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(54) Title: SYNTHETIC LINEAR APELIN MIMETICS FOR THE TREATMENT OF HEART FAILURE

X1-X2-X3-R-X5-X6-X7-X8-X9-X10-X11-X12-X13

(57) Abstract: The invention relates to novel compositions comprising modified apelin-13 peptide sequences designed to treat cardiovascular disease in subjects to whom they are administered, and which exhibit greater resistance to degradation, and equivalent or greater bioactivity than their wild type counterparts. The invention also relates to methods of making said compositions and using said compositions as pharmaceutically active agents to treat cardiovascular disease.



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AMENDED CLAIMS

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

X1-X2-X3-R-X5-X6-X7-X8-X9-X10-X11-X12-X13

wherein:

X1 is the N-terminus of the polypeptide and is either absent, Q, A or pE;

X2 is R or r;

X3 is P or 4-PhP;

X5 is L, Cha, D-L, F, Y, Y(Bzl), 3,4-Cl₂-F or Nal;

X6 is a D-amino acid, S or A;

X7 is a D-amino acid, L, H or Aib; and at least one of X6 and X7 is D-amino acid or Aib;

X8 is K, k, Q or E;

X9 is G or D;

X10 is P or pipecolic acid;

X11 is D-Nle, Nle, f or D-Nva;

X12 is absent, P or a D-amino acid;

X13 is the C-terminus and is absent, F or a D-amino acid; and at least one of X11, X12 and X13 is a D-amino acid;

wherein:

Nle is L-norleucine;

D-Nle is D-norleucine;

Nal is L-naphthyl)alanine;

D-Nva is D-norvaline;

Aib is α -aminoisobutyric acid;

Cha is (S)- β -cyclohexylalanine;

D-Tic is D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

pE is L-pyroglutamic acid;

3,4-Cl₂-F is (S)-3,4-dichlorophenylalanine;

Y is L-tyrosine; and

Y(Bzl) is L-benzyl-tyrosine;

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

2. The polypeptide of claim 1 wherein X6 and X12 are D-amino acids (SEQ ID NO: 4); or an amide, an ester or a salt thereof.

3. The polypeptide of claim 2 wherein X13 is D-amino acid (SEQ ID NO: 5); or an amide, an ester or a salt thereof.

4. The polypeptide of claim 3 wherein X11 is D-amino acid (SEQ ID NO: 6); or an amide, an ester or a salt thereof.

5. The polypeptide of claim 1 wherein X6 and X13 are D-amino acids (SEQ ID NO: 7); or an amide, an ester or a salt thereof.

6. The polypeptide of claim 1 wherein X7 and X12 are D-amino acids (SEQ ID NO: 8); or an amide, an ester or a salt thereof.

7. The polypeptide of claim 6 wherein X13 is a D-amino acid (SEQ ID NO: 9); or an amide, an ester or a salt thereof.

8. A polypeptide according to anyone of claims 1 to 7 having the following formula (SEQ ID NO: 10):

X1-R-P-R-X5-a-X7-X8-G-P-X11-X12-X13

II

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

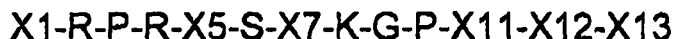
9. The polypeptide according to anyone of claims 1 to 8 having Formula III (SEQ ID NO: 11):

X1-R-P-R-X5-X6-X7-K-G-P-X11-a-f

III;

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

10. The polypeptide according to anyone of claims 1, 6, 7 and 9 having Formula IV (SEQ ID NO: 12):



IV;

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

11. The polypeptide according to anyone of claims 1 to 9 wherein X6 is a D-amino acid selected from a, D-Leu, k, s, d, nva, abu, f, h, v and D-Cys(tBu) (SEQ ID NO: 13); or an amide, an ester or a salt thereof.

12. The polypeptide according to anyone of claims 1 to 11 wherein X7 is Aib or a D-amino acid selected from a, f and h (SEQ ID NO: 14); or an amide, an ester or a salt thereof.

13. The polypeptide of anyone of claims 1 to 12 wherein X12 is absent or a D-amino acid selected from a, f, p, e, r, abu, nva, and D-Leu (SEQ ID NO: 15); or an amide, an ester or a salt thereof.

