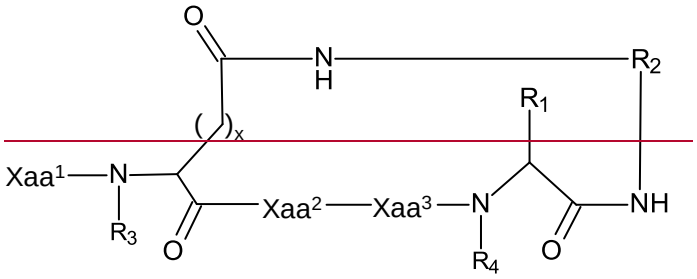
CLAIMS

We claim:

1. A side chain-to-tail diamine-linked cyclized peptide of formula I:



(I)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is $-R_5-R_6$;

Xaa^2 and Xaa^3 are each independently from one to three L- or D-isomer amino acids, or a combination thereof, linked by backbone amide bonds, wherein any backbone nitrogen atom is optionally alkylated with a C_1 to C_8 linear or branched alkyl, and if optionally alkylated, the alkyl optionally forms a ring with the side chain of the same amino acid if said side chain is aliphatic, wherein the ring is optionally substituted;

R_1 is H or an L- or D-isomer amino acid side chain;

R_2 is $-(CH_2)_u-$ or $-(CH_2)_v-O-(CH_2)_w-$;

R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;

R_4 is H or a C_1 to C_8 linear or branched alkyl;

R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, linked by backbone amide bonds, wherein any backbone nitrogen atom is optionally methylated;

R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;

x is from 1 to 5;

u is from 2 to 8;

v is from 2 to 5; and

w is from 2 to 5.

2. The peptide of claim 1 of formula I wherein Xaa^2-Xaa^3 comprises the amino acid sequence D-Phe-Arg- or Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted.

3. The peptide of claim 1 of formula I wherein R_1 is a side chain of the L- or D-isomer amino acid Trp.

4. The peptide of claim 1 of formula I wherein Xaa^2-Xaa^3 comprises the amino acid sequence -His-D-Phe-Arg- or -His-Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

5. The peptide of claim 4 wherein Xaa^2-Xaa^3 consists of the amino acid sequence -His-D-Phe-Arg- or -His-Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted.

6. The peptide of claim 1 of formula I wherein Xaa^2-Xaa^3 comprises the amino acid sequence -His-D-Phe- -His-Phe- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Arg.

7. The peptide of claim 1 of formula I wherein R_5 is an L- or D-isomer of Nle or Arg.

8. The peptide of claim 7 wherein Xaa^2-Xaa^3 comprises the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted.

9. The peptide of claim 7 wherein Xaa^2-Xaa^3 comprises the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

10. The peptide of claim 1 of formula I wherein R_3 is not present and R_4 is a C_1 to C_{17} acyl group.

11. The peptide of claim 10 wherein Xaa^2-Xaa^3 comprises the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted.

12. The peptide of claim 10 wherein Xaa^2-Xaa^3 comprises the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.

13. The peptide of claim 1 of formula I wherein R_5 is an L- or D-isomer of Nle or Arg and R_6 is a C_1 to C_{17} acyl group.

14. The peptide of claim 13 wherein Xaa^2 and Xaa^3 comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optionally substituted.

~~15. The peptide of claim 13 wherein Xaa^2 and Xaa^3 comprise the amino acid sequence -D-Phe-Arg- or -Phe-Arg- wherein the phenyl ring of D-Phe or Phe is optinally substituted and R_1 is a side chain of the L- or D-isomer amino acid Trp.~~

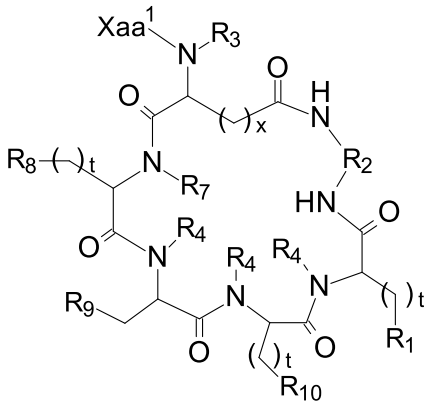
~~16. The peptide of any of claims 2, 4, 5, 6, 8, 9, 11, 12, 15 or 14, wherein the phenyl ring of D-Phe or Phe is optionally substituted with between one and three ring substituents wherein the substituents are the same or different, and each independently comprise halo, $(C_1$-$C_{10})$alkyl halo, $(C_1$-$C_{10})$alkyl, $(C_1$-$C_{10})$alkoxy, $(C_1$-$C_{10})$alkylthio, aryl, $(C_1$-$C_{10})$alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.~~

~~17. The peptide of any of the foregoing claims 1-16 wherein R_2 is $-(CH_2)_u$-.~~

~~18. The peptide of any of the foregoing claims 1-16 wherein R_2 is $-(CH_2)_v$-O-$(CH_2)_w$-.~~

~~19. The peptide of claim 1 wherein the L- or D-isomer amino acids consist of alpha amino acids, beta amino acids, gamma amino acids or delta amino acids, or a combination thereof.~~

1~~20~~. A~~The~~ cyclic peptide of ~~claim 1 wherein the peptide is of~~ formula II:



(II)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is -R_5-R_6;

R_1 is substituted or unsubstituted indole, phenyl or naphthyl;

R_2 is $–(CH_2)_u$- or $–(CH_2)_v$-O-$(CH_2)_w$-;

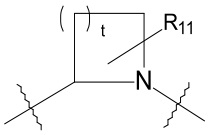
R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;

R_4 is -H or -CH_3;

R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, wherein any backbone nitrogen atom is optionally methylated;

R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;

R_7 is -H, $-CH_3$ or $-CH_2-$, and if it is $-CH_2-$ forms with R_8 a ring of the general structure



;

