CLAIMS

What is claimed is:

1. A polypeptide having the following formula I':

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10-X11-X12-X13 I'

wherein:

X1 is the N-terminus of the polypeptide and is either absent or is selected from pE, R, Isn, Q, A, K, and 5-amino-valeric acid;
X2 is R, A, r, N-Me-R, K, H, hF, hK, F, E or Orn;
X3 is P, A, a, p, 4-PhP, K, D, pipecolic acid, or cysteine wherein the side chain of cysteine forms a disulfide bond with the side chain of the cysteine at the X7 position;
X4 is R, A, r, N-Me-R, F, E or cysteine wherein the side chain of cysteine forms a disulfide bond with the side chain of the cysteine at the X7 position;
X5 is L, Cha, A, D-L, N-Me-L, K, D, 4-PhF or F;

X6 and X12 are independently a natural or unnatural amino acid selected from C, c, hC, D-hC, K, D, Orn, Dab or E wherein the side chain of X6 and X12 are linked together via a covalent bond forming either a monosulfide (-S-), a disulfide (-S-S-) or an amide bond (-NHC(O)- or -C(O)-NH-) or a linkage of Formula –S-CH_2-C(=Z)-CH_2-S-; wherein Z is O, N-O-CH_2C(O)-L^1-R^1 or N-NH-CH_2C(O)-L^1-R^1 wherein R^1 is a fatty acid derivative and L^1 is a linker containing one or more amino acids and/or one or more –NH-C_{2-6}-alkylene-NH- units;
or alternatively X6 is K, X13 is absent and X12 is F or f wherein the C-terminus of X12 form an amide bond with the amino side chain of X6;
X7 is H, h, A, N-Me-A, a, Aib, K, Nal, F, P, Dap, N, E or cysteine wherein the side chain of the cysteine forms a disulfide bond with the side chain of the cysteine at position X3 or with the side chain of the cysteine at position X4;
X8 is K, k, F, f, A, hF, N-Me-R, E or 4-amino-Isn;
X9 is G, N-Me-G, A, D, L, R or Aib;
X10 is P, A, p, 4-PhP or pipecolic acid,
X11 is M, D-Nle, Nle, N-Me-Nle, M(O), A, F, Y, L, K, 3-PyA or Cha; and

X13 is the C-terminus and is absent or is selected from F, f, N-Me-F, Nal, D-Nal, 3-Br-F, (S)-β-3-F, I, A, a, K, Dap, H and E;

wherein:

Nle is L-norleucine;

D-hC is D-homocysteine

hC is L-homocysteine;

hF is L-homophenylalanine;

hK is L-lysine;

Nal is L-naphathaline;

Orn is ornithine;

Aib is α-aminoisobutyric acid;

Dab is (S)-diaminobutyric acid;

Dap is (S)-2,3-diaminopropionic acid;

M(O) is methionine sulfone;

Cha is (S)-β-cyclohexylalanine;

4-amino-Isn is 4-aminopiperidine-4-carboxylic acid;

Isn is isonipecotinoyl;

pE is L-pyroglutamic acid;

3-PyA is 3-(3-pyridyl)-L-alanine;

4-PhF is 4-Phenyl-L-phenylalanine;

wherein the N-terminus and the C-terminus optionally form a ring together with 1, 2, 3 or 4 glycine amino acids; and

wherein the amino group in the side chain of K, Orn, Dab, Dap, hK or 4-amino-Isn is optionally linked to a lipophilic group via an amide bond;

or an amide, an ester or a salt of the polypeptide; or a polypeptide substantially equivalent thereto.

2. A polypeptide having the following formula:

X1-R-P-R-X5-X6-X7-X8-X9-P-X11-X12-X13

II

X1 is absent, pE, R, Q or Isn;

X5 is L or Cha;

X7 is H, Aib, F, K(Lauroyl) or K(Palmitoyl);

X8 is K, F or 4-amino-Isn;
X9 is G or Aib;
X11 is Nle or Cha;
X13 is absent or is F, f, K(Lauroyl), K(Palmitoyl);
X6 and X12 are independently a natural or unnatural amino acid selected from C, c, hc, D-hc, K, D, Orn, Dab or E wherein the side chain of X6 and X12 are linked together via a covalent bond forming either a disulfide or an amide bond;and wherein the N-terminus and the C-terminus optionally form a ring together with 1, 2, 3 or 4 glycine amino acids; or an amide, an ester or a salt of the polypeptide; or a polypeptide substantially equivalent thereto.

3. The polypeptide according to claim 1 or 2 wherein:
X6 and X12 are independently selected from K, Orn, Dab, E and D and wherein the side chain of X6 and X12 form together an amide bond; or an amide, an ester or a salt of the polypeptide.