14. The polypeptide of anyone of claims 1 to 13 wherein X13 is absent or is a D-amino acid selected from f, y, d, and D-Tic (SEQ ID NO: 16), or an amide, an ester or a salt thereof.

15. The polypeptide according to claim 14 wherein X13 is absent or f (SEQ ID NO: 17); or an amide, an ester or a salt of the polypeptide.

16. The polypeptide according to anyone of the preceding claims wherein X1 is pE (SEQ ID NO: 18); or an amide, an ester or a salt of the polypeptide.

17. The polypeptide according to anyone of claims 1 to 16 wherein X5 is L (SEQ ID NO: 20); or an amide, an ester or a salt of the polypeptide.

18. The polypeptide according to anyone of claims 1 to 17 wherein X8 is K (SEQ ID NO: 21); or an amide, an ester or a salt of the polypeptide.

19. The polypeptide according to anyone of claims 1 to 18 wherein X11 is Nle or nle (SEQ ID NO: 22); or an amide, an ester or a salt of the polypeptide.
20. The polypeptide according to anyone of the preceding claims 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 -NH₂, -NH-(CH₂)₂-Ph or 4-phenoxyperidine; or a salt of the polypeptide.
22. The polypeptide according to claim 1 selected from:

pE-R-P-R-L-a-H-K-G-P-lp-nle-a-f-OH (SEQ ID NO: 24)
pE-R-P-R-(D-Leu)-S-a-K-G-P-nle-a-f-OH (SEQ ID NO: 25)
pE-r-P-R-L-a-H-K-G-P-nle-a-f-OH (SEQ ID NO: 26)
pE-R-P-R-(D-Leu)-S-Aib-K-G-P-nle-a-f-OH (SEQ ID NO: 27)
pE-R-P-R-L-S-Aib-k-G-P-nle-a-f-OH (SEQ ID NO: 28)
pE-R-P-R-L-a-H-K-G-P-nle-f-OH (SEQ ID NO: 29)
pE-R-P-R-L-c(tBu)-H-K-G-P-nle-a-f-OH (SEQ ID NO: 30)
pE-R-P-R-L-d-H-K-G-P-nle-a-f-OH (SEQ ID NO: 31)
pE-R-(trans-4-PhP)-R-L-a-H-K-G-P-nle-a-f-OH (SEQ ID NO: 32)
pE-R-P-R-L-(D-Leu)-H-K-G-P-nle-a-f-OH (SEQ ID NO: 33)
pE-R-P-R-L-k-H-K-G-P-nle-a-f-OH (SEQ ID NO: 34)
pE-R-P-R-L-s-H-K-G-P-nle-a-f-OH (SEQ ID NO: 35)
pE-R-P-R-L-a-H-K-G-P-nle-p-f-OH (SEQ ID NO: 36)
pE-R-P-R-L-a-H-K-G-P-nle-(D-Leu)-f-OH (SEQ ID NO: 37)
pE-R-P-R-L-a-Aib-K-G-P-nle-a-f-OH (SEQ ID NO: 38)
pE-R-P-R-L-a-h-K-G-P-nle-a-f-OH (SEQ ID NO: 39)
pE-R-P-R-L-a-F-K-G-P-nle-a-f-OH (SEQ ID NO: 40)
pE-R-P-R-L-a-H-K-G-P-nle-F-OH (SEQ ID NO: 41)
pE-R-P-R-L-a-H-K-G-P-nle-e-f-OH (SEQ ID NO: 42)
pE-R-P-R-L-a-H-K-G-P-nle-r-f-OH (SEQ ID NO: 43)
pE-R-P-R-L-a-H-K-G-P-nle-a-y-OH (SEQ ID NO: 44)
pE-R-P-R-L-a-H-K-G-P-nle-a-d-OH (SEQ ID NO: 45)
pE-R-P-R-Cha-a-H-K-G-P-nle-a-f-OH (SEQ ID NO: 46)