R_8 is -H if R_8 forms the ring with R_7, or R_8 is

$-(CH_2)_3$,

$-N(R_{12a})(R_{12b})$,

$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,

$-C(=O)-N(R_{12a})(R_{12b})$,

$-O-(R_{12a})$,

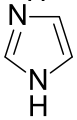
$-S-(=O)_2-CH_3$,

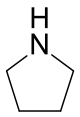
$-S-(=O)-CH_3$,

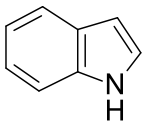
substituted or unsubstituted phenyl,

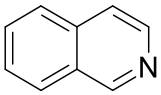
$-O-CH_2-$phenyl, where phenyl is substituted or unsubstituted,

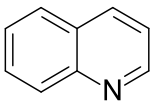

,


,


,


,


, or


;

R_9 is substituted or unsubstituted phenyl or naphthyl;

R_{10} is

$-N(R_{12a})(R_{12b})$,

$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,

$-NH-C(=NH)-N(R_{12a})(R_{12b})$,

$-NH-C(=O)-N(R_{12a})(R_{12b})$,

$-O(R_{12a})$,

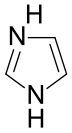
$-C_1$ to C_{17} linear, branched or cyclic alkyl chain,

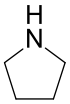
-S(=O)$_2$-CH$_3$,

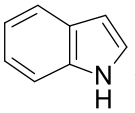
-S(=O)-CH$_3$,

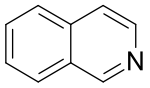
-C(=O)-O(R_{12a}),

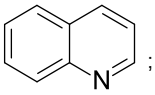
,

,

,

,

 , or

;

R_{11} is -O-CH$_2$-phenyl, where phenyl is substituted or unsubstituted;

R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;

t is in each instance independently from 1 to 4;

x is from 1 to 5;

u is from 2 to 8;

v and w are each independently from 2 to 5; and

z is from 1 to 3.

2~~21~~. The cyclic peptide of claim 1~~20~~ wherein:

(a) R_9 is unsubstituted naphthyl; or~~.~~

22~~.~~ (b) ~~The cyclic peptide of claim 20 wherein~~ any substituted phenyl or naphthyl is in each instance independently substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl; or~~.~~

23~~.~~ (c) ~~The cyclic peptide of claim 20 wherein~~ R_5 comprises at least one L- or D-isomer amino acid; optionally~~.~~

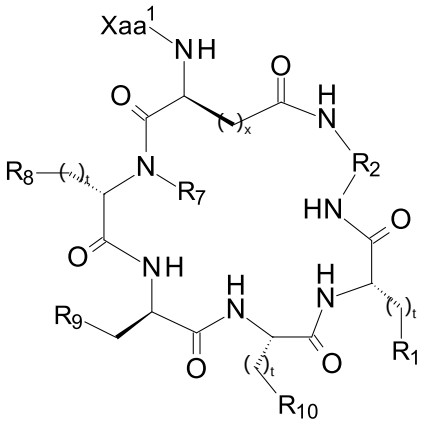
~~24. The cyclic peptide of claim 23~~ wherein R_5 is a single L- or D-isomer amino acid with an aliphatic side chain; optionally~~.~~

~~25. The cyclic peptide of claim 24~~ wherein the aliphatic side chain is -$(CH_2)_3$-CH_3; or~~.~~

~~26.~~ (d) ~~The cyclic peptide of claim 20 wherein~~ R_5 is a single L- or D-isomer amino acid with a side chain comprising at least one nitrogen atom; optionally~~.~~

~~27. The cyclic peptide of claim 26~~ wherein R_5 is an L- or D-isomer of Arg, Lys, Orn, Dab, Dap or Cit.

3~~28~~. The cyclic peptide of claim 1~~20~~ wherein the cyclic peptide of formula II is a cyclic peptide of the formula:



4~~29~~. The cyclic peptide of claim 1~~20~~ or 3~~28~~ wherein Xaa^1 is Ac-Arg, Ac-D-Arg, Ac-Nle, Ac-D-Nle, Ac-Trp, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, acetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl.

5~~30~~. The cyclic peptide of claim 1~~20~~ or 3~~28~~ wherein:

(a) R_1 is indole or naphthalene; or~~.~~

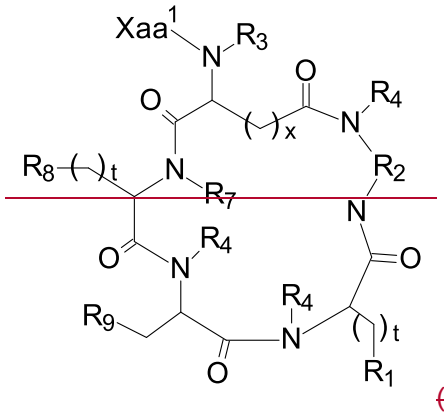
~~31.~~(b) ~~The cyclic peptide of claim 20 or 28 wherein~~ R_7 and R_8 comprise pyrrolidine; optionally ~~.~~

~~32. The cyclic peptide of claim 31~~ wherein pyrrolidine is substituted; optionally ~~.~~

~~33. The cyclic peptide of claim 32~~ wherein the substituent is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted~~.~~; or

~~34.~~ (c) ~~The cyclic peptide of claim 20 or 28 wherein~~ R_9 is substituted phenyl.