4. The polypeptide according to claim 1 or 2 wherein:
X6 and X12 are independently C wherein the side chain of X6 and X12 form together a disulfide bond; or an amide, an ester or a salt of the polypeptide.

5. The polypeptide of claim 1, 2 or 4 having Formula III:

X1-R-P-R-X6-C-X7-X8-X9-P-X11-C-X13

III;

or an amide, an ester or a salt of the polypeptide.

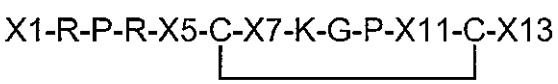
6. The polypeptide according to anyone of claims 1 to 5 having Formula IV:

X1-R-P-R-X5-X6-X7-K-G-P-X11-X12-X13

IV;

or an amide, an ester or a salt of the polypeptide.

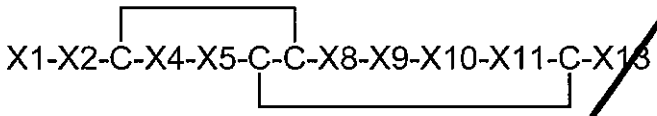
7. The polypeptide according to anyone of claims 1, 2 and 4 to 6 having Formula V:



V;

or an amide, an ester or a salt of the polypeptide.

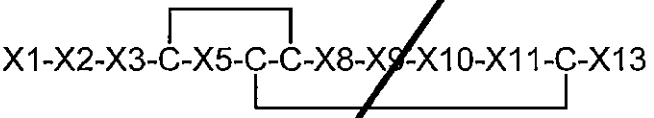
8. The polypeptide according to claim 1 having Formula VI:



VI

or an amide, an ester or a salt of the polypeptide.

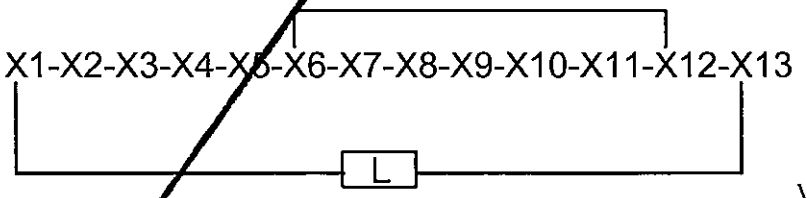
9. The polypeptide according to claim 1 having Formula VII:



VII

or an amide, an ester or a salt of the polypeptide.

10. The polypeptide according to claim 1, 2, 5, 6 or 7 having Formula VIII:



VIII

wherein the N-terminus of X1 and the C-terminus of X13 form a ring together with a linker L; and wherein L is $(G)_r$, G is glycine and r is 1, 2, 3 or 4; or a salt of the polypeptide.

11. The polypeptide according to claim 10 wherein X1 is Q, X13 is F and r is 2; or a salt of the polypeptide.

12. The polypeptide according to claim 1 wherein X6 is K, X13 is absent and X12 is F or f wherein the C-terminus of X12 forms an amide bond with the amino side chain of X6; and having Formula IX:

X1-X2-X3-X4-X5-K-X7-X8-X9-X10-X11-X12

IX,

or an ester, an amide or a salt of the polypeptide.

13. The polypeptide according to anyone of claims 1 to 9 and 12 wherein X1 is pE; or an amide, an ester or a salt of the polypeptide.

14. The polypeptide according to anyone of claims 1 to 9 and 12 wherein X1 is absent; or an amide, an ester or a salt of the polypeptide.

15. The polypeptide according to claim 14 wherein the N-terminus is an amide; or a salt of the polypeptide.

16. The polypeptide according to claim 15 wherein the N-terminus is an amide of Formula –NHR and R is Acetyl, benzoyl, phenacyl, succinyl, octanoyl, 4-phenylbutanoyl, 4-Cl-Ph-$(CH_2)_3C(O)$-, or Ph-$CH_2CH_2NHC(O)$-; or a salt of the polypeptide.

17. The polypeptide of anyone of claims 1 to 9 and 12 wherein the N-terminus is an amide of Formula NHR1 wherein R1 is $CH_3C(O)$, CH_3-$(O-CH_2CH_2)_m$-C(O)-, Palmitoyl$(O2Oc)_p$, Myristoyl$(O2Oc)_p$, Lauroyl$(O2Oc)_p$ or Ph-$CH_2CH_2NHC(O)$-; and wherein
p is an integer of 1 to 4;
m is an integer of 1 to 12;
Lauroyl(O2Oc) is $C_{11}H_{23}C(O)NH$-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-C(O)-;
Myristoyl(O2Oc) is $C_{13}H_{27}C(O)NH$-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-C(O)-;
Palmitoyl(O2Oc) is $C_{15}H_{31}C(O)NH$-$(CH_2)_2$-O-$(CH_2)_2$-O-CH_2-C(O)-; or a salt of the polypeptide

18. The polypeptide according to anyone of claims 1 to 9 wherein X13 is F; or an amide, an ester or a salt of the polypeptide.

