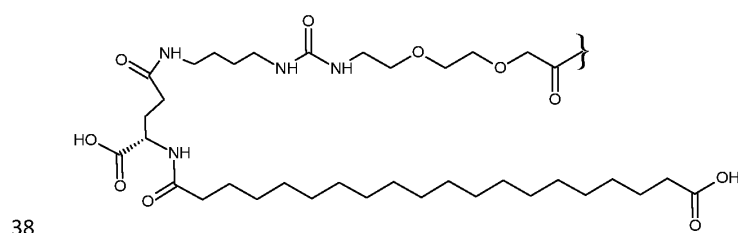
33 Moiety C is



35 Moiety D is



37 Moiety E is



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

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

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

1 **42.** A polypeptide or pharmaceutically acceptable salt thereof or a pharmaceutical
2 composition for use according to claim 41, wherein said disease is selected from the group
3 consisting of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes,
4 obesity, hypertension, hyperlipidemia, syndrome X, dyslipidemia, cognitive disorders,
5 atherosclerosis, myocardial infarction, coronary heart disease, stroke, inflammatory bowel
6 syndrome, dyspepsia, alcoholism and gastric ulcers

1 **43.** The polypeptide or pharmaceutically acceptable salt thereof or a pharmaceutical
2 composition for use according to claims 40-42 wherein said polypeptide or
3 pharmaceutically acceptable salt thereof or said pharmaceutical composition is provided
4 simultaneously, separately, or sequentially in combination with an effective amount of one
5 or more additional therapeutic agents.

1 **44.** A method of treating or preventing hyperglycemia, type 2 diabetes, impaired glucose
2 tolerance, type 1 diabetes, obesity, hypertension, hyperlipidemia, syndrome X,
3 dyslipidemia, cognitive disorders, atherosclerosis, myocardial infarction, coronary heart
4 disease, stroke, inflammatory bowel syndrome, dyspepsia, alcoholism and gastric ulcers in
5 a patient, comprising administering to a patient in need thereof, an effective amount of the
6 polypeptide or pharmaceutically acceptable salt thereof according to any one of claims 1-
7 38 .

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

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

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