35. The peptide of claim 1 wherein the peptide is of formula III:



(III)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is $-R_5-R_6$;

R_1 is

$-N(R_{12a})(R_{12b})$,

$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,

$-NH-C(=NH)-N(R_{12a})(R_{12b})$,

$-NH-C(=O)-N(R_{12a})(R_{12b})$,

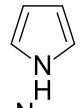
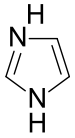
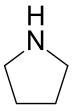
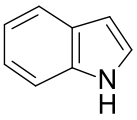
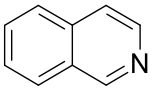
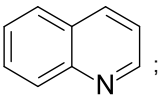
$-O(R_{12a})$,

$-C_1$ to C_{17} linear, branched or cyclic alkyl chain,

$-S(=O)_2-CH_3$,

$-S(=O)-CH_3$,

$-C(=O)-O(R_{12a})$,

5 ——  ,  ,  ,  ,  , or  ;

~~R_2 is $-(CH_2)_u-$ or $-(CH_2)_v-O-(CH_2)_w-$;~~

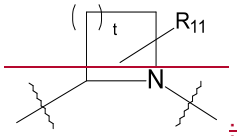
~~R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;~~

~~R_4 is -H or $-CH_3$;~~

~~R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, wherein any backbone nitrogen atom is optionally methylated;~~

~~R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;~~

~~R_7 is -H, $-CH_3$ or $-CH_2-$, and if it is $-CH_2-$ forms with R_8 a ring of the general structure~~



~~;~~

~~R_8 is -H if R_8 forms the ring with R_7, or R_8 is~~

~~-H,~~

~~$-(CH_2)_3$,~~

~~$-N(R_{12a})(R_{12b})$,~~

~~$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,~~

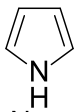
~~$-C(=O)-N(R_{12a})(R_{12b})$,~~

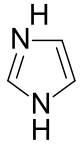
~~$-O-(R_{12a})$,~~

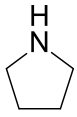
~~$-S-(=O)_2-R_{12a}$,~~

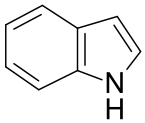
~~substituted or unsubstituted phenyl,~~

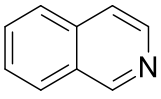
~~$-O-CH_2$-phenyl, where phenyl is substituted or unsubstituted,~~

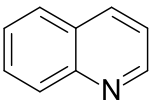

,


,


,


,


, or


;

~~R_9 is substituted or unsubstituted phenyl or naphthyl;~~

~~R_{11} is $-O-CH_2$-phenyl, where phenyl is substituted or unsubstituted;~~

~~R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;~~

~~t is in each instance independently from 1 to 4;~~

~~x is from 1 to 5;~~

~~u is from 2 to 8;~~

~~v and 2 are each independently 2 to 5; and~~

~~z is from 1 to 3.~~

~~36. The cyclic peptide of claim 35 wherein R_9 is unsubstituted naphthyl.~~

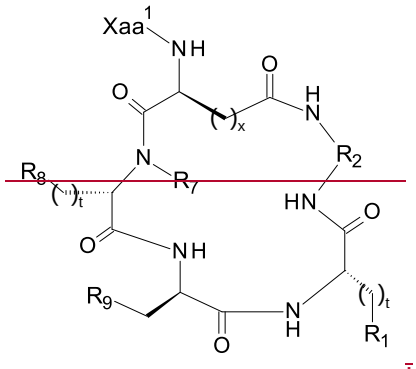
~~37. The cyclic peptide of claim 35 wherein any substituted phenyl or naphthyl is in each instance independently substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.~~

~~38. The cyclic peptide of claim 35 wherein R_5 comprises at least one L- or D-isomer amino acid.~~

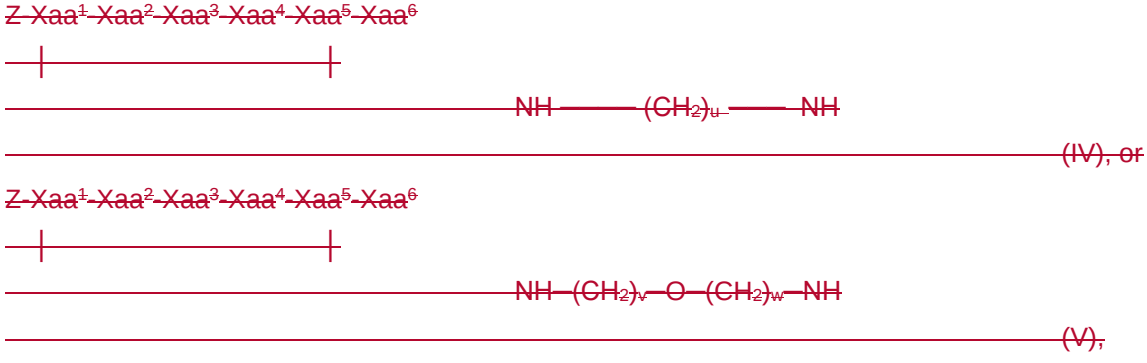
~~39. The cyclic peptide of claim 38 wherein R_5 is a single L- or D-isomer amino acid with an aliphatic side chain.~~

~~40. The cyclic peptide of claim 35 wherein R_6 is acetyl, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl.~~

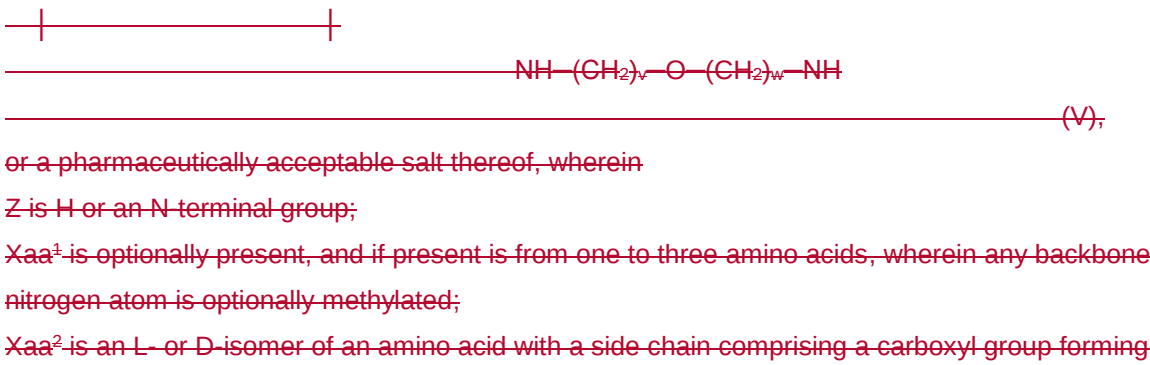
~~41. The cyclic peptide of claim 35 wherein the cyclic peptide of formula III is a cyclic peptide of the formula:~~