19. The polypeptide according to anyone of claims 1 to 9 wherein X13 is absent; or an amide, an ester or a salt of the polypeptide.

20. The polypeptide according to claim 19 wherein the C-terminus is an amide; or a salt of the polypeptide.

21. The polypeptide according to claim 20 wherein the C-terminus is an amide of Formula –C(O)-R2 and R2 is $-NH_2$, -NH-Me, -NH-NHBn, or $-NH-(CH_2)_2$-Ph; or a salt of the polypeptide.

22. The polypeptide according to anyone of claims 1-21 wherein X5 is L; or an amide, an ester or a salt of the polypeptide.

23. The polypeptide according to anyone of claims 1 to 7 and 10 to 22 wherein X7 is H; or an amide, an ester or a salt of the polypeptide.

24. The polypeptide according to anyone of claims 1 to 5 and 8 to 23 wherein X8 is K; or an amide, an ester or a salt of the polypeptide.

25. The polypeptide according to anyone of claims 1 to 5 and 8 to 24 wherein X9 is G; or an amide, an ester or a salt of the polypeptide.

26. The polypeptide according to anyone of claims 1 to 25 wherein X11 is Nle, or an amide, an ester or a salt of the polypeptide.

27. The polypeptide according to claim 1 selected from:
*p*E-R-P-R-L-K*-H-F-G-P-Nle-D*-Phenethylamine,
*p*E-R-P-R-L-K*-H-F-G-P-Nle-E*-Phenethylamine,
*p*E-R-P-R-L-Orn*-H-F-G-P-Nle-D*-Phenethylamine,
*p*E-R-P-R-L-Dab*-H-F-G-P-Nle-D*-Phenethylamine,
*p*E-R-P-R-L-K*-F-K-G-P-Nle-F*,
*p*E-R-P-R-L-K*-F-K-G-P-Nle-f*,
Q-R-P-R-L-C*-F-K-G-P-Nle-C*-F-G-G,
*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,
*p*E-R-P-R-L-C*-Aib-K-G-P-Nle-C*-F-*OH*,
*p*E-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-*OH*,
H-Isn-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-*OH*,
*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-Phenethylamine,
*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-f-*OH*,
pE-R-P-R-Cha-C*-H-K-G-P-Cha-C*-F-*OH*,

*p*E-R-P-R-L-C*-F-K-G-P-Nle-C*-F-*OH*,

H-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,

H-R-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,

H-Isn-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,

*p*E-R-P-R-L-C*-H-F-G-P-Nle-C*-Phenethylamine,

*p*E-R-P-R-L-C*-H-K-Aib-P-Nle-C*-F-*OH*,

*p*E-R-P-R-L-C*-H-(4-NH-Isn)-G-P-Nle-C*-F-*OH*,

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-K(Palmitoyl)-*OH*,

*p*E-R-P-R-L-C*-K(Palmitoyl)-K-G-P-Nle-C*-F-*OH*,

Palmitoyl-O2Oc-Q-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,

Lauroyl-O2Oc-Q-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH*,

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-K(Lauroyl)-*OH*,

*p*E-R-P-R-L-C*-K(Lauroyl)-K-G-P-Nle-C*-F-*OH*,

*p*E-R-P-C**-L-C*-C**-K-G-P-Nle-C*-F-*OH*,

*p*E-R-C**-R-L-C*-C**-K-G-P-Nle-C*-F-*OH*;

*p*E-r-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-F-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-E-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-p-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-K-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-D-R-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-F-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-K-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-E-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-D-P-Nle-C*-F-*OH;*

*p*E-R-P-E-L-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-(4-PhF)-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-D-C*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-E-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-L-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-R-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-G-(Pipecolic acid)-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-(3-PyA)-C-F-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-H-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-E-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-NH_2;

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-F-NH_2;

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-*h*C*-F-*OH;*

*p*E-R-P-R-L-*h*C*-H-K-G-P-Nle-*h*C*-F-*OH;*

*p*E-R-P-R-L-c*-H-K-G-P-Nle-C*-F-*OH;*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-(D-*h*C)*-F-*OH;*

*p*E-R-P-R-L-(D-*h*C)*-H-K-G-P-Nle-(D-*h*C)*-F-*OH;*

MyristoylO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C*-f-*OH;*

MyristoylO2OcO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C*-f-*OH;*

MyristoylO2OcO2OcO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C-f-*OH;*

*p*E-R-P-R-L-C*H-K-G-P-Nle-c*-F-*OH;*

*p*E-R-P-R-L-c*-H-K-G-P-Nle-c*-F-*OH;and*

*p*E-R-P-R-L-C*-H-K(Myr)-G-P-Nle-C*-F-OH.