<i>pE-R-P-R-(3,4-Cl₂-F)-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 47)
<i>pE-R-P-R-(2-Nal)-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 48)
<i>pE-R-P-R-L-a-H-K-G-P-nle-a-tic-OH</i> (SEQ ID NO: 49)
<i>pE-R-P-R-Y(Bzl)-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 50)
<i>pE-R-P-R-Y-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 51)
<i>pE-R-P-R-L-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 52)
<i>pE-R-P-R-L-a-H-K-G-P-Nle-a-f-OH</i> (SEQ ID NO: 53)
<i>pE-R-P-R-L-a-H-k-G-P-Nle-a-f-OH</i> (SEQ ID NO: 54)
<i>pE-R-P-R-L-a-H-K-G-P-nle-NH(Phenethyl)</i> (SEQ ID NO: 55)
<i>pE-R-P-R-L-a-H-K-G-P-nle-a-f-NH₂</i> (SEQ ID NO: 56)
<i>pE-R-P-R-L-a-H-K-G-P-Nle-P-f-OH</i> (SEQ ID NO: 57)
<i>pE-R-P-R-L-a-H-K-G-P-Nle-f-OH</i> (SEQ ID NO: 58)
<i>pE-R-P-R-L-a-H-K-G-P-nle-a-NH(Phenethyl)</i> (SEQ ID NO: 59)
<i>pE-R-P-R-L-S-Aib-K-G-P-nle-a-F-OH</i> (SEQ ID NO: 60)
<i>pE-R-P-R-L-S-Aib-K-G-P-Nle-a-f-OH</i> (SEQ ID NO: 61)
<i>pE-R-P-R-L-a-H-K-G-P-Nle-a-F-OH</i> (SEQ ID NO: 62)
<i>pE-R-P-R-L-S-Aib-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 63)
<i>pE-R-P-R-L-S-Aib-K-G-P-Nle-P-f-OH</i> (SEQ ID NO: 64)
<i>pE-R-P-R-L-S-Aib-K-G-P-Nle-a-F-OH</i> (SEQ ID NO: 65)
<i>pE-R-P-R-L-a-H-K-G-P-nle-(4-Phenoxypiperidin-1-yl)</i> (SEQ ID NO: 66)
<i>pE-R-P-R-L-abu-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 67)
<i>pE-R-P-R-L-a-H-K-G-P-nle-abu-f-OH</i> (SEQ ID NO: 68)
<i>pE-R-P-R-L-a-f-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 69)
<i>pE-R-P-R-L-a-L-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 70)
<i>pE-R-P-R-L-a-a-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 71)
<i>pE-R-a-R-L-a-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 72)
<i>H-R-P-R-L-a-H-K-G-P-nle-f-OH</i> (SEQ ID NO: 73)
<i>pE-R-P-R-L-S-a-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 74)
<i>pE-R-P-R-L-nva-H-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 75)
<i>pE-R-P-R-L-a-H-K-G-P-nva-a-f-OH</i> (SEQ ID NO: 76)
<i>pE-R-P-R-L-a-H-K-G-P-nle-nva-f-OH</i> (SEQ ID NO: 77)
<i>pE-R-P-R-L-S-f-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 78)
<i>pE-R-P-R-L-S-h-K-G-P-nle-a-f-OH</i> (SEQ ID NO: 79)

pE-R-P-R-L-a-H-K-G-P-f-a-f-OH (SEQ ID NO: 80)
pE-R-P-R-L-A-h-K-G-P-nle-a-f-OH (SEQ ID NO: 81)
pE-R-P-R-L-a-H-Q-G-P-nle-a-f-OH (SEQ ID NO: 82)
pE-R-P-R-L-a-H-E-G-P-nle-a-f-OH (SEQ ID NO: 83)
pE-R-P-R-L-v-H-K-G-P-nle-a-f-OH (SEQ ID NO: 84)
pE-R-P-R-L-a-H-K-D-P-nle-a-f-OH (SEQ ID NO: 85);
pE-R-P-R-Cha-nva-H-K-G-P-nle-a-f-OH (SEQ ID NO: 86)

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

23. The polypeptide of claim 22 selected from:

pE-R-P-R-L-a-H-K-G-P-nle-a-f-OH (SEQ ID NO: 52)
pE-R-P-R-L-a-H-K-G-Pip-nle-a-f-OH (SEQ ID NO: 24)
pE-R-P-R-(D-Leu)-S-Aib-K-G-P-nle-a-f-OH (SEQ ID NO: 27)
pE-R-P-R-L-a-H-K-G-P-Nle-a-f-OH (SEQ ID NO: 53)
pE-R-P-R-L-a-H-K-G-P-nle-f-OH (SEQ ID NO: 29)
pE-R-P-R-L-d-H-K-G-P-nle-a-f-OH (SEQ ID NO: 31)
pE-R-P-R-L-a-H-K-G-P-nle-(D-Leu)-f-OH (SEQ ID NO: 37)
pE-R-P-R-L-a-Aib-K-G-P-nle-a-f-OH (SEQ ID NO: 38)
pE-R-P-R-L-a-h-K-G-P-nle-a-f-OH (SEQ ID NO: 39)
pE-R-P-R-L-a-F-K-G-P-nle-a-f-OH (SEQ ID NO: 40);
pE-R-P-R-L-a-H-K-G-P-f-a-f-OH (SEQ ID NO: 80);

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

24. The polypeptide according to anyone of the preceding claims wherein the polypeptide has a plasma stability of at least 100 minutes and an IC₅₀ of less than 10 nM.

25. A bloconjugate or multimer thereof comprising:

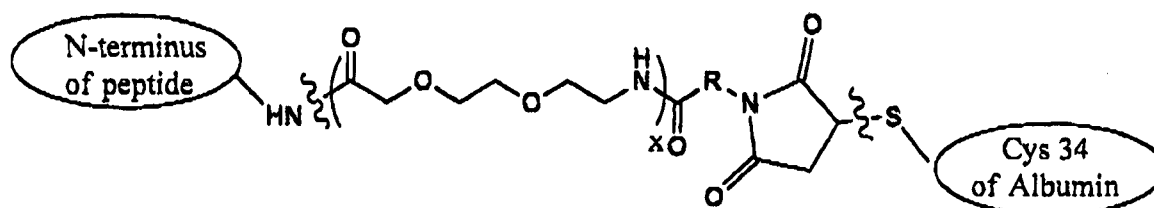
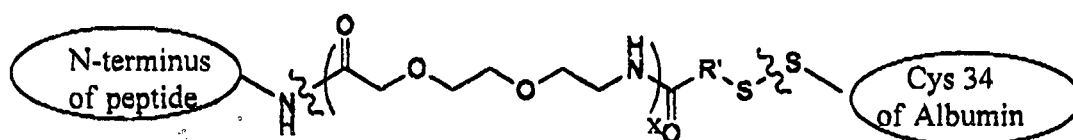
a. a peptide or polypeptide according to any one of claims 1 to 18, or an amide, an ester or a salt thereof, and

b. a half-life extending moiety;

wherein said peptide or polypeptide and half-life extending moiety are covalently linked or fused, optionally via a linker.

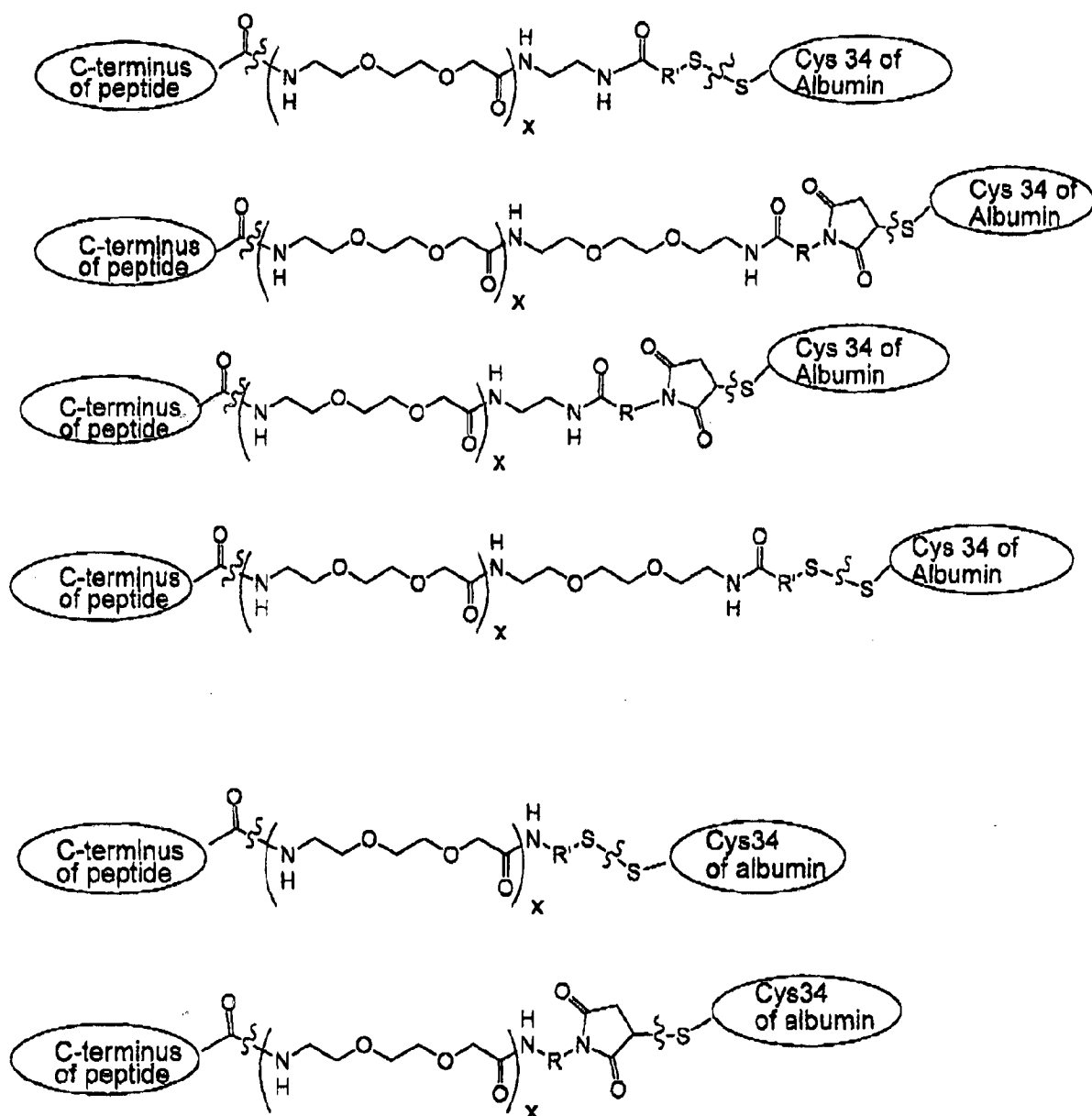
26. The bioconjugate or a mutimer thereof, according to claim 25, wherein the half-life extending moiety is a human Serum Albumin.

27. The bioconjugate according to claim 25 or 26 wherein the Human Serum Albumin is chemically linked to the N-terminus of a polypeptide of any one of Formulae I to IV via a linker of the following Formulae:



wherein x is 1- 20, R is linear or branched alkylene, cycloalkyl, aryl or heteroaryl or combination thereof, R' is linear or branched alkylene, aryl or cycloalkyl or combination thereof.

28. The bioconjugate according to claim 25 or 26 wherein the Human Serum Albumin is chemically linked to the C-terminus of a polypeptide of any one of Formulae I to IV via a linker of the following Formulae:



wherein x is 1-20, R is linear or branched alkylene, cycloalkyl, aryl or heteroaryl or combination thereof, R' is linear or branched alkylene, aryl or cycloalkyl or combination thereof,

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 or an amide, an ester or a salt thereof, or a bioconjugate thereof according to any one of claims 1 to 28.

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

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

33. A polypeptide or an amide, an ester or a salt thereof, or a bioconjugate thereof according to any one of claims 1 to 28, 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 or an amide, an ester or a salt thereof, or a bioconjugate thereof according to any one of claims 1 to 28, 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 or an amide, an ester or a salt thereof, or a bioconjugate thereof according to any one of claims 1 to 28, and one or more pharmaceutically acceptable carriers.