42. A cyclic peptide of formula IV or V:



(IV), or



(V),

or a pharmaceutically acceptable salt thereof, wherein

Z is H or an N-terminal group;

Xaa^1 is optionally present, and if present is from one to three amino acids, wherein any backbone nitrogen atom is optionally methylated;

Xaa^2 is an L- or D-isomer of an amino acid with a side chain comprising a carboxyl group forming an amide bond with a first -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

Xaa^3 is an L- or D-isomer amino acid of Pro, optionally substituted with hydroxyl, halogen, sulfonamide, alkyl, -O-alkyl, aryl, alkyl-aryl, alkyl-O-aryl, alkyl-O-alkyl-aryl, -O-alkyl-aryl, or -O-aryl, or

Xaa^3 is an L- or D-isomer amino acid with a side chain comprising at least one primary amine, secondary amine, alkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, ether, sulfide, or carboxyl;

Xaa^4 is an L- or D-isomer amino acid with a side chain comprising substituted or unsubstituted aryl;

Xaa^5 is an L- or D-isomer amino acid with a side chain comprising at least one primary amine, secondary amine, guanidine, urea, alkyl, cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, or ether, and if Xaa^6 is not present, with a C-terminal carboxyl group forming an amide bond with a second -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

Xaa^6 is optionally present, and if present is an L- or D-isomer amino acid with a side chain comprising at least one aryl or heteroaryl, optionally substituted with one or more ring substituents, and when one or more are present, are the same or different and independently hydroxyl, halogen, sulfonamide, alkyl, -O-alkyl, aryl, or -O-aryl, and with a C-terminal carboxyl group forming an amide bond with a second -NH- of the group $-NH-(CH_2)_u-NH-$ or $-NH-(CH_2)_v-O-(CH_2)_w-NH-$;

u is from 2 to 8; and

v and w are each independently from 2 to 5;

wherein the groups $-NH-(CH_2)_u-NH-$ and $-NH-(CH_2)_v-O-(CH_2)_w-NH-$ each comprise a first -NH- and a second -NH-.

43. The cyclic peptide of claim 42 of formula IV or V wherein Z is an N-terminal group selected from the group consisting of a C_1 to C_{17} acyl group comprising a linear or branched alkyl, cycloalkyl, alkyl cycloalkyl, aryl or aralkyl.

44. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^1 is a single amino acid residue selected from the group consisting of Gly or an L- or D-isomer of Ala, Nle, Leu, Ile or Val.

45. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^1 is a single amino acid with a side chain including at least one primary amine, guanidine or urea group.

46. The cyclic peptide of claim 45 of formula IV or V wherein Xaa^1 is an L- or D-isomer of Arg, Lys, Orn, Dab, Dap or Cit.

47. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^4 is D-Phe or Phe, optionally substituted with from one to three ring substituents.

48. The cyclic peptide of claim 47 of formula IV or V wherein the ring substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carboxy, or alkoxy-carbonyl.

49. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^4 is D-Nal 1 or D-Nal 2.

50. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^5 is an L- or D-isomer of of Arg, Lys, Orn, Dab or Dap.

51. The cyclic peptide of claim 42 of formula IV or V wherein Xaa^6 is an L- or D-isomer of Trp, Nal 1 or Nal 2.

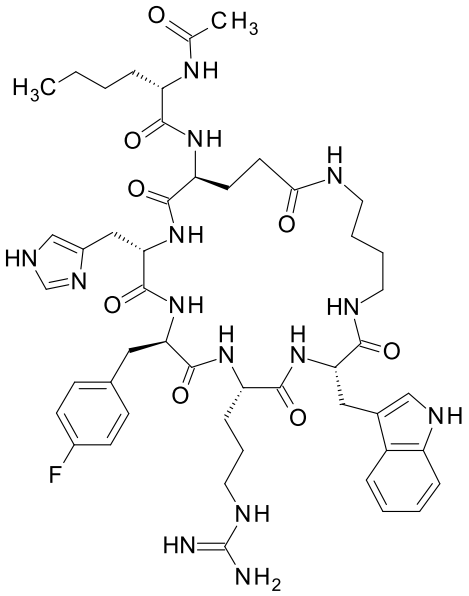
52. The cyclic peptide of claim 42 of formula IV or V wherein:
Z is a C_1 to C_7 linear alkyl acyl group;
Xaa^1 is an L- or D-isomer of Nle or Arg;
Xaa^2 is an L- or D-isomer of Asp or Glu wherein the side chain carboxyl group forms an amide bond with a first -NH- of the group -NH-$(CH_2)_u$-NH- or -NH-$(CH_2)_v$-O-$(CH_2)_w$-NH-;
Xaa^3 is an L- or D-isomer of His, Hyp(Bzl), Met(O_2), or Asn;
Xaa^4 is an L- or D-isomer of substituted or unsubstituted Phe, Nal 1 or Nal 2;
Xaa^5 is an L- or D-isomer of Arg; and
Xaa^6 is an L- or D-isomer of Trp, Nal 1 or Nal 2, wherein the C-terminal carboxyl group thereof forms an amide bond with a second -NH- of the group -NH-$(CH_2)_u$-NH- or -NH-$(CH_2)_v$-O-$(CH_2)_w$-NH-.

53. The cyclic peptide of claim 42 that is of formula IV wherein the side chain carboxyl group of Xaa^2 forms an amide bond with a first -NH- of the group -NH-$(CH_2)_u$-NH and the C-terminal carboxyl group of Xaa^6 forms an amide bond with a second -NH- of the group -NH-$(CH_2)_u$-NH-.

54. The cyclic peptide of claim 42 of formula IV or V wherein at least one backbone nitrogen atom thereof comprises a methyl group.