*pE-R-P-R-L-C***-H-K-G-P-Nle-C***-F-OH*

wherein the two amino acids labeled with "*" represent the amino acids forming a disulfide or amide bond via their side chain or terminus, respectively and wherein the two amino acids labeled with "**" represent the amino acids forming a disulfide via their side chain or an amide bond via their termini; and wherein the 2 amino acids labeled with "***" represent the amino acids forming a monosulfide bond or a –S-CH_2-C(O)-CH_2-S- linkage via their side chain; or an amide, an ester or a salt of the polypeptide.

28. The polypeptide of claim 27 selected from:

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH,*

*p*E-R-P-R-L-C*-Aib-K-G-P-Nle-C*-F-*OH,*

*p*E-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-*OH,*

H-Isn-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-*OH,*

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-Phenethylamine,

*p*E-R-P-R-L-C*-H-K-G-P-Nle-C*-f-*OH,*

*p*E-R-P-R-Cha-C*-H-K-G-P-Cha-C*-F-*OH,*

*p*E-R-P-R-L-C*-F-K-G-P-Nle-C*-F-*OH,*

H-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH,*
H-R-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH,*
H-Isn-R-P-R-L-C*-H-K-G-P-Nle-C*-F-*OH,* and
*p*E-R-P-R-L-C*-H-F-G-P-Nle-C*-Phenethylamine; wherein the side chains of the 2 cysteine amino acids C* form together a disulfide bond; or an amide, an ester or a salt of the polypeptide.

29. A method of treating or preventing a disease or disorder responsive to the agonism of the APJ receptor, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a polypeptide according to any one of claims 1 to 28 or an amide, an ester or a salt thereof.

30. The method of claim 29 wherein the disease or disorder is selected from acute decompensated heart failure (ADHF), chronic heart failure, pulmonary hypertension, atrial fibrillation, Brugada syndrome, ventricular tachycardia, atherosclerosis, hypertension, restenosis, ischemic cardiovascular diseases, cardiomyopathy, cardiac fibrosis, arrhythmia, water retention, diabetes (including gestational diabetes), obesity, peripheral arterial disease, cerebrovascular accidents, transient ischemic attacks, traumatic brain injuries, amyotrophic lateral sclerosis, burn injuries (including sunburn) and preeclampsia.

31. A polypeptide according to any one of claims 1 to 28 or an amide, an ester or a salt thereof, for use as a medicament.

32. A polypeptide according to any one of claims 1 to 28 or an amide, an ester of a salt thereof, for use in the treatment or prevention of a disease or disorder responsive to the agonism of the APJ receptor.

33. A polypeptide according to any one of claims 1 to 28 or an amide, an ester of a salt thereof, for use in the treatment of acute decompensated heart failure (ADHF), chronic heart failure, pulmonary hypertension, atrial fibrillation, Brugada syndrome, ventricular tachycardia, atherosclerosis, hypertension, restenosis, ischemic cardiovascular diseases, cardiomyopathy, cardiac fibrosis, arrhythmia, water retention, diabetes (including gestational diabetes), obesity, peripheral arterial disease, cerebrovascular accidents, transient ischemic

attacks, traumatic brain injuries, amyotrophic lateral sclerosis, burn injuries (including sunburn) or preeclampsia.

34. A Combination comprising a therapeutically effective amount of a polypeptide according to anyone of claims 1-28 or an amide, an ester or a salt thereof, and one or more therapeutically active co-agent.

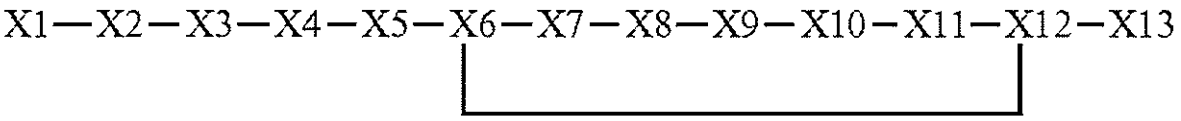
35. A combination according to claim 34 wherein the co-agent is selected from inotropes, beta adrenergic receptor blockers, HMG-Co-A reductase inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) Inhibitors, calcium channel blockers (CCB), endothelin antagonists, renin inhibitors, diuretics, ApoA-I mimics, anti-diabetic agents, obesity-reducing agents, aldosterone receptor blockers, endothelin receptor blockers, aldosterone synthase inhibitors (ASI), a CETP inhibitor, anti-coagulants, relaxin, BNP (nesiritide) and/or a NEP inhibitor..