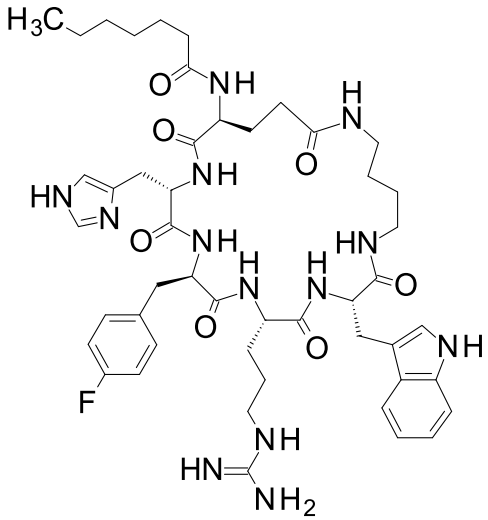
~~55. The cyclic peptide of claim 42 of formula IV or V wherein no backbone nitrogen atom thereof comprises a methyl group.~~

6~~56~~. ~~A~~ The cyclic peptide of claim 1 having the structure



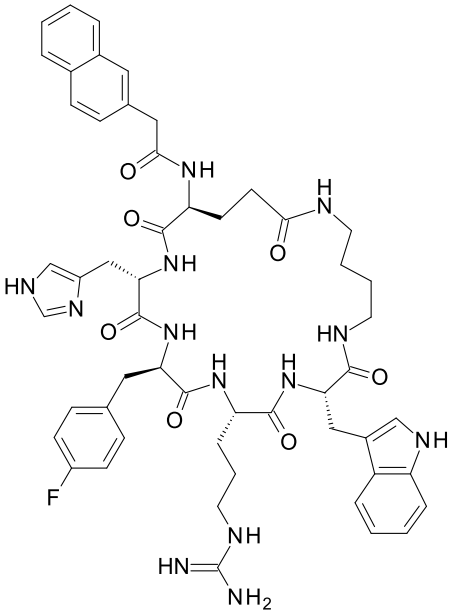
or a pharmaceutically acceptable salt thereof.

7. The cyclic peptide of claim 1 having the structure



or a pharmaceutically acceptable salt thereof.

8. The cyclic peptide of claim 1 having the structure



or a pharmaceutically acceptable salt thereof.

9~~57~~. The cyclic peptide according to any of claims 6-8~~56~~, which is an acetate salt or ~~.~~

~~58. The cyclic peptide according to claim 56, which is~~ a trifluoroacetate salt.

10~~59~~. The~~A~~ cyclic peptide of claim 1 which is

Ac-Nle-Glu-His-D-Phe(4-F)-Arg-Trp
NH ——(CH2)4—— NH

or a pharmaceutically acceptable salt thereof.

11. The cyclic peptide of claim 1 which is

Heptanoyl-Glu-His-D-Phe(4-F)-Arg-Trp
NH ——(CH2)4—— NH

or a pharmaceutically acceptable salt thereof.

12. The cyclic peptide of claim 1 which is

2-Naphthylacetyl -Glu-His-D-Phe(4-F)-Arg-Trp
NH ——(CH2)4—— NH

or a pharmaceutically acceptable salt thereof.

~~60~~13. A pharmaceutical composition comprising the cyclic peptide according to any of claims 6-8~~56~~,

or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~61. A pharmaceutical composition comprising the cyclic peptide according to claim 59, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.~~

1462. The pharmaceutical composition of claim 13 for use in a~~A~~ method for treatment of:

(a) a melanocortin receptor-mediated disease, indication, condition or syndrome in a human or non-human mammal~~, comprising the step of administering pharmaceutical composition of claim 60 or 61~~; or~~.~~

~~63.~~(b) ~~A method for treating~~ a condition responsive to changes in melanocortin receptor function in a human or non-human mammal~~, comprising the step of administering the pharmaceutical composition of claim 60 or 61~~; optionally~~.~~

~~64. The method of claim 63,~~ wherein the melanocortin receptor-mediated disease, indication, condition or syndrome in a human is ocular inflammation; optionally~~.~~

~~65. The method of claim 64,~~ wherein:

(i) the pharmaceutical composition is an aqueous pharmaceutical composition for administration to the surface of the eye; or~~.~~

~~66.~~ (ii) ~~The method of claim 64, wherein~~ the inflammation is caused by an ocular condition, wherein the ocular condition is dry eye disease, corneal ulcer, corneal erosion, corneal abrasion, corneal degeneration, corneal perforation, corneal scarring, epithelial defect, keratoconjunctivitis, idiopathic uveitis, corneal transplantation, age-related macular degeneration, diabetic eye, blepharitis, glaucoma, ocular hypertension, post-operative eye pain and inflammation, posterior segment neovascularization, proliferative vitreoretinopathy, cytomegalovirus retinitis, endophthalmitis, choroidal neovascular membrane, vascular occlusive disease, allergic eye disease, tumor, retinitis pigmentosa, eye infection, scleritis, ptosis, miosis, eye pain, mydriasis, neuralgia, cicatrizing ocular surface disease, ocular infection, inflammatory ocular disease, ocular surface disease, corneal disease, retinal disease, ocular manifestations of systemic diseases, hereditary eye condition, ocular tumor, increased intraocular pressure, herpetic infection, pterygium, a wound sustained to ocular surface, post-photorefractive keratotomy eye pain and inflammation, thermal or chemical burn to the cornea, scleral wound, keratoconus or conjunctival wound; optionally~~.~~

~~67. The method of claim 66,~~ wherein the inflammation is caused by dry eye disease or keratoconjunctivitis sicca.

1568. The pharmaceutical composition of claim ~~60 or 61~~13 wherein the pharmaceutically acceptable carrier is an aqueous solution comprising about 2.79 mg/mL of trisodium citrate dihydrate, about 9 mg/mL of sodium chloride and about 1 mg/mL of polysorbate 80; optionally wherein:~~.~~

the aqueous solution is at about pH 6.5, and the composition further comprises sodium hydroxide or hydrochloric acid as needed to adjust pH.

1669. The pharmaceutical composition of claim 1568 wherein the cyclic peptide is in a trifluoroacetic acid salt form at a concentration of about 1.0 µg/mL.

1770. The pharmaceutical composition of claim 1669 further comprising about 0.10 mg/mL anhydrous citric acid.

~~71. The pharmaceutical composition of claim 68 wherein the aqueous solution is at about pH 6.5, and the composition further comprises sodium hydroxide or hydrochloric acid as needed to adjust pH.~~

1872. The pharmaceutical composition of claim 16 for use in a~~A~~ method of treating dry eye disease or keratoconjunctivitis sicca comprising administering no more than about 50 µL of the pharmaceutical composition of claim 1669 per eye no more often than about three times per day~~.~~; optionally

~~73. The method of claim 72~~ wherein no more than about 150 ng of cyclic peptide or pharmaceutically acceptable salt thereof is administered per eye per day.

1974. An aqueous solution of a melanocortin receptor-specific peptide with an EC_{50} value of less than 1 nM at each of MC1r and MC5r for use in a method of treating dry eye disease or keratoconjunctivitis sicca wherein the method comprises~~es~~ing administering the~~an~~ aqueous solution of a melanocortin receptor-specific peptide with an EC_{50} value of less than 1 nM at each of MC1r and MC5r to the surface of each eye~~.~~; optionally

~~75. The method of claim 74~~ wherein:

(a) ~~~~ no more than about 150 ng of the melanocortin receptor-specific peptide is administered per eye per day as an eye drop; or~~.~~

~~76.~~ (b) ~~The method of claim 74 wherein~~ the melanocortin receptor-specific peptide has an EC_{50} value that at MC1r and MC5r is no greater than the EC_{50} value for at least one of MC3r or MC4r; optionally~~.~~

~~77. The method of claim 76~~ wherein the melanocortin receptor-specific peptide has an EC_{50} value that is at least four times lower at MC1r and MC5r than at least one of MC3r or MC4r; optionally~~.~~

~~78. The method of claim 77~~ wherein the EC_{50} value is at least four times lower at MC1r

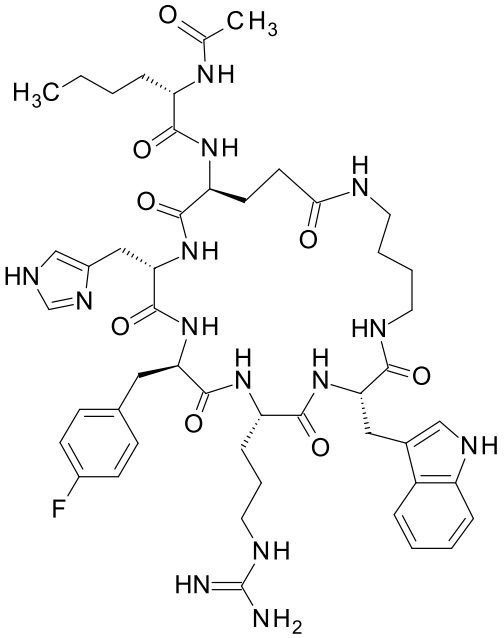
and MC5r than at both MC3r and MC4r; or.

79. (c) The method of claim 74 wherein the peptide is either an agonist or partial agonist at each of MC1r and MC5r; or.

80. (d) The method of claim 74 wherein EC_{50} values are determined by cAMP production using the HTRF detection method as performed by CEREP; or.

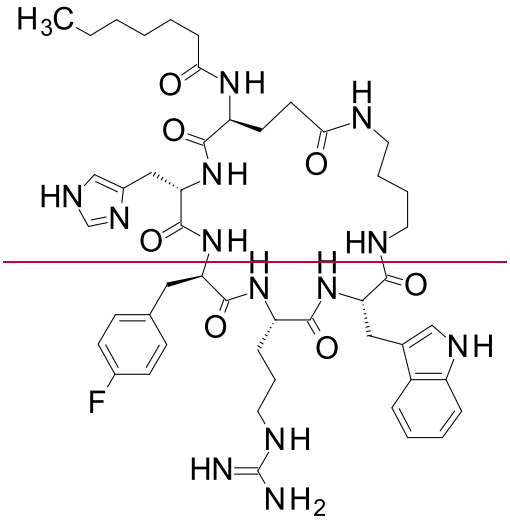
81. (e) The method of claim 74 wherein the melanocortin receptor-specific peptide is a peptide of claim 1; optionally .

82. The method of claim 74 wherein the melanocortin receptor-specific peptide is



.

83. A cyclic peptide having the structure



or a pharmaceutically acceptable salt thereof.

84. The cyclic peptide according to claim 83, which is an acetate salt.

85. The cyclic peptide according to claim 83, which is a trifluoroacetate salt.

86. A cyclic peptide which is

Heptanoyl-Glu-His-D-Phe(4-F)-Arg-Trp

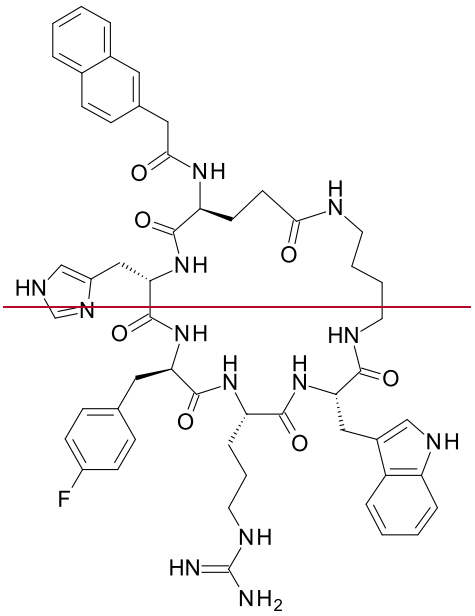


or a pharmaceutically acceptable salt thereof.

87. A pharmaceutical composition comprising the cyclic peptide according to claim 83, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

88. A pharmaceutical composition comprising the cyclic peptide according to claim 86, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

89. A cyclic peptide having the structure



or a pharmaceutically acceptable salt thereof.