36. A pharmaceutical composition comprising a therapeutically effective amount of a polypeptide according to any one of claims 1 to 28 or an amide, an ester or a salt thereof, and one or more pharmaceutically acceptable carriers.

What is claimed is:

1. A polypeptide having the following formula I' (SEQ ID NO: 74):

I'



wherein:

X1 is the N-terminus of the polypeptide and is either absent or is selected from pE, R, Isn, Q, A, K, and 5-amino-valeric acid;

X2 is R, A, r, N-Me-R, K, H, hF, hK, F, E or Orn;

X3 is P, A, a, p, 4-PhP, K, D, pipecolic acid, or cysteine wherein the side chain of cysteine forms a disulfide bond with the side chain of the cysteine at the X7 position;

X4 is R, A, r, N-Me-R, F, E or cysteine wherein the side chain of cysteine forms a disulfide bond with the side chain of the cysteine at the X7 position;

X5 is L, Cha, A, D-L, N-Me-L, K, D, 4-PhF or F;

X6 and X12 are independently a natural or unnatural amino acid selected from C, c, hC, D-hC, K, D, Orn, Dab or E wherein the side chain of X6 and X12 are linked together via a covalent bond forming either a monosulfide (—S—), a disulfide (—S—S—) or an amide bond (—NHC(O)— or —C(O)—NH—) or a linkage of Formula —S—CH_2—C(=Z)—CH_2—S—; wherein Z is O, N—O—CH_2C(O)—L^1-R^1 or N—NH—CH_2C(O)—L^1-R^1 wherein R^1 is a fatty acid derivative and L^1 is a linker containing one or more amino acids and/or one or more —NH—C_{2-6}-alkylene-NH— units;

or alternatively X6 is K, X13 is absent and X12 is F or f wherein the C-terminus of X12 form an amide bond with the amino side chain of X6;

X7 is H, h, A, N-Me-A, a, Aib, K, NaI, F, P, Dap, N, E or cysteine wherein the side chain of the cysteine forms a disulfide bond with the side chain of the cysteine at position X3 or with the side chain of the cysteine at position X4;

X8 is K, k, F, f, A, hF, N-Me-R, E or 4-amino-Isn;

X9 is G, N-Me-G, A, D, L, R or Aib;

X10 is P, A, p, 4-PhP or pipecolic acid,

X11 is M, D-Nle, Nle, N-Me-Nle, M(O), A, F, Y, L, K, 3-PyA or Cha; and

X13 is the C-terminus and is absent or is selected from F, f, N-Me-F, NaI, D-NaI, 3-Br—F, (S)-β-3-F, I, A, a, K, Dap, H and E;

wherein:

Nle is L-norleucine;

D-hC is D-homocysteine

hC is L-homocysteine;

hF is L-homophenylalanine;

hK is L-lysine;

NaI is L-naphathaline;

Orn is ornithine;

Aib is α-aminoisobutyric acid;

Dab is (S)-diaminobutyric acid;

Dap is (S)-2,3-diaminopropionic acid;

M(O) is methionine sulfone;

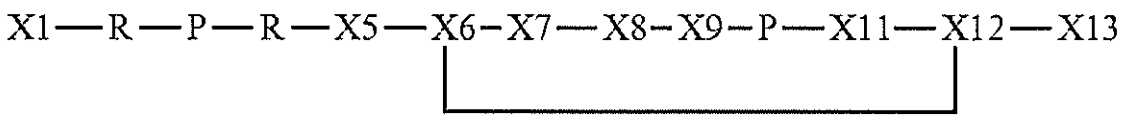
Cha is (S)-β-cyclohexylalanine;

4-amino-Isn is 4-aminopiperidine-4-carboxylic acid;

Isn is isonipecotinoyl;
pE is L-pyroglutamic acid;
3-PyA is 3-(3-pyridyl)-L-alanine;
4-PhF is 4-Phenyl-L-phenylalanine;
wherein the N-terminus and the C-terminus optionally form a ring together with 1, 2, 3 or 4 glycine amino acids; and
wherein the amino group in the side chain of K, Orn, Dab, Dap, hK or 4-amino-Isn is optionally linked to a lipophilic group via an amide bond;
or an amide, an ester or a salt of the polypeptide; or a polypeptide substantially equivalent thereto.

2. The polypeptide according to claim **1** having the following formula (SEQ ID NO: 75):

II



X1 is absent, pE, R, Q or Isn;
X5 is L or Cha;
X7 is H, Aib, F, K(Lauroyl) or K(Palmitoyl);
X8 is K, F or 4-amino-Isn;
X9 is G or Aib;
X11 is Nle or Cha;
X13 is absent or is F, f, K(Lauroyl), K(Palmitoyl);

X6 and X12 are independently a natural or unnatural amino acid selected from C, c, hc, D-hc, K, D, Orn, Dab or E wherein the side chain of X6 and X12 are linked together via a covalent bond forming either a disulfide or an amide bond; and wherein the N-terminus and the C-terminus optionally form a ring together with 1, 2, 3 or 4 glycine amino acids; or an amide, an ester or a salt of the polypeptide; or a polypeptide substantially equivalent thereto.

3. The polypeptide according to claim **1** having the sequence of (SEQ ID NO:76) wherein:

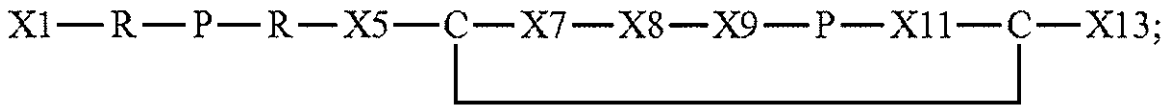
X6 and X12 are independently selected from K, Orn, Dab, E and D and wherein the side chain of X6 and X12 together form an amide bond; or a salt of the polypeptide.

4. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 77) wherein:

X6 and X12 are independently C wherein the side chain of X6 and X12 together form a disulfide bond; or a salt of the polypeptide.

5. The polypeptide of claim **1** having Formula III (SEQ ID NO: 78):

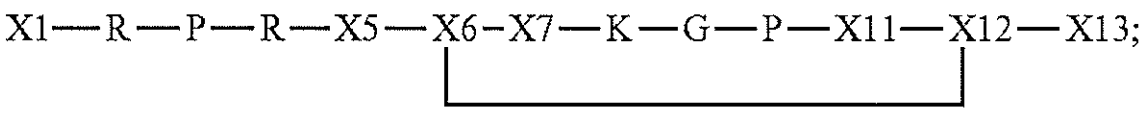
III



or a salt of the polypeptide.

6. The polypeptide according to claim **1** having Formula IV (SEQ ID NO: 79):

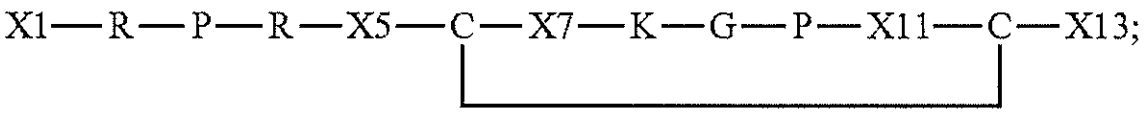
IV



or a salt of the polypeptide.

7. The polypeptide according to claim **1** having Formula V (SEQ ID NO: 80):

V



or a salt of the polypeptide.

8. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 86) wherein X1 is pE; or a salt of the polypeptide.

9. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 87) wherein X1 is absent; or a salt of the polypeptide.

10. The polypeptide according to claim **9** wherein the N-terminus is an amide; or a salt of the polypeptide.

11. The polypeptide according to claim **10** wherein the N-terminus is an amide of Formula —NHR and R is Acetyl,

benzoyl, phenacyl, succinyl, octanoyl, 4-phenylbutanoyl, 4-Cl-Ph-$(CH_2)_3C(O)$—, or Ph-$CH_2CH_2NHC(O)$—; or a salt of the polypeptide.

12. The polypeptide of claim **1** wherein the N-terminus is an amide of Formula NHR1 wherein R1 is $CH_3C(O)$—, CH_3—$(O$—$CH_2CH_2)_m$—C(O)—, Palmitoyl$(O2Oc)_p$, Myristoyl$(O2Oc)_p$, Lauroyl$(O2Oc)_p$ or Ph-$CH_2CH_2NHC(O)$—; and wherein

p is an integer of 1 to 4;

m is an integer of 1 to 12;

Lauroyl(O2Oc) is $C_{11}H_{23}C(O)NH$—$(CH_2)_2$—O—$(CH_2)_2$—O—CH_2—C(O)—;

Myristoyl(O2Oc) is $C_{13}H_{27}C(O)NH$—$(CH_2)_2$—O—$(CH_2)_2$—O—CH_2—C(O)—;

Palmitoyl(O2Oc) is $C_{15}H_{31}C(O)NH$—$(CH_2)_2$—O—$(CH_2)_2$—O—CH_2—C(O)—; or a salt of the polypeptide.

13. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 88) wherein X13 is F; or a salt of the polypeptide.

14. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 89) wherein X13 is absent; or a salt of the polypeptide.

15. The polypeptide according to claim **14** wherein the C-terminus is an amide; or a salt of the polypeptide.

16. The polypeptide according to claim **15** wherein the C-terminus is an amide of Formula —C(O)—R2 and R2 is —NH_2, —NH-Me, —NH—NHBn, or —NH—$(CH_2)_2$-Ph; or a salt of the polypeptide.

17. The polypeptide according to claim **16** having the sequence of (SEQ ID NO: 90) wherein X5 is L; or a salt of the polypeptide.

18. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 91) wherein X7 is H; or a salt of the polypeptide.

19. The polypeptide according to claim **1** having the sequence of (SEQ ID NO: 94) wherein X11 is Nle, or a salt of the polypeptide.

20. The polypeptide according to claim **1** selected from:

pE-R-P-R-L-K*-H-F-G-P-Nle-D*-Phenethylamine (SEQ ID NO: 8),

pE-R-P-R-L-K*-H-F-G-P-Nle-E*-Phenethylamine (SEQ ID NO: 9),

pE-R-P-R-L-Orn*-H-F-G-P-Nle-D*-Phenethylamine (SEQ ID NO: 10),

pE-R-P-R-L-Dab*-H-F-G-P-Nle-D*-Phenethylamine (SEQ ID NO: 11),

pE-R-P-R-L-K*-F-K-G-P-Nle-F* (SEQ ID NO: 12),

pE-R-P-R-L-K*-F-K-G-P-Nle-f* (SEQ ID NO: 13),

Q-R-P-R-L-C*-F-K-G-P-Nle-C*-F-G-G (SEQ ID NO: 14),

pE-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 15),

pE-R-P-R-L-C*-Aib-K-G-P-Nle-C*-F-OH (SEQ ID NO: 16),

pE-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-OH (SEQ ID NO: 17),

H-Isn-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-OH (SEQ ID NO: 18),

pE-R-P-R-L-C*-H-K-G-P-Nle-C*-Phenethylamine (SEQ ID NO: 19),

pE-R-P-R-L-C*-H-K-G-P-Nle-C*-f-OH (SEQ ID NO: 20),

pE-R-P-R-Cha-C*-H-K-G-P-Cha-C*-F-OH (SEQ ID NO: 21),

pE-R-P-R-L-C*-F-K-G-P-Nle-C*-F-OH (SEQ ID NO: 22),

H-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 23),
H-R-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 24),
H-Isn-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 25),
pE-R-P-R-L-C*-H-F-G-P-Nle-C*-Phenethylamine (SEQ ID NO: 26),
pE-R-P-R-L-C*-H-K-Aib-P-Nle-C*-F-OH (SEQ ID NO: 27),
pE-R-P-R-L-C*-H-(4-NH-Isn)-G-P-Nle-C*-F-OH (SEQ ID NO: 28),
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-K(Palmitoyl)-OH (SEQ ID NO: 29),
pE-R-P-R-L-C*-K(Palmitoyl)-K-G-P-Nle-C*-F-OH (SEQ ID NO: 30),
Palmitoyl-O2Oc-Q-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 31),
Lauroyl-O2Oc-Q-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 32),
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-K(Lauroyl)-OH (SEQ ID NO: 33),
pE-R-P-R-L-C*-K(Lauroyl)-K-G-P-Nle-C*-F-OH (SEQ ID NO: 34),

pE-R-P-C**-L-C*-C**-K-G-P-Nle-C*-F-OH (SEQ ID NO: 35),
pE-R-C**-R-L-C*-C**-K-G-P-Nle-C*-F-OH (SEQ ID NO: 36);
pE-r-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 37);
pE-F-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 38);
pE-E-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 39);
pE-R-p-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 40);
pE-R-K-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 41);
pE-R-D-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 42);
pE-R-P-F-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 43);
pE-R-P-R-K-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 44);
pE-R-P-R-L-C*-H-E-G-P-Nle-C*-F-OH (SEQ ID NO: 45);
pE-R-P-R-L-C*-H-K-D-P-Nle-C*-F-OH (SEQ ID NO: 46);
pE-R-P-E-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 47);
pE-R-P-R-(4-PhF)-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 48);
pE-R-P-R-D-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 49);
pE-R-P-R-L-C*-E-K-G-P-Nle-C*-F-OH (SEQ ID NO: 50);

pE-R-P-R-L-C*-H-K-L-P-Nle-C*-F-OH (SEQ ID NO: 51);
pE-R-P-R-L-C*-H-K-R-P-Nle-C*-F-OH (SEQ ID NO: 52);
pE-R-P-R-L-C*-H-K-G-(Pipecolic acid)-Nle-C*-F-OH (SEQ ID NO: 53);
pE-R-P-R-L-C*-H-K-G-P-(3-PyA)-C-F-OH (SEQ ID NO: 54);
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-H-OH (SEQ ID NO 55);

pE-R-P-R-L-C*-H-K-G-P-Nle-C*-E-OH (SEQ ID NO 56);
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-NH_2(SEQ ID NO: 70);
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-F-NH_2(SEQ ID NO: 69);
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-OH (SEQ ID NO: 57);
pE-R-P-R-L-C*-H-K-G-P-Nle-hC*-F-OH (SEQ ID NO: 58);
pE-R-P-R-L-hC*-H-K-G-P-Nle-hC*-F-OH (SEQ ID NO: 59);
pE-R-P-R-L-c*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 60);
pE-R-P-R-L-C*-H-K-G-P-Nle-(D-hC)*-F-OH (SEQ ID NO 61);
pE-R-P-R-L-(D-hC)*-H-K-G-P-Nle-(D-hC)*-F-OH (SEQ ID NO 62);
MyristoylO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C*-f-OH (SEQ ID NO 65);
MyristoylO2OcO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C*-f-OH (SEQ ID NO 66);
MyristoylO2OcO2OcO2OcO2OcQ-R-P-R-L-C*-H-K-G-P-Nle-C-f-OH (SEQ ID NO 67);

pE-R-P-R-L-C*H-K-G-P-Nle-c*-F-OH (SEQ ID NO 63);
pE-R-P-R-L-c*-H-K-G-P-Nle-c*-F-OH (SEQ ID NO: 64);
pE-R-P-R-L-C*-H-K(Myr)-G-P-Nle-C*-F-OH (SEQ ID NO: 68) and
pE-R-P-R-L-C***-H-K-G-P-Nle-C***-F-OH (SEQ ID NO: 71);
wherein the two amino acids labeled with "*" represent the amino acids forming a disulfide or amide bond via their side chain or terminus, respectively and wherein the two amino acids labeled with "**" represent the amino acids forming a disulfide via their side chain or an amide bond via their termini; and wherein the 2 amino acids labeled with "***" represent the amino acids forming a mono-sulfide bond or a —S—CH_2—C(O)—CH_2—S— linkage via their side chain; or a salt of the polypeptide.

21. The polypeptide of claim **20** selected from:
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 15),
pE-R-P-R-L-C*-Aib-K-G-P-Nle-C*-F-OH (SEQ ID NO: 16),
pE-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-OH (SEQ ID NO: 17),
H-Isn-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-OH (SEQ ID NO: 18),
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-Phenethylamine (SEQ ID NO: 19),
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-f-OH (SEQ ID NO: 20),

pE-R-P-R-Cha-C*-H-K-G-P-Cha-C*-F-OH (SEQ ID NO: 21),
pE-R-P-R-L-C*-F-K-G-P-Nle-C*-F-OH (SEQ ID NO: 22),
H-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 23),
H-R-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 24),
H-Isn-R-P-R-L-C*-H-K-G-P-Nle-C*-F-OH (SEQ ID NO: 25), and
pE-R-P-R-L-C*-H-F-G-P-Nle-C*-Phenethylamine (SEQ ID NO: 26); wherein the side chains of the 2 cysteine amino acids C* together form a disulfide bond; or a salt of the polypeptide.

22. A pharmaceutical composition comprising a therapeutically effective amount of the polypeptide according to claim **1** or an amide, an ester or a salt thereof, and one or more pharmaceutically acceptable carriers.

23. A polypeptide, or a salt thereof, selected from:
H-Isn-R-P-R-L-C*-Aib-K-G-P-Nle-C*-f-OH (SEQ ID NO: 18),
pE-R-P-R-L-C*-H-K-G-P-Nle-C*-Phenethylamine (SEQ ID NO: 19),

pE-R-P-R-Cha-C*-H-K-G-P-Cha-C*-F-OH (SEQ ID NO: 21)
pE-R-P-R-L-C*-F-K-G-P-Nle-C*-F-OH (SEQ ID NO: 22); wherein the side chains of the 2 cysteine amino acids C* together form a disulfide bond.

24. A pharmaceutical composition comprising a therapeutically effective amount of the polypeptide according to claim **23**, or a salt thereof, and one or more pharmaceutically acceptable carriers.