90. The cyclic peptide according to claim 89, which is an acetate salt.

91. The cyclic peptide according to claim 89, which is a trifluoroacetate salt.

92. A cyclic peptide which is

2-Naphthylacetyl-Glu-His-D-Phe(4-F)-Arg-Trp



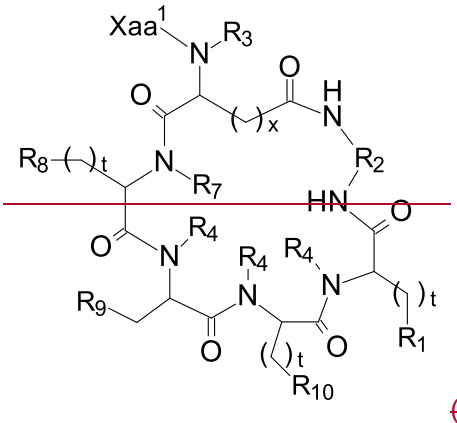
NH $(CH_2)_4$ NH

or a pharmaceutically acceptable salt thereof.

93. A pharmaceutical composition comprising the cyclic peptide according to claim 89, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

94. A pharmaceutical composition comprising the cyclic peptide according to claim 92, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

95. A cyclic peptide of formula II:



(II)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is $-R_5-R_6$;

R_1 is substituted or unsubstituted indole, phenyl or naphthyl;

R_2 is $-(CH_2)_u-$ or $-(CH_2)_v-O-(CH_2)_w-$;

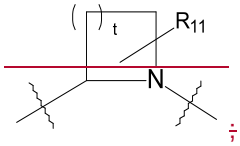
R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;

R_4 is -H or $-CH_3$;

R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, wherein any backbone nitrogen atom is optionally methylated;

R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;

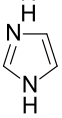
R_7 is -H, $-CH_3$ or $-CH_2-$, and if it is $-CH_2-$ forms with R_8 a ring of the general structure

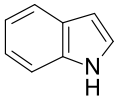
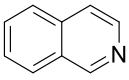
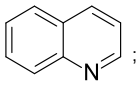


;

R_8 is -H if R_8 forms the ring with R_7, or R_8 is

- ~~$(CH_2)_3$,~~
- ~~$N(R_{12a})(R_{12b})$,~~
- ~~$NH-(CH_2)_z-N(R_{12a})(R_{12b})$,~~
- ~~$C(=O)-N(R_{12a})(R_{12b})$,~~
- ~~$O-(R_{12a})$,~~
- ~~$-S-(=O)_2-CH_3$,~~
- ~~$S-(=O)-CH_3$,~~
- ~~substituted or unsubstituted phenyl,~~
- ~~$-O-CH_2$-phenyl, where phenyl is substituted or unsubstituted,~~


,

,

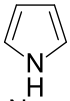
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,

, or

;

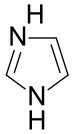
~~R_9 is substituted or unsubstituted phenyl or naphthyl;~~

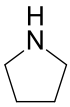
~~R_{10} is~~

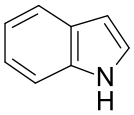
- ~~$-N(R_{12a})(R_{12b})$,~~
- ~~$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,~~
- ~~$-NH-C(=NH)-N(R_{12a})(R_{12b})$,~~
- ~~$-NH-C(=O)-N(R_{12a})(R_{12b})$,~~
- ~~$-O(R_{12a})$,~~
- ~~$-C_1$ to C_{17} linear, branched or cyclic alkyl chain,~~
- ~~$S(=O)_2-CH_3$,~~
- ~~$-S(=O)-CH_3$,~~

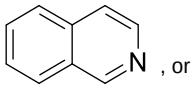
~~C(=O) O(R_{12a}),~~

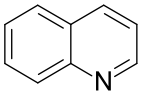

,


,


,


,


, or


;

~~R_{11} is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted;~~

~~R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;~~

~~t is in each instance independently from 1 to 4;~~

~~x is from 1 to 5;~~

~~u is from 2 to 8;~~

~~v and w are each independently from 2 to 5; and~~

~~z is from 1 to 3.~~

~~96. The cyclic peptide of claim 95 wherein R_9 is unsubstituted naphthyl.~~

~~97. The cyclic peptide of claim 95 wherein any substituted phenyl or naphthyl is in each instance independently substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.~~

~~98. The cyclic peptide of claim 05 wherein R_5 comprises at least one L- or D-isomer amino acid.~~

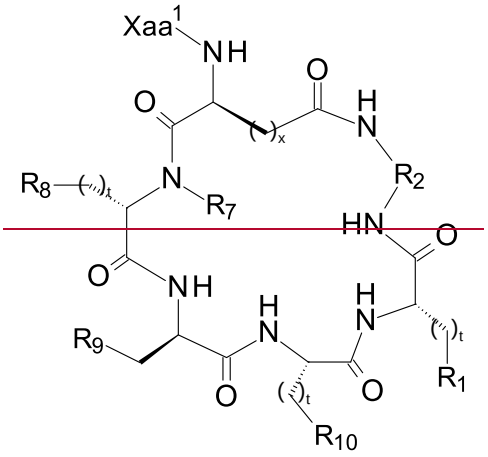
~~99. The cyclic peptide of claim 98 wherein R_5 is a single L- or D-isomer amino acid with an aliphatic side chain.~~

~~100. The cyclic peptide of claim 99 wherein the aliphatic side chain is -(CH_2)$_3$-CH_3.~~

101. The cyclic peptide of claim 95 wherein R_5 is a single L- or D-isomer amino acid with a side chain comprising at least one nitrogen atom.

102. The cyclic peptide of claim 101 wherein R_5 is an L- or D-isomer of Arg, Lys, Orn, Dab, Dap or Cit.

103. The cyclic peptide of claim 95 wherein the cyclic peptide of formula II is a cyclic peptide of the formula:



.

104. The cyclic peptide of claim 95 or 103 wherein Xaa^1 is Ac-Arg, Ac-D-Arg, Ac-Nle, Ac-D-Nle, Ac-Trp, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, acetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl.

105. The cyclic peptide of claim 95 or 103 wherein R_1 is indole or naphthalene.

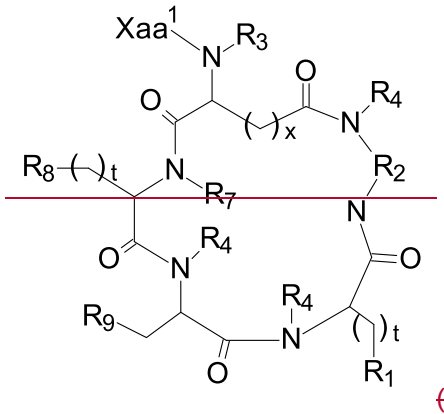
106. The cyclic peptide of claim 95 or 103 wherein R_7 and R_8 comprise pyrrolidine.

107. The cyclic peptide of claim 106 wherein pyrrolidine is substituted.

108. The cyclic peptide of claim 107 wherein the substituent is -O-CH_2-phenyl, where phenyl is substituted or unsubstituted.

109. The cyclic peptide of claim 95 or 103 wherein R_9 is substituted phenyl.

110. A peptide of formula III:



(III)

including all enantiomers, stereoisomers or diastereomers thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein:

Xaa^1 is R_5 R_6;

R_1 is

$N(R_{12a})(R_{12b})$,

$NH(CH_2)_z N(R_{12a})(R_{12b})$,

$NH C(=NH) N(R_{12a})(R_{12b})$,

$NH-C(=O)-N(R_{12a})(R_{12b})$,

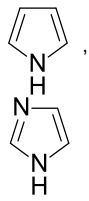
$O(R_{12a})$,

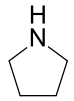
C_1 to C_{17} linear, branched or cyclic alkyl chain,

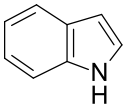
$S(=O)_2-CH_3$,

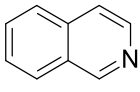
$S(=O)-CH_3$,

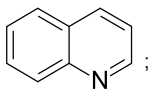
$C(=O) O(R_{12a})$,











;

R_2 is $(CH_2)_u$ or $(CH_2)_v O (CH_2)_w$;

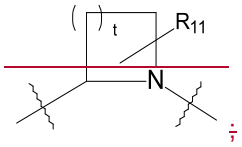
~~R_3 is H or a C_1 to C_9 linear or branched aliphatic chain, optionally comprising one or more C=C double bonds;~~

~~R_4 is -H or $-CH_3$;~~

~~R_5 is optionally present, and if present, is from one to three L- or D-isomer amino acids, or a combination thereof, wherein any backbone nitrogen atom is optionally methylated;~~

~~R_6 is H or a C_1 to C_{17} acyl group comprising optionally substituted linear or branched alkyl, cycloalkyl, alkylcycloalkyl, aryl, aralkyl or heteroaryl;~~

~~R_7 is -H, $-CH_3$ or $-CH_2-$, and if it is $-CH_2-$ forms with R_8 a ring of the general structure~~



;

~~R_8 is -H if R_8 forms the ring with R_7, or R_8 is~~

~~-H,~~

~~$-(CH_2)_3$,~~

~~$-N(R_{12a})(R_{12b})$,~~

~~$-NH-(CH_2)_z-N(R_{12a})(R_{12b})$,~~

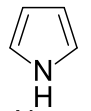
~~$-C(=O)-N(R_{12a})(R_{12b})$,~~

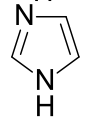
~~$-O-(R_{12a})$,~~

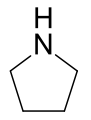
~~$-S-(=O)_2-R_{12a}$,~~

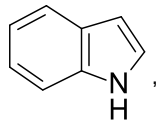
~~substituted or unsubstituted phenyl,~~

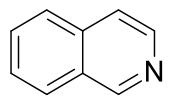
~~$-O-CH_2$-phenyl, where phenyl is substituted or unsubstituted,~~

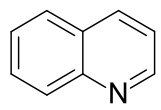

,


,


,


,


, or


;

~~R_9 is substituted or unsubstituted phenyl or naphthyl;~~

~~R_{11} is $-O-CH_2$-phenyl, where phenyl is substituted or unsubstituted;~~

R_{12a} and R_{12b} are each independently and independently in each instance H or a C_1 to C_4 linear, branched or cyclic alkyl chain;

t is in each instance independently from 1 to 4;

x is from 1 to 5;

u is from 2 to 8;

v and 2 are each independently 2 to 5; and

z is from 1 to 3.

111. The cyclic peptide of claim 110 wherein R_9 is unsubstituted naphthyl.

112. The cyclic peptide of claim 110 wherein any substituted phenyl or naphthyl is in each instance independently substituted with between one and three ring substituents wherein the substituents are the same or different, and are each independently halo, (C_1-C_{10})alkyl-halo, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, aryl, (C_1-C_{10})alkylaryl, aryloxy, nitro, nitrile, sulfonamide, amino, monosubstituted amino, disubstituted amino, hydroxy, carbamoyl, carboxy, carbamoyl, alkoxy-carbonyl, or aryloxy-carbonyl.

113. The cyclic peptide of claim 110 wherein R_5 comprises at least one L- or D-isomer amino acid.

114. The cyclic peptide of claim 113 wherein R_5 is a single L- or D-isomer amino acid with an aliphatic side chain.

115. The cyclic peptide of claim 110 wherein R_6 is acetyl, cyclopentyl acetyl, hexanoyl, 3-phenylpropanoyl, cyclopentylacetyl, 2-naphthylacetyl, or 3-(1-naphthyl)propanoyl.

116. The cyclic peptide of claim 110 wherein the cyclic peptide of formula III is a cyclic peptide of the formula:

