

Peptides and Pharmaceutical Compositions for Treating Eye Diseases

Related Applications

This application claims the benefit of priority to United States Provisional Patent
5 Application serial number 62/767,180, filed November 14, 2018; the contents of which are hereby incorporated by reference.

Technical Field

The present invention relates to peptides and pharmaceutical compositions for treating eye diseases.

Background

Dry eye syndrome or keratoconjunctivitis sicca may be defined, in a broad sense, as damage to the ocular surface due to tear secretion disorders (Joossen C *et al.*, *Exp. Eye Res.*, 146:172-8, 2016). Dry eye syndrome is known to cause tear secretion disorders and damage and discomfort to the eyeball due to a combination of various factors. Although the onset of
15 dry eye syndrome is closely related to age, the incidence thereof is increasing in younger age groups due to a long-term exposure to a dry environment as the use of contact lenses, computers, and smart devices (Stern ME *et al.*, *Int. Rev. Immunol.*, 32: 19-41, 2013).

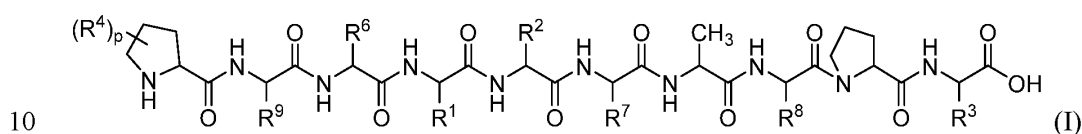
Specifically, dry eye syndrome reduces the mucus secretion of the corneal and conjunctival epithelia and that of the mucus-secreting goblet cells, resulting in a sharp
20 decrease in the lubrication of the eyeball. In addition, dry eye syndrome causes damage to the corneal surface, thereby increasing the penetration of a fluorescein dye into the cornea. These symptoms of dry eye syndrome can be evaluated as changes in the tear secretion through the Schirmer test, which uses cobalt chloride paper. Further, the damage to the cornea that may accompany dry eye syndrome can be easily evaluated using a general
25 fluorescent dye and a slit-lamp fluorophotometer.

In the meantime, most of the treatments for dry eye syndrome are confined to symptom therapies, the treatment efficiency of which is often very low. Currently, artificial tears are the first choice for the treatment of dry eye syndrome. Artificial tears as a representative symptom therapy merely supplement the insufficient tears; moreover, they
30 suffer from the disadvantage that they need to be administered to the eyes frequently (Kim CS *et al.*, *Nutrients* 8. pii: E750, 2016). Sodium hyaluronate and eye drops derived from autologous serum have been developed and used in patients suffering from dry eye syndrome. In addition, such synthetic compounds as rebamipide (OPC-127959) and

diquafosol sodium, which promote the secretion of tears and mucus, have been developed and used. Long-term use of these drugs, however, may give rise to various side effects such as ocular hyperemia and corneal calcification (Bernauer W *et al.*, *Br. J. Ophthalmol.*, 90:285-8, 2006). Therefore, there has been a demand for the development of a safe and effective therapeutic agent for treating dry eye syndrome.

Summary of Invention

In certain aspects, the present invention provides a salt of a compound represented by Formula (I):



wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

15 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

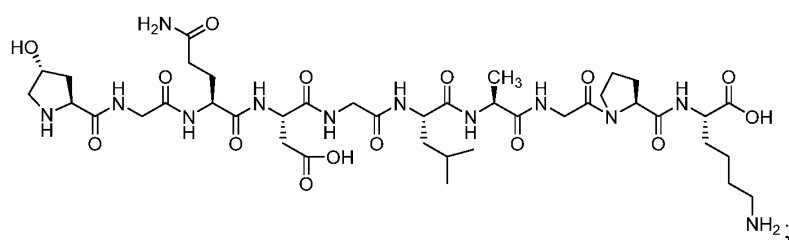
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

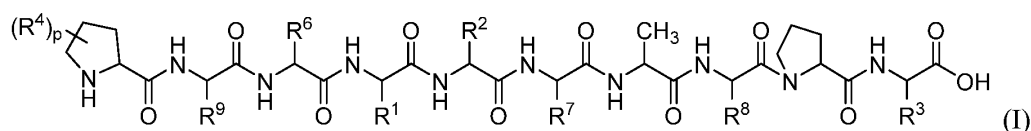
20 R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

wherein the compound is not:



preferably wherein the compound comprises at least one D-amino acid residue.

In further aspects, the present invention provides a compound represented by
25 Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

wherein at least one of:

(a) at least one of R^1 , R^2 , and R^3 is substituted or unsubstituted (C₂-C₁₀)haloalkyl;

(b) at least one of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is substituted with one or more substituents selected from $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$; and

at least one occurrence of R^a or R^c is heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl;

(c) the compound comprises at least one D-amino acid residue; or

(d) at least two occurrences of R^a ;

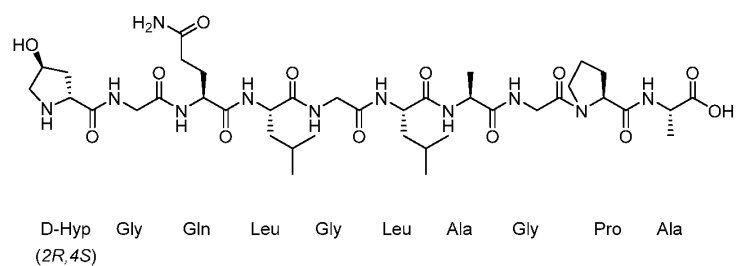
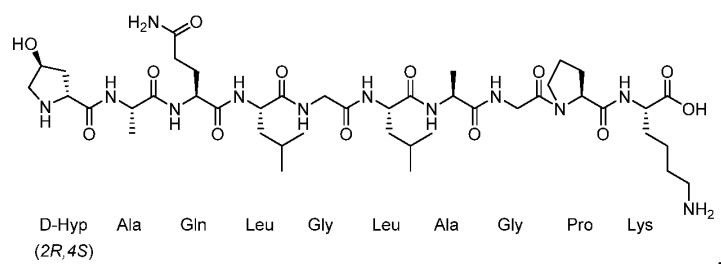
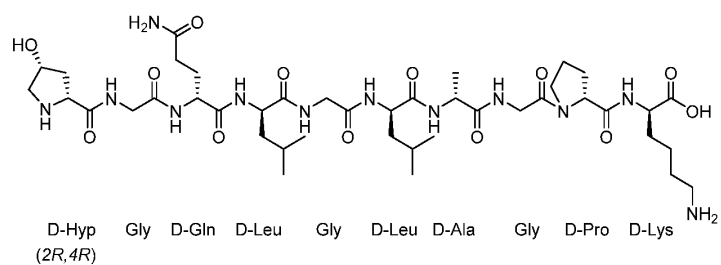
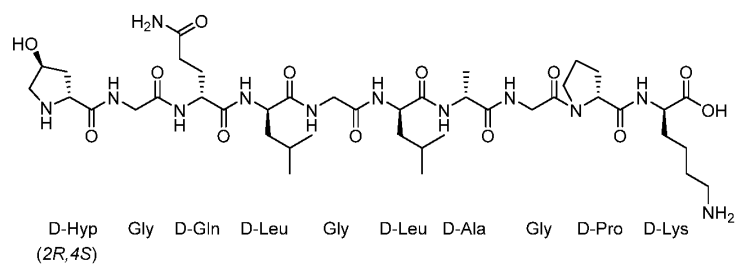
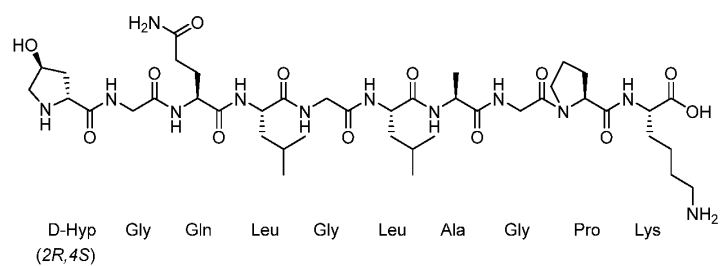
at least two occurrences of R^c ; or

at least one occurrence of R^a and at least one occurrence of R^c ; and

at least one occurrence of R^a and/or R^c differs from the other occurrences;

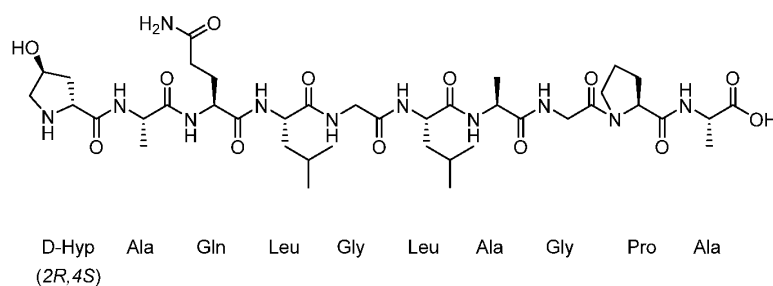
and

wherein the compound is not:

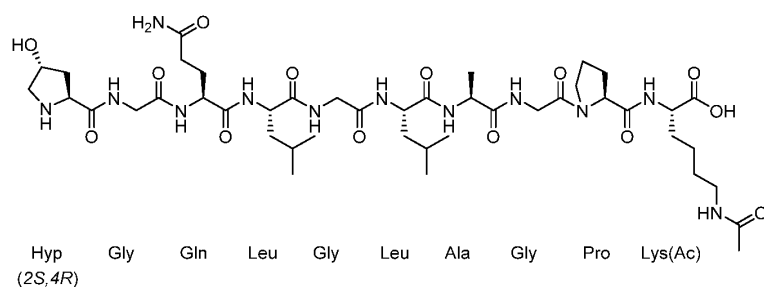


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, or



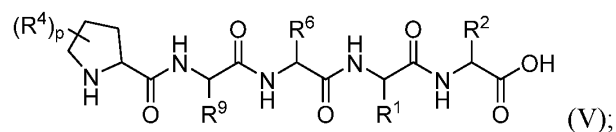
In some aspects, the invention provides a compound having the following structure:



; or a pharmaceutically

acceptable salt thereof.

5 In further aspects, the invention provides a compound represented by Formula (V):



or a pharmaceutically acceptable salt thereof;

wherein:

10 R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

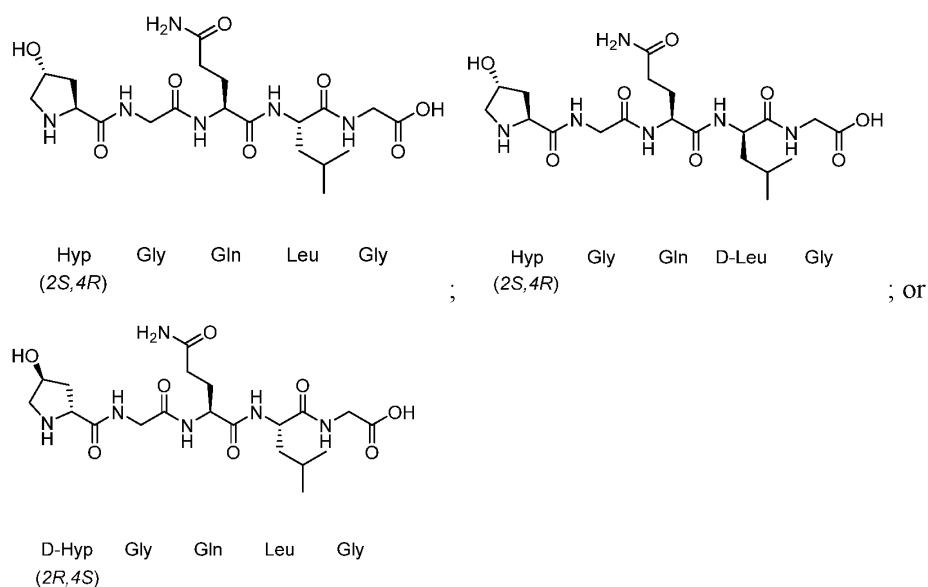
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

15 p is 0, 1, or 2;

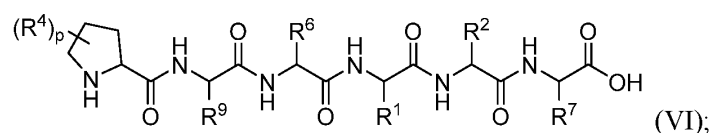
R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



In further aspects, the invention provides a compound represented by Formula (VI):



5 or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl

10 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

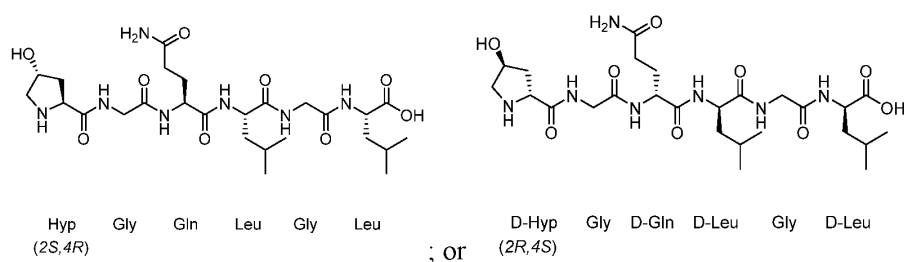
p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

15 R^7 is hydrogen or alkyl; and

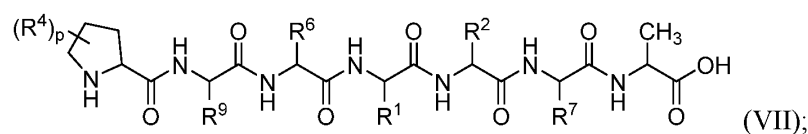
R^9 is hydrogen or alkyl;

wherein the compound is not:



In still further aspects, the invention provides a compound represented by Formula

(VII):



5 or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

10 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

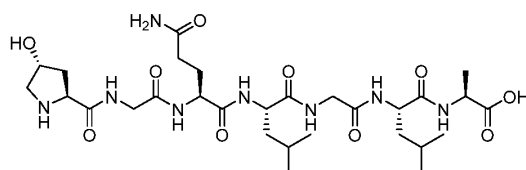
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

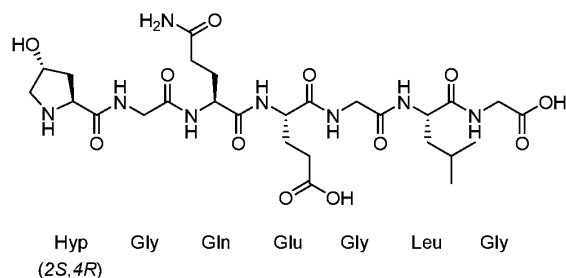
R^6 is hydrogen or substituted or unsubstituted alkyl;

15 R^7 is hydrogen or alkyl; and

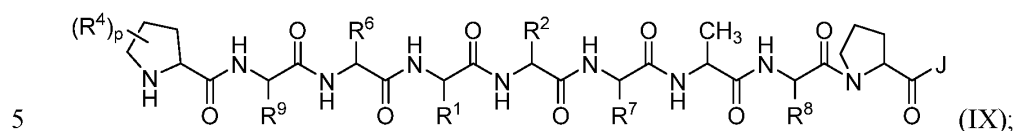
R^9 is hydrogen or alkyl;



wherein the compound is not: Hyp (2S,4R) Gly Gln Leu Gly Leu Ala or



In still further aspects, the invention provides compounds represented by Formula (IX):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

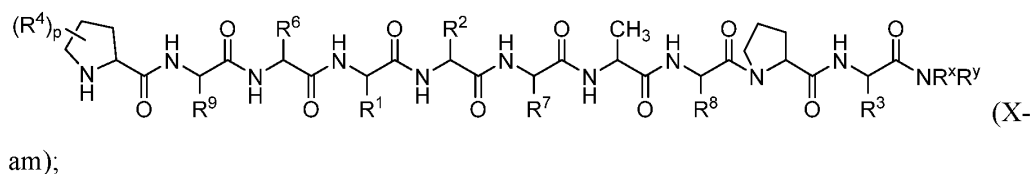
R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

J is OH or $-NR^xR^y$; and

R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

The present invention also provides compounds represented by Formula (X-am):



am);

or a pharmaceutically acceptable salt thereof;

5

wherein:

R¹, R², and R³ are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

10 R⁴, independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, -OR^b, -CH₂OR^b, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R⁶ is hydrogen or substituted or unsubstituted alkyl;

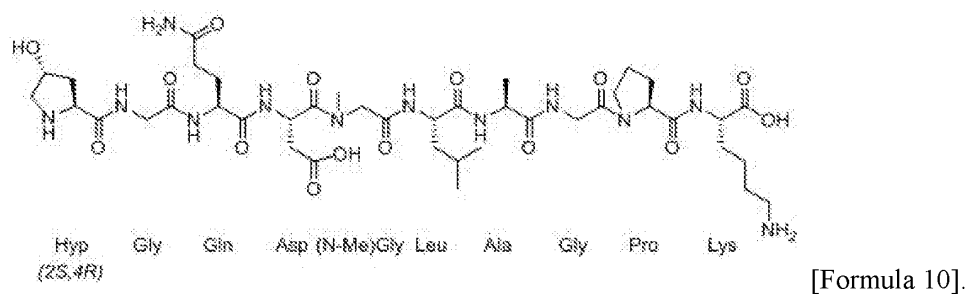
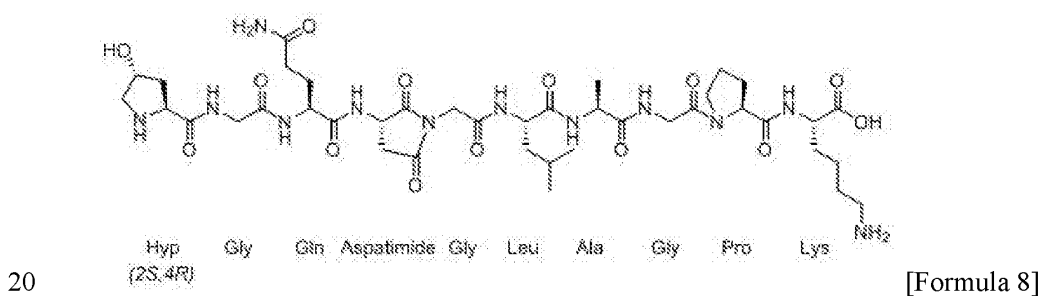
R⁷, R⁸, and R⁹ are each independently hydrogen or alkyl;

15

J is OH or -NR^xR^y; and

R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

The invention also provides salts of the following compounds:



Also provided by the invention are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound or salt of the invention.

The invention also provides methods of treating eye disease, such as eye disease is selected from retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, heratoconjunctivitis sicca and keratoconjunctival epithelium disorder, by administering a compound or salt of the invention, or a pharmaceutical composition comprising the same.

Brief Description of the Drawings

Fig. 1 is a diagram showing the sequence and characteristics of the peptides prepared according to an embodiment of the present invention.

Fig. 2 is a diagram showing a process for synthesizing the peptides prepared according to an embodiment of the present invention.

Fig. 3 is a diagram showing a purification procedure of the peptides prepared according to an embodiment of the present invention.

Fig. 4 is a photograph showing a procedure of extraorbital lacrimal gland excision.

Fig. 5 is a diagram showing a change in the body weight of a rat model whose eyes have been administered with YDE-001 to YDE-028.

Fig. 6 is a diagram showing a change in the body weight of a rat model whose eyes have been administered with YDE-029 to YDE-043.

Fig. 7 is a photograph showing a procedure of administering an agent to the eyes of a rat model.

Fig. 8 is a photograph showing a procedure of measuring the amount of tear secretion of a rat model using cobalt chloride paper.

Fig. 9 is a photograph showing the results of measuring the amount of tear secretion of a rat model whose eyes have been administered with YDE-001 to YDE-028 using cobalt chloride paper.

Fig. 10 is a diagram showing the changes in the amount of tear secretion of a rat model whose eyes have been administered with YDE-001 to YDE-028.

Fig. 11 is a photograph showing the results of measuring the amount of tear secretion of a rat model whose eyes have been administered with YDE-029 to YDE-043 using cobalt chloride paper.

Fig. 12 is a diagram showing the changes in the amount of tear secretion of a rat model whose eyes have been administered with YDE-029 to YDE-043.

Fig. 13 is a photograph showing a procedure of administering a fluorescent substance to the eyes of a rat model for confirming damage to the cornea thereof.

5 Fig. 14 is a photograph showing the results of measuring damage to the cornea of a rat model whose eyes have been administered with YDE-001 to YDE-028 using a fluorescent substance.

10 Fig. 15 is a diagram showing the permeability of a fluorescence dye to confirm the recovery of corneal damage of a rat model whose eyes have been administered with YDE-001 to YDE-028.

Fig. 16 is a photograph showing the results of measuring damage to the cornea of a rat model whose eyes have been administered with YDE-029 to YDE-043 using a fluorescent substance.

15 Fig. 17 is a diagram showing the permeability of a fluorescence dye to confirm the recovery of corneal damage of a rat model whose eyes have been administered with YDE-029 to YDE-043.

FIG. 18 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 1.

20 FIG. 19 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 2.

FIG. 20 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 3.

FIG. 21 is a diagram showing the cell growth rate after 48 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 4.

25 FIG. 22 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 1.

FIG. 23 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 2.

30 FIG. 24 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 3.

FIG. 25 is a diagram showing the cell growth rate after 72 hours from the treatment of hEGF on human corneal epithelial cells of plate No. 4.

FIG. 26 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YY-101 on human corneal epithelial cells.

FIG. 27 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YY-102 on human corneal epithelial cells.

5 FIG. 28 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-011 on human corneal epithelial cells.

FIG. 29 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-038 on human corneal epithelial cells.

10 FIG. 30 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-042 on human corneal epithelial cells.

FIG. 31 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-043 on human corneal epithelial cells.

FIG. 32 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-044 on human corneal epithelial cells.

15 FIG. 33 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-045 on human corneal epithelial cells.

FIG. 34 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-049 on human corneal epithelial cells.

20 FIG. 35 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-054 on human corneal epithelial cells.

FIG. 36 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-057 on human corneal epithelial cells.

FIG. 37 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-058 on human corneal epithelial cells.

25 FIG. 38 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-059 on human corneal epithelial cells.

FIG. 39 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-060 on human corneal epithelial cells.

30 FIG. 40 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-072 on human corneal epithelial cells.

FIG. 41 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-073 on human corneal epithelial cells.

FIG. 42 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-074 on human corneal epithelial cells.

FIG. 43 is a diagram showing the cell growth rate after (a) 48 hours or (b) 72 hours from the treatment of YDE-075 on human corneal epithelial cells.

5 FIG. 44 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-078 on human corneal epithelial cells.

FIG. 45 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-080 on human corneal epithelial cells.

10 FIG. 46 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-081 on human corneal epithelial cells.

FIG. 47 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-083 on human corneal epithelial cells.

FIG. 48 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-084 on human corneal epithelial cells.

15 FIG. 49 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-086 on human corneal epithelial cells.

FIG. 50 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-001 on human corneal epithelial cells.

20 FIG. 51 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-010 on human corneal epithelial cells.

FIG. 52 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-029 on human corneal epithelial cells.

FIG. 53 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-092 on human corneal epithelial cells.

25 FIG. 54 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-053 on human corneal epithelial cells.

FIG. 55 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-064 on human corneal epithelial cells.

30 FIG. 56 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-066 on human corneal epithelial cells.

FIG. 57 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-012 on human corneal epithelial cells.

FIG. 58 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-019 on human corneal epithelial cells.

FIG. 59 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-055 on human corneal epithelial cells.

5 FIG. 60 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-085 on human corneal epithelial cells.

FIG. 61 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-047 on human corneal epithelial cells.

10 FIG. 62 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-048 on human corneal epithelial cells.

FIG. 63 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-050 on human corneal epithelial cells.

FIG. 64 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-051 on human corneal epithelial cells.

15 FIG. 65 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-052 on human corneal epithelial cells.

FIG. 66 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-056 on human corneal epithelial cells.

20 FIG. 67 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-061 on human corneal epithelial cells.

FIG. 68 is a diagram showing the cell growth rate after 48 hours and 72 hours from the treatment of YDE-062 on human corneal epithelial cells.

Detailed Description of the Invention

25 The present invention is based on the surprising discovery of therapeutic agents for treating eye diseases such as dry eye syndrome. The effectiveness of the agents has been demonstrated by synthesizing these peptides, administering them to the eyes of rats with dry eye syndrome, and confirming the eye protection effect through the Schirmer test and the fluorescent dye deposition test.

30 When the novel peptide of the present invention is administered to the eye, it increases the amount of tear secretion and promotes recovery of the damaged cornea. Hence, they can be advantageously used as therapeutic agents for treating eye diseases.

Definitions

According to the convention used in the art, “ $\overset{\text{R}}{\text{---}}$ ” in the formulae herein is used to indicate that a moiety or substituent “R” is attached to a backbone structure.

“Alkyl” is a hydrocarbon having primary, secondary, tertiary, and/or quaternary carbon atoms, and encompasses straight, branched, and cyclic groups, or a combination thereof. For example, an alkyl group may have 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkyl), 1 to 10 carbon atoms (i.e., C₁-C₁₀ alkyl), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkyl). Examples of a suitable alkyl group include methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-butyl (n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)₂), 2-butyl (s-Bu, s-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH₃)₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃), but it is not limited thereto.

“Alkoxy” refers to a group having the formula -O-alkyl, wherein the alkyl group as defined above is attached to the parent compound via an oxygen atom. The alkyl moiety of the alkoxy group may have, for example, 1 to 20 carbon atoms (i.e., C₁-C₂₀ alkoxy), 1 to 12 carbon atoms (i.e., C₁-C₁₂ alkoxy), 1 to 10 carbon atoms (i.e., C₁-C₁₀ alkoxy), or 1 to 6 carbon atoms (i.e., C₁-C₆ alkoxy). Examples of a suitable alkoxy group include methoxy (-O-CH₃ or -OMe), ethoxy (-OCH₂CH₃ or -OEt), and t-butoxy (-OC(CH₃)₃ or -O-tBu), but it is not limited thereto.

“Haloalkyl” is an alkyl group in which at least one of the hydrogen atoms of the alkyl group as defined above is replaced by a halogen atom. The alkyl moiety of the haloalkyl group may have 1 to 20 carbon atoms (i.e., C₁-C₂₀ haloalkyl), 1 to 12 carbon atoms (i.e., C₁-C₁₂ haloalkyl), 1 to 10 carbon atoms (i.e., C₁-C₁₀ haloalkyl), or 1 to 6 carbon atoms (i.e.,

C₁-C₆ haloalkyl). Examples of a suitable haloalkyl group include -CF₃, -CHF₂, -CFH₂, and -CH₂CF₃, but it is not limited thereto.

“Alkenyl” is a hydrocarbon having primary, secondary, tertiary, and/or quaternary carbon atoms, and encompasses straight, branched, and cyclic groups, or a combination thereof, and having at least one unsaturated region, i.e., a carbon-carbon sp² double bond. For example, an alkenyl group may have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkenyl), 2 to 12 carbon atoms (i.e., C₂-C₁₂ alkenyl), 2 to 10 carbon atoms (i.e., C₂-C₁₀ alkenyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkenyl). Examples of a suitable alkenyl group include vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂), but it is not limited thereto.

“Alkynyl” is a hydrocarbon having primary, secondary, tertiary, and/or quaternary carbon atoms, and encompasses straight, branched, and cyclic groups, or a combination thereof, and having at least one carbon-carbon sp triple bond. For example, an alkynyl group may have 2 to 20 carbon atoms (i.e., C₂-C₂₀ alkynyl), 2 to 12 carbon atoms (i.e., C₂-C₁₂ alkynyl), 2 to 10 carbon atoms (i.e., C₂-C₁₀ alkynyl), or 2 to 6 carbon atoms (i.e., C₂-C₆ alkynyl). Examples of a suitable alkenyl group include acetylenic (-C≡CH) and propargyl (-CH₂C≡CH), but it is not limited thereto.

“Alkylene” refers to a saturated hydrocarbon group that may be branched, straight, or cyclic (or may have a combination of branched, straight, or cyclic moieties) and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkane. For example, an alkylene group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of a typical alkylene group include 1,2-ethylene (-CH₂-CH₂-), but it is not limited thereto.

“Alkenylene” refers to an unsaturated hydrocarbon group that may be branched, straight, or cyclic (or may have a combination of branched, straight, or cyclic moieties) and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkene. For example, an alkenylene group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of a typical alkenylene group include 1,2-ethenylene (-CH=CH-), but it is not limited thereto.

“Alkynylene” refers to an unsaturated hydrocarbon group that may be branched, straight, or cyclic (or may have a combination of branched, straight, or cyclic moieties) and has two valencies derived by a removal of two hydrogen atoms from the same carbon atom or two different carbon atoms of a parent alkyne. For example, an alkynylene group may

have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Examples of a typical alkynylene radical include acetylenylene ($-\text{C}\equiv\text{C}-$), propargylene ($-\text{CH}_2\text{C}\equiv\text{C}-$), and 4-pentynylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{C}-$), but it is not limited thereto.

“Aryl” refers to an aromatic hydrocarbon group. For example, an aryl group may have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Examples of a typical aryl group include a radical derived from benzene (e.g., phenyl), substituted benzene, substituted or unsubstituted naphthalene, substituted or unsubstituted anthracene, and the like, but it is not limited thereto.

“Arylalkyl” refers to an acyclic alkyl group in which one hydrogen atom bonded to a carbon atom, typically a terminal or other sp^3 carbon atom, is replaced by an aryl group. Examples of a typical arylalkyl group include benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl, and the like (each of which may be substituted or unsubstituted), but it is not limited thereto. An arylalkyl group may have 7 to 20 carbon atoms. For example, the alkyl moiety thereof may have 1 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Arylalkenyl” refers to an acyclic alkenyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or other sp^3 carbon atom, although an sp^2 carbon atom may also be used, is replaced by an aryl group. The aryl moiety of the arylalkenyl may be, for example, any aryl group described herein, and the alkenyl moiety of the arylalkenyl may comprise, for example, any of the alkenyl groups described herein. An arylalkenyl group may have 8 to 20 carbon atoms. For example, the alkenyl moiety thereof may have 2 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Arylalkynyl” refers to an acyclic alkynyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or other sp^3 carbon atom, although an sp carbon atom may also be used, is replaced by an aryl group. The aryl moiety of the arylalkynyl may be, for example, any aryl group described herein, and the alkynyl moiety of the arylalkynyl may comprise, for example, any of the alkynyl groups described herein. An arylalkynyl group may have 8 to 20 carbon atoms. For example, the alkynyl moiety thereof may have 2 to 6 carbon atoms, and the aryl moiety thereof may have 6 to 14 carbon atoms.

“Cycloalkyl” refers to a saturated monocycle or polycycle that comprises only carbon atoms in the ring. A cycloalkyl group may have 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. A

monocyclic cycloalkyl has 3 to 7 ring atoms, more typically 5 or 6 ring atoms. A bicyclic cycloalkyl may have 7 to 12 ring atoms and may be a fused ring system, a spirocyclic ring system, or a bridged ring system. In exemplary cycloalkyl groups, the atoms may be arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6] system. Non-limiting examples of a
 5 monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl (each of which may be substituted or unsubstituted).

The term “substituted” with respect to alkyl, alkylene, aryl, arylalkyl, heterocyclyl, and the like, for example, “substituted alkyl,” “substituted alkylene,” “substituted aryl,” “substituted arylalkyl,” “substituted heterocyclyl,” and “substituted carbocyclyl (e.g.,
 10 substituted cycloalkyl),” means that at least one hydrogen atom of the alkyl, alkylene, aryl, arylalkyl, heterocyclyl, or carbocyclyl (e.g., cycloalkyl) is each independently replaced by a non-hydrogen substituent. Examples of the typical substituent include halo, haloalkyl, oxo, -CN, -NO₂, =N-OH, -N₃, -R, -OR, -SR, -N(R)₂, -N(R)₃⁺, =NR, -NHC(=O)R, -C(=O)R, -C(=O)N(R)₂, -S(=O)₂R, -OS(=O)₂OR, -S(=O)₂OR, -S(=O)₂N(R)₂, -S(=O)R, -
 15 OP(=O)(OR)₂, -(alkylene)-C(=O)R, -C(=S)R, -C(=O)OR, -(alkylene)-C(=O)OR, -C(=S)OR, -C(=O)SR, -C(=S)SR, -(alkylene)-C(=O)N(R)₂, -C(=S)N(R)₂, and -C(-NR)N(R)₂, and R is independently H, alkyl, aryl, arylalkyl, or heterocyclyl, but it is not limited thereto. The alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

Those skilled in the art will understand that when a moiety such as “alkyl,” “aryl,” “heterocyclyl,” and the like is substituted with at least one substituent, they may optionally be referred to as a moiety of “alkylene,” “arylene,” “heterocyclylene,” or the like (that is, at least one hydrogen atom of the parent “alkyl,” “aryl,” or “heterocyclyl” moiety is replaced by the substituent as described herein). If the moiety of “alkyl,” “aryl,” “heterocyclyl,” or
 25 the like is described herein as “substituted” or depicted in the drawings as substituted (or optionally substituted, for example, the number of substituents is 0 or a positive number), the term “alkyl,” “aryl,” “heterocyclyl,” or the like should be understood to be interchangeable with “alkylene,” “arylene,” “heterocyclylene,” or the like.

Those skilled in the art will recognize that the substituents and other moieties of the
 30 compound of Formula I should be selected so as to provide a compound that is sufficiently stable as a pharmaceutically useful compound that can be formulated into an acceptably stable pharmaceutical composition. The compound of Formula I having such stability is to be understood to fall within the scope of the present invention.

“Heteroalkyl” refers to an alkyl group in which at least one carbon atom is replaced by a heteroatom such as O, N, or S. For example, if a carbon atom of the alkyl group attached to a parent molecule is replaced by a heteroatom (e.g., O, N, or S), the resulting heteroalkyl group may be an alkoxy group (e.g., -OCH₃), an amine group (e.g., -NHCH₃, -N(CH₃)₂, or the like), or a thioalkyl group (e.g., -SCH₃), respectively. If a non-terminal carbon atom of the alkyl group that is not attached to a parent molecule is replaced by a heteroatom (e.g., O, N, or S), the resulting heteroalkyl group may be an alkyl ether (e.g., -CH₂CH₂-O-CH₃ or the like), an alkylamine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, or the like), or a thioalkyl ether (e.g., -CH₂-S-CH₃), respectively. If the terminal carbon atom of the alkyl group is replaced by a heteroatom (for example, O, N, or S), the resulting heteroalkyl group may be a hydroxyalkyl group (e.g., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkylthiol group (e.g., -CH₂CH₂-SH), respectively. For example, a heteroalkyl group may have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Preferably, a heteroalkyl group has from 2 to 20, 2 to 10, or 2 to 6 total atoms in the chain (i.e., carbon atoms plus heteroatoms combined). A C₁-C₆ heteroalkyl group refers to a heteroalkyl group having 1 to 6 carbon atoms.

The term “heterocycle” or “heterocyclyl” used herein includes those described in the documents such as Paquette, Leo A., Principles of Modern Heterocyclic Chemistry (W. A. Benjamin, New York, 1968), specifically Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs (John Wiley & Sons, New York, from 1950 to the present), specifically Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566, but it is not limited thereto. In a specific embodiment of the present invention, “heterocycle” includes carbocycle as defined herein in which at least one (e.g., 1, 2, 3, or 4) carbon atom is replaced by a heteroatom (e.g., O, N, or S). The term “heterocycle” or “heterocyclyl” includes saturated, partially unsaturated, and aromatic rings (i.e., a heteroaromatic ring). Substituted heterocycle, for example, includes a heterocyclic ring substituted with any of the substituents disclosed herein, inclusive of a carbonyl group.

Exemplary heterocycles include pyridyl, dihydropyridyl, tetrahydropyridyl(piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur-oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidinyl, pyrrolidinyl, 2-pyrrolidinyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocynyl, triazinyl,

6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxatiny, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phtheridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazoliny, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, and benzoxazoliny (each of which may be substituted or unsubstituted), but it is not limited thereto.

As an example, a carbon-bonded heterocycle may be bonded at the 2, 3, 4, 5, or 6-position of pyrazine, at the 3, 4, 5, or 6-position of pyridazine, at the 2, 4, 5, or 6-position of pyrimidine, at the 2, 3, 5, or 6-position of pyrazine, at the 2, 3, 4, or 5-position of furan, tetrahydrofuran, thiofuran, thiophene, pyrrole, or tetrahydropyrrole, at the 2, 4, or 5-position of oxazole, imidazole, or thiazole, at the 3, 4, or 5-position of isoxazole, pyrazole, or isothiazole, at the 2 or 3-position of aziridine, at the 2, 3, or 4-position of azetidine, at the 2, 3, 4, 5, 6, 7, or 8-position of quinoline, or at the 1, 3, 4, 5, 6, 7, or 8-position of isoquinoline, but it is not limited thereto. More typically, examples of a carbon-bonded heterocycle include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, and 5-thiazolyl (each of which may be substituted or unsubstituted).

As an example, a nitrogen-bonded heterocycle may be bonded at the 1-position of aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, or 1H-indazole, at the 2-position of isoindole or isoindoline, at the 4-position of morpholine, and at the 9-position of carbazole or β -carboline (each of which may be substituted or unsubstituted), but it is not limited thereto. More typically, examples of a nitrogen-bonded heterocycle include 1-aziridinyl, 1-azetidyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl (each of which may be substituted or unsubstituted).

“Heterocyclalkyl” refers to an acyclic alkyl radical in which one hydrogen atom bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced by a

heterocyclyl radical (i.e., a heterocyclyl-alkylene moiety). Examples of a typical heterocyclylalkyl group include heterocyclyl-CH₂-, 2-(heterocyclyl)ethan-1-yl, and the like, but it is not limited thereto. The “heterocyclyl” moiety thereof used herein includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocyclyl group described above. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocyclyl group may be attached to the alkyl moiety of the heterocyclylalkyl through a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclylalkyl group may have 2 to 20 carbon atoms. For example, the alkyl moiety of the heterocyclylalkyl group may have 1 to 6 carbon atoms, and the heterocyclyl moiety thereof may have 2 to 14 carbon atoms. Examples of the heterocyclylalkyl include a 5-membered heterocycle containing sulfur, oxygen, and/or nitrogen such as thiazolylmethyl, 2-thiazolyethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, and the like; and a 6-membered heterocycle containing sulfur, oxygen, and/or nitrogen such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridazylmethyl, pyrimidinylmethyl, pyrazinylmethyl, and the like (each of which may be substituted or unsubstituted), but it is not limited thereto.

“Heterocyclylalkenyl” refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom although an sp² carbon atom may also be used, is replaced by a heterocyclyl radical (i.e., a heterocyclyl-alkenylene moiety). The heterocyclyl moiety of the heterocyclylalkenyl group includes those described in the document such as “Principles of Modern Heterocyclic Chemistry” and any heterocyclyl group described herein. The alkenyl moiety of the heterocyclylalkenyl group includes any alkenyl group described herein. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocyclyl group may be attached to the alkenyl moiety of the heterocyclylalkenyl via a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclylalkenyl group may have 3 to 20 carbon atoms. For example, the alkenyl moiety of the heterocyclylalkenyl group may have 2 to 6 carbon atoms, and the heterocyclyl moiety thereof may have 2 to 14 carbon atoms.

“Heterocyclylalkynyl” refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom although an sp carbon atom may also be used, is replaced by a heterocyclyl radical (i.e., a heterocyclyl-alkynylene moiety). The heterocyclyl moiety of the heterocyclylalkynyl group includes those described in the document such as “Principles of Modern Heterocyclic

Chemistry” and any heterocyclyl group described herein. The alkynyl moiety of the heterocyclalkynyl group includes any alkynyl group described herein. Those skilled in the art will understand that if the resulting group is chemically stable, the heterocycl group may be attached to the alkynyl moiety of the heterocyclalkynyl via a carbon-to-carbon bond or a carbon-to-heteroatom bond. A heterocyclalkynyl group may have 3 to 20 carbon atoms. For example, the alkynyl moiety of the heterocyclalkynyl group may have 2 to 6 carbon atoms, and the heterocycl moiety thereof may have 2 to 14 carbon atoms.

“Heteroaryl” refers to an aromatic heterocycl containing at least one heteroatom in the ring. Non-limiting examples of a suitable heteroatom that may be contained in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of a heteroaryl ring include all of those enumerated in the definition of “heterocycl” herein, inclusive of pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, and the like (each of which may be substituted or unsubstituted).

“Carbocycle” or “carbocyclyl” refers to a saturated, partially unsaturated, or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. A monocyclic carbocycle has 3 to 7 ring atoms, more typically 5 or 6 ring atoms. A bicyclic cycloalkyl may have 7 to 12 ring atoms and may be a fused ring system, a spirocyclic ring system, or a bridged ring system. In exemplary cycloalkyl groups, the atoms are arranged in a bicyclo[4,5], [5,5], [5,6], or [6,6] system. Non-limiting examples of a monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl (each of which may be substituted or unsubstituted).

“Acyl” refers to -C(=O)-alkyl, -C(=O)-carbocycle (which is substituted or unsubstituted), and -C(=O)-heterocycle (which is substituted or unsubstituted), wherein the alkyl, carbocycle, or heterocycle moiety is as defined herein. Non-limiting examples of “acyl” include -C(=O)CH₃, -C(=O)CH₂CH₃, -C(=O)CH(CH₃)₂, -C(=O)C(CH₃)₃, -C(=O)-phenyl (which is substituted or unsubstituted), -C(=O)-cyclopropyl (which is substituted or unsubstituted), -C(=O)-cyclobutyl (which is substituted or unsubstituted), -C(=O)-cyclopentyl (which is substituted or unsubstituted), -C(=O)-cyclohexyl (which is substituted or unsubstituted), and -C(=O)-pyridyl (which is substituted or unsubstituted).

“Arylheteroalkyl” refers to a heteroalkyl as defined herein, wherein a hydrogen atom (which may be attached to either a carbon atom or a heteroatom) is replaced by an aryl group as defined herein. If the resulting group is chemically stable, the aryl group may be attached to a carbon atom of the heteroalkyl group or the heteroatom of the heteroalkyl group. For example, an arylheteroalkyl group may have a formula of -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, or the like. In addition, any alkylene moiety in the above formulae may be further substituted with any of the substituents defined or exemplified herein.

“Heteroarylalkyl” refers to an alkyl group as defined herein, wherein a hydrogen atom is replaced by a heteroaryl group as defined herein. Non-limiting examples of heteroarylalkyl include -CH₂-pyridinyl, -CH₂-pyrrolyl, -CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-furanyl, -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl, -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl, -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazyl, -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl, -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl, -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl, -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl, -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl, -CH(CH₃)-pyridazyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-pyrazyl, and the like.

“Silyloxy” refers to the group -O-SiR₃, wherein each R independently is alkyl, aryl (which is substituted or unsubstituted), or heteroaryl (which is substituted or unsubstituted). Non-limiting examples of silyloxy include -O-Si(CH₃)₃, -O-Si(CH₃)₂tBu, -O-Si(tBu)₂CH₃, -O-Si(tBu)₃, -O-Si(CH₃)₂Ph, -O-Si(Ph)₂CH₃, and -O-Si(Ph)₃.

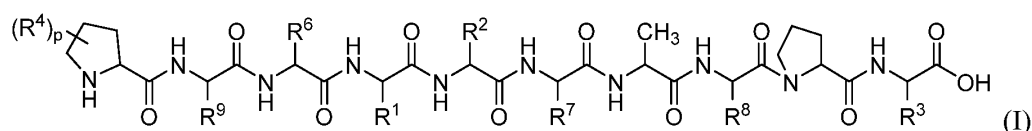
The term “optionally substituted” refers to a particular moiety (e.g., an optionally substituted aryl group) of the compound of Formula I that optionally has one, two, or more substituents.

The term “ester thereof” refers to any ester of a compound wherein any -COOH functional group of the molecule is modified to be a -COOR functional group or any -OH functional group of the molecule is modified to be a -OC(=O)R. Here, the R moiety of the ester may be any carbon-containing group that forms a stable ester moiety, which includes, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl,

heterocyclyl, heterocyclalkyl, and substituted derivatives thereof. Examples of the ester may also include an ester such as those described above of a “tautomeric enol” as described below.

5 Compounds of the Invention

In certain embodiments, the invention provides a salt of a compound represented by Formula (I):



wherein:

10 R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

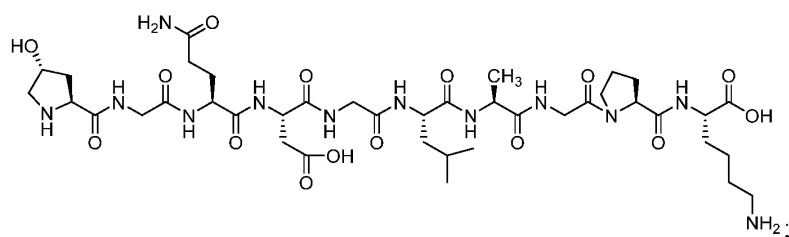
15 R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

wherein the compound is not:



20

preferably wherein the compound comprises at least one D-amino acid residue.

In certain embodiments, R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

25 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, $-OR^b$, hydroxyalkyl, $-CH_2OR^b$, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl.

In some embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, -CN, -NO₂, =N-OH, -N₃, -R^a, -OR^a, -SR^a, -N(R^a)₂, -N(R^a)₃⁺, =NR^a, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -S(=O)₂R^c, -OS(=O)₂OR^a, -S(=O)₂OR^a, -S(=O)₂N(R^a)₂, -S(=O)R^c, -OP(=O)(OR^a)₂, -(alkylene)-C(=O)R^c, -C(=S)R^c, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, -C(=S)OR^a, -C(=O)SR^a, -C(=S)SR^a, -(alkylene)-C(=O)N(R^a)₂, -C(=S)N(R^a)₂, and -C(-NR^a)N(R^a)₂;

R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

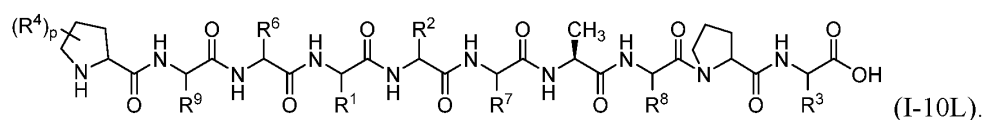
In more particular embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, -R^a, -OR^a, -N(R^a)₂, -N(R^a)₃⁺, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, and -(alkylene)-C(=O)N(R^a)₂;

R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

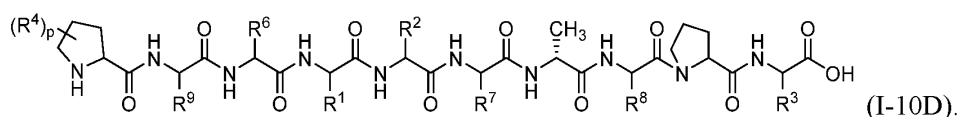
R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

In certain such embodiments, R^a , independently for each occurrence, is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl; and R^c , independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl.

In certain embodiments, the compound has the structure of formula (I-10L):

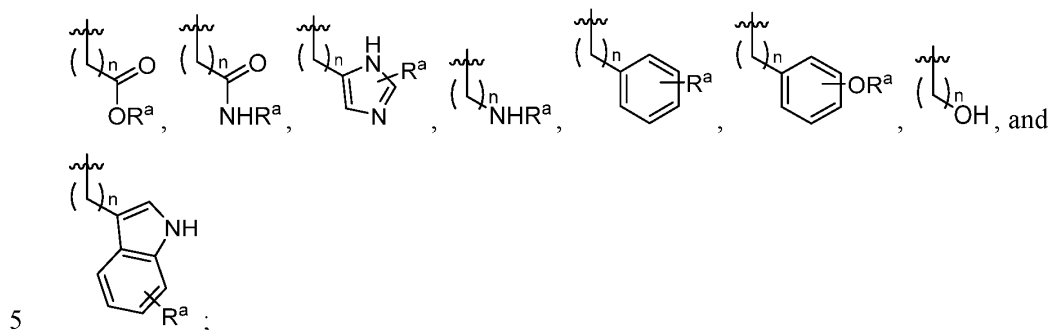


Alternatively, the compound may have the structure of formula (I-10D):



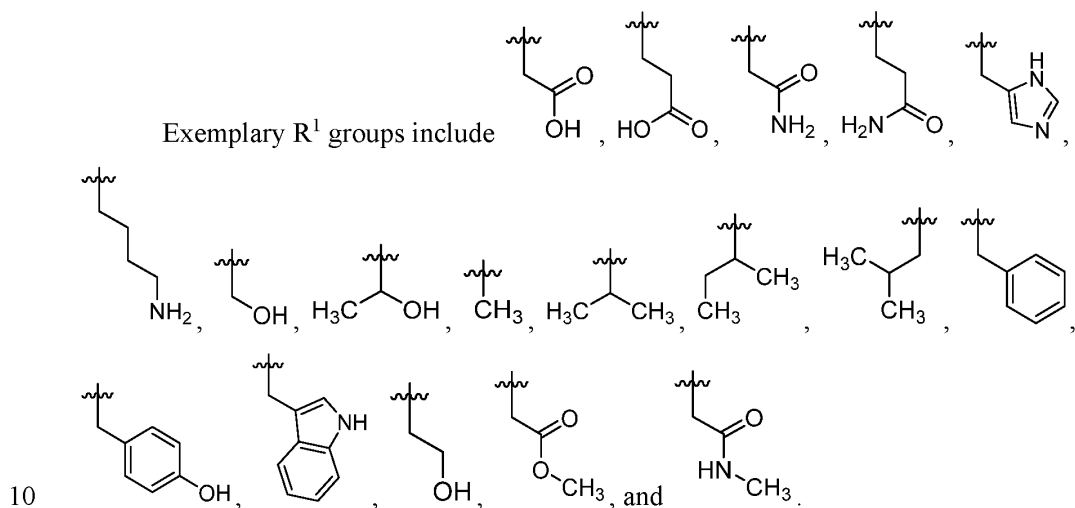
In certain embodiments, R¹ is substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

More specifically, R¹ may be selected from substituted or unsubstituted alkyl,

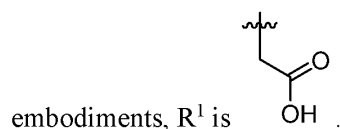


R^a is hydrogen or alkyl; and

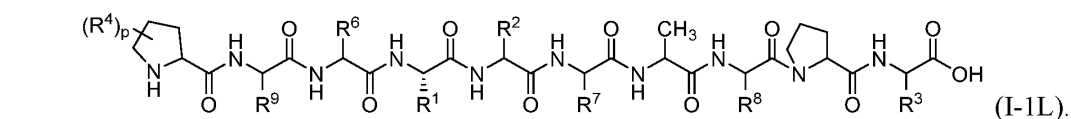
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.



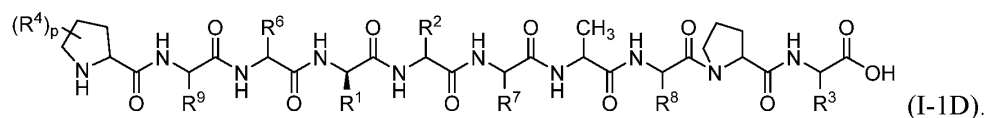
In some preferred embodiments, R¹ is $\dot{\text{C}}\text{H}_3$. In alternative preferred



In certain embodiments, the compound has the structure of formula (I-1L):

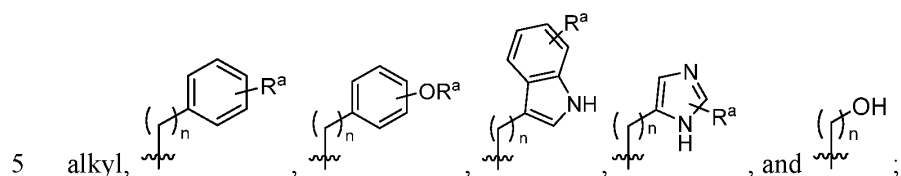


Alternatively, the compound may have the structure of formula (I-1D)



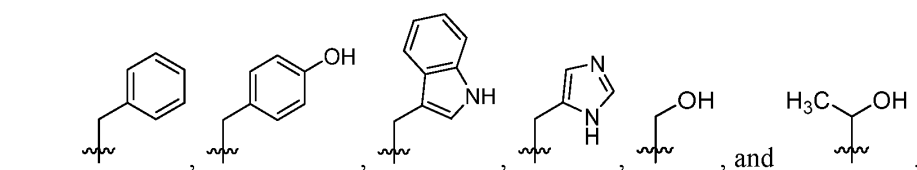
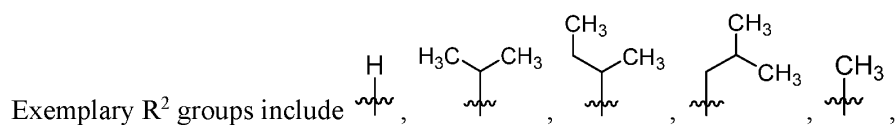
In certain embodiments, R^2 is H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclylalkyl.

In some embodiments, R^2 is selected from hydrogen, substituted or unsubstituted



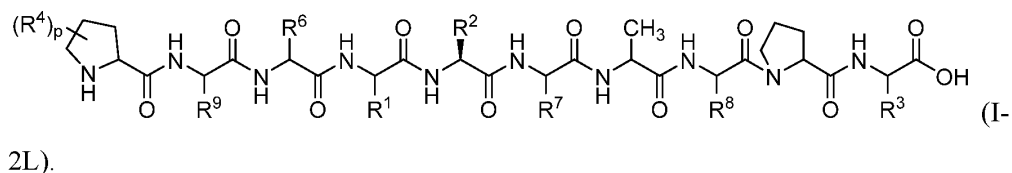
R^a is hydrogen or alkyl; and

n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

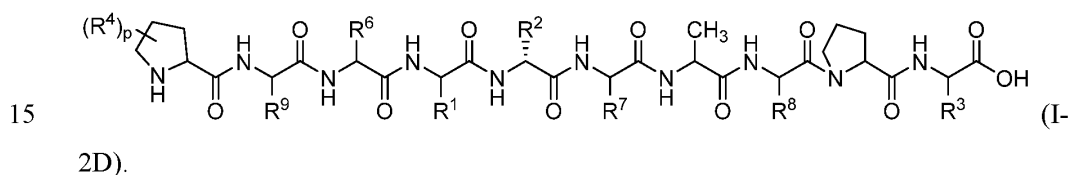


10 Preferably, R^2 is hydrogen.

In certain embodiments, the compound has the structure of formula (I-2L):

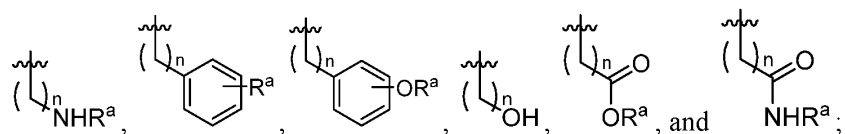


Alternatively, the compound may have the structure of formula (I-2D):



In certain embodiments, R^3 is substituted or unsubstituted alkyl or arylalkyl.

In some embodiments, R^3 is selected from substituted or unsubstituted alkyl,

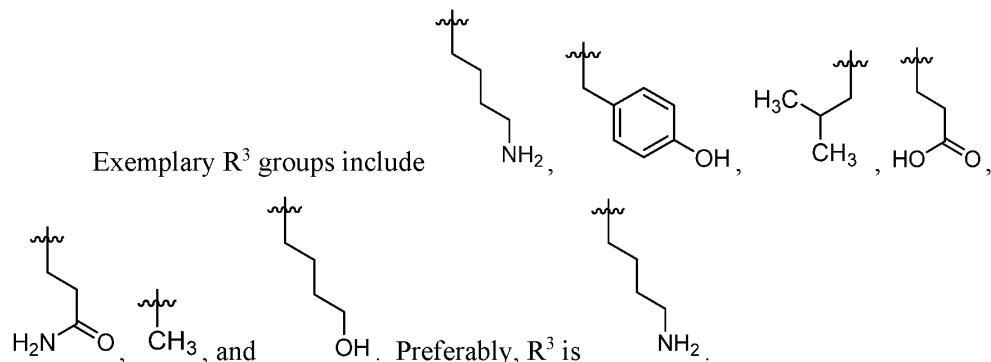


R^a is hydrogen or alkyl; and

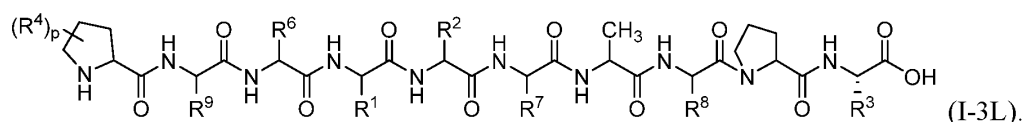
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

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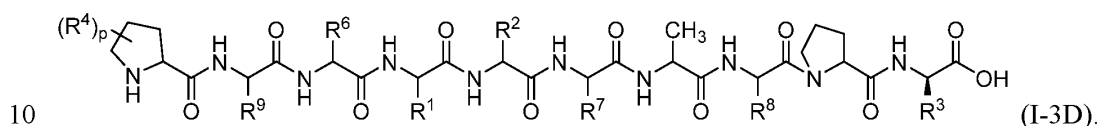
Exemplary R^3 groups include



In certain embodiments, the compound has the structure of formula (I-3L):



Alternatively, the compound may have the structure of formula (I-3D):



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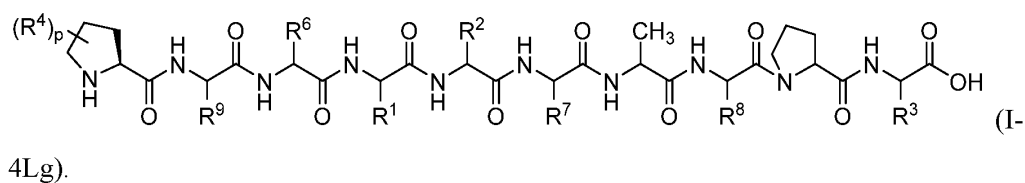
In certain embodiments, p is 1 or 2; and R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl.

15 In certain embodiments, p is 1 or 2; and R^4 , independently for each occurrence, is selected from $-CH_3$, halo, hydroxyl, and hydroxyalkyl.

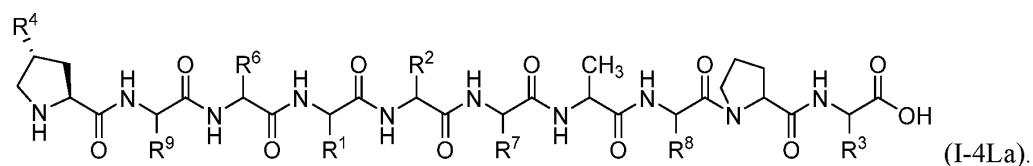
In certain preferred embodiments, R^4 is hydroxyl. In alternative preferred embodiments, R^4 is $-CH_3$.

In any of the above embodiments, p may be 1.

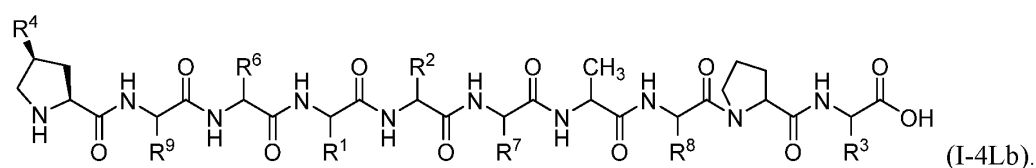
In certain embodiments, the compound has the structure of formula (I-4Lg):



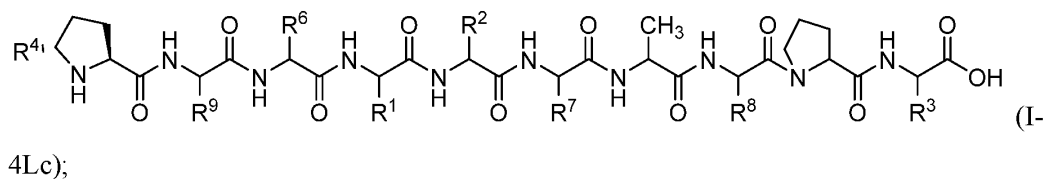
In certain embodiments, the compound has the structure of formula (I-4La):



5 In certain embodiments, the compound has the structure of formula (I-4Lb):

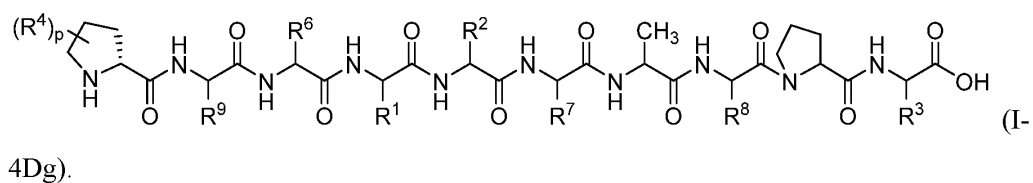


In certain embodiments, the compound has the structure of formula (I-4Lc):

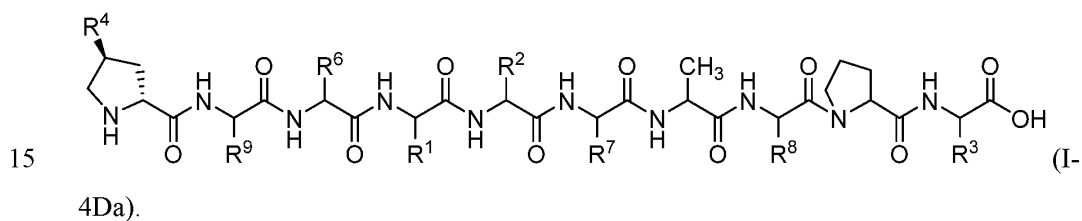


10 provided that R⁴ is not hydroxyl.

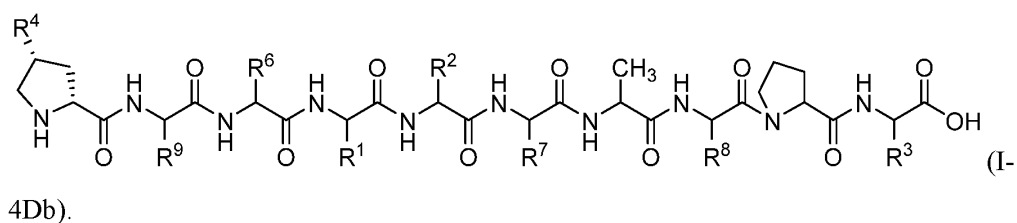
In certain embodiments, the compound has the structure of formula (I-4Dg):



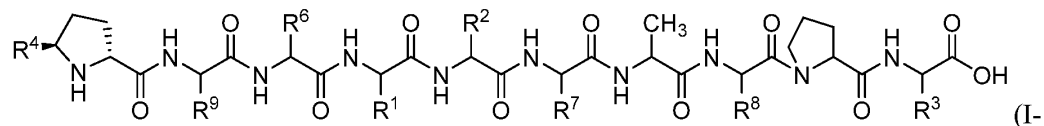
In certain embodiments, the compound has the structure of formula (I-4Da):



In certain embodiments, the compound has the structure of formula (I-4Db):



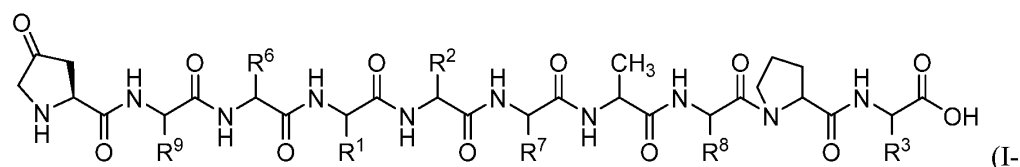
In certain embodiments, the compound has the structure of formula (I-4Dc):



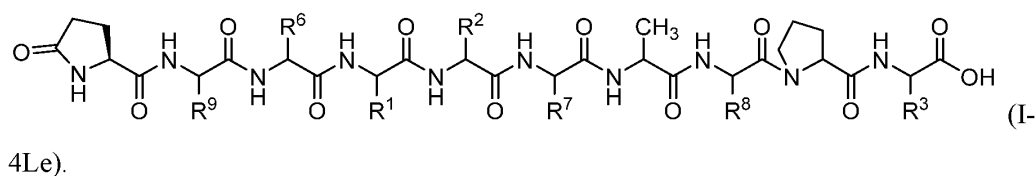
provided that R⁴ is not hydroxyl.

In certain embodiments, R⁴ is oxo.

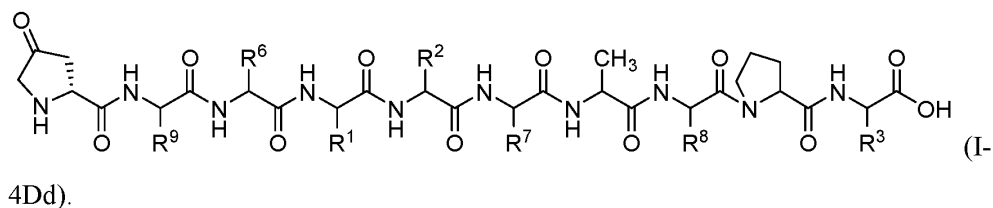
In certain embodiments, the compound has the structure of formula (I-4Ld):



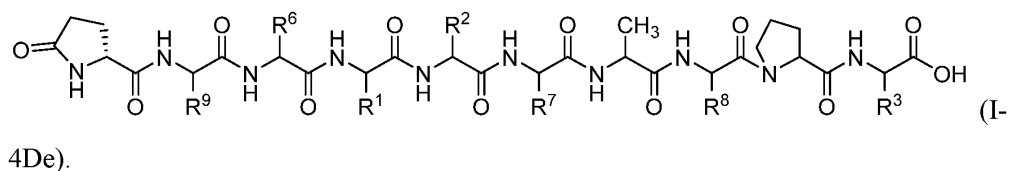
In certain embodiments, the compound has the structure of formula (I-4Le):



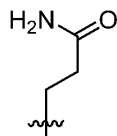
In certain embodiments, the compound has the structure of formula (I-4Dd):



In certain embodiments, the compound has the structure of formula (I-4De):

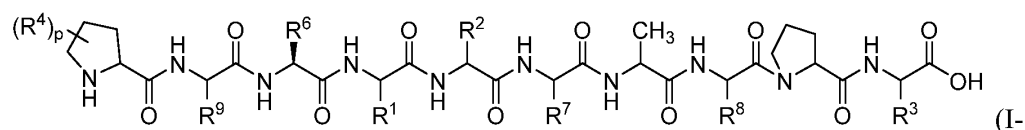


In certain embodiments, R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$. In certain embodiments, wherein R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$. For example, R^6 may be -



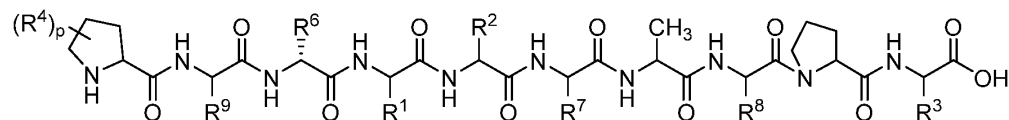
CH₃. Alternatively, R^6 may be

5 In certain embodiments, the compound has the structure of formula (I-6L):



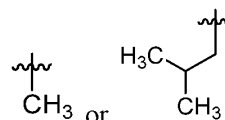
(I-6L).

Alternatively, the compound may have the structure of formula (I-6D):

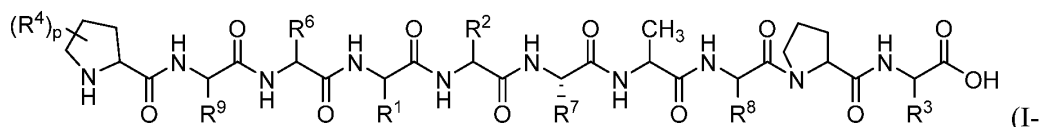


10 (I-6D).

In certain embodiments, R^7 is (C₁-C₁₀)alkyl, preferably

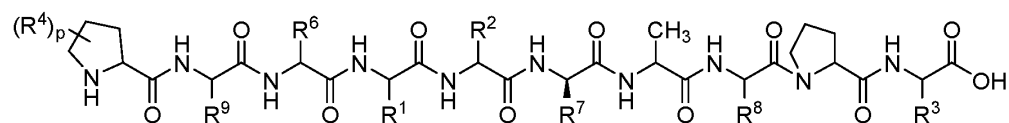


In certain embodiments, the compound has the structure of formula (I-7L):



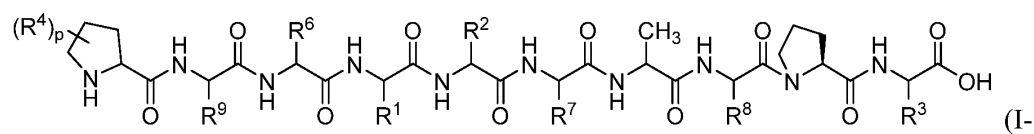
(I-7L).

15 Alternatively, the compound may have the structure of formula (I-7D):



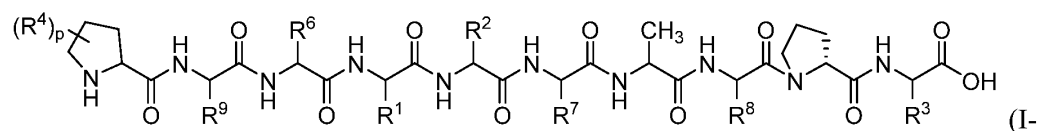
(I-7D).

In certain embodiments, the compound has the structure of formula (I-11L):



11L).

Alternatively, the compound may have the structure of formula (I-11D):



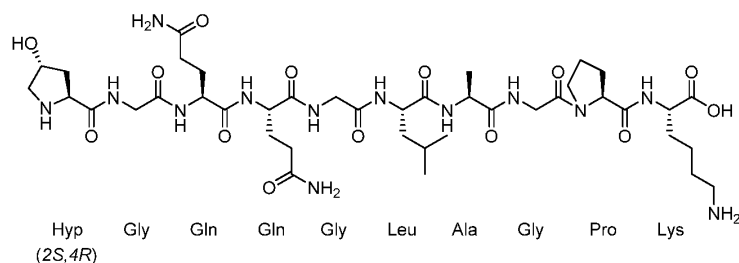
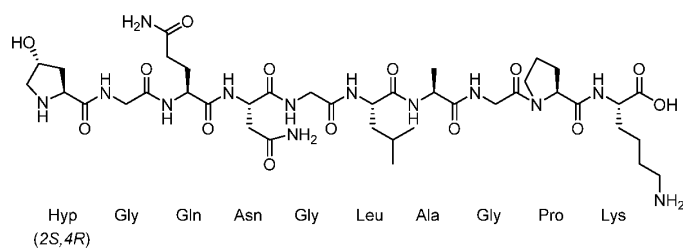
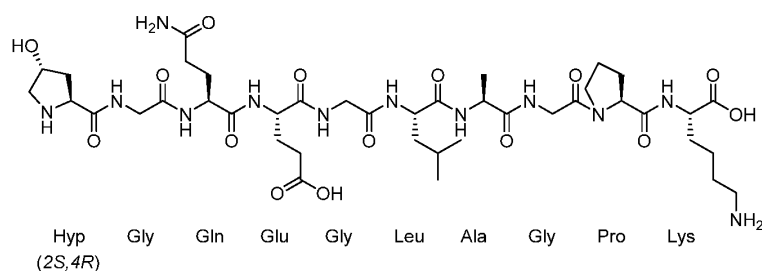
5 11D).

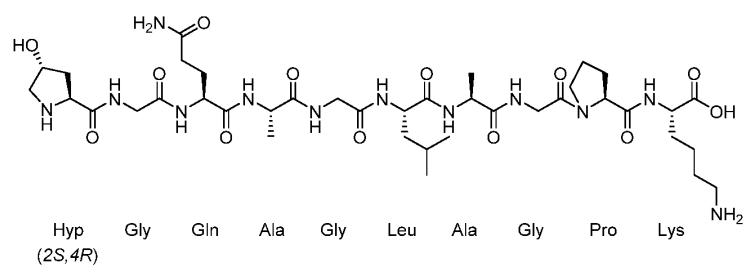
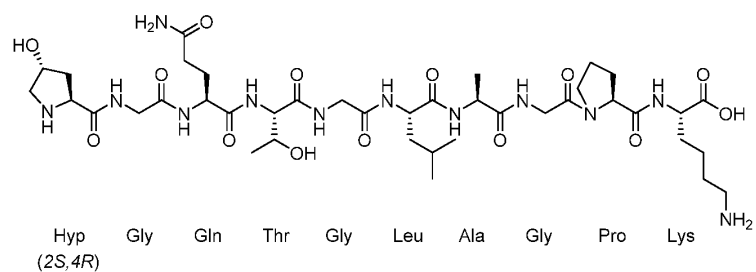
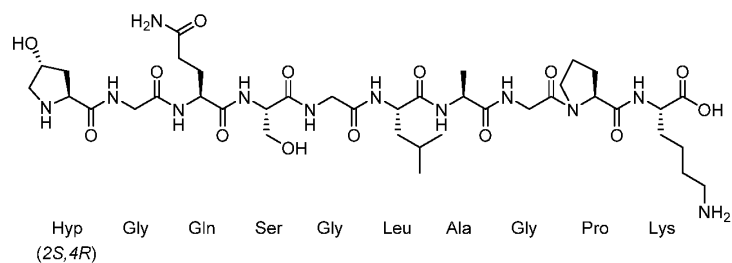
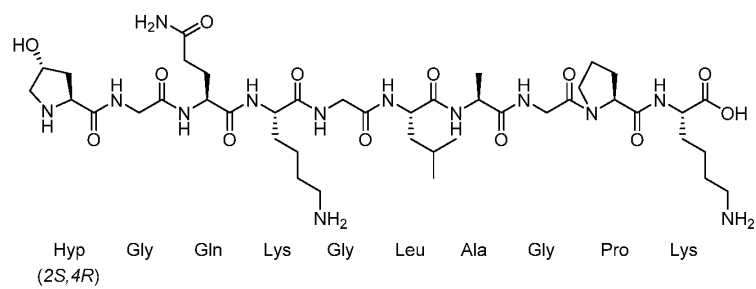
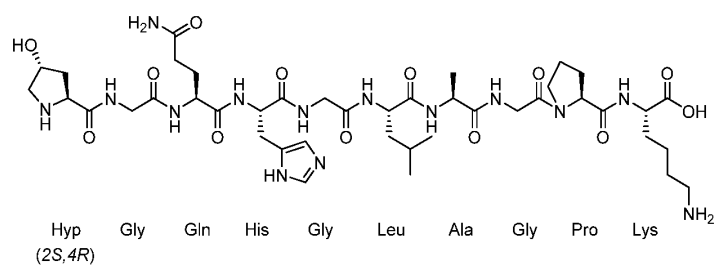
In certain embodiments, R^8 is $-\text{CH}_3$ or $-\text{H}$, preferably $-\text{H}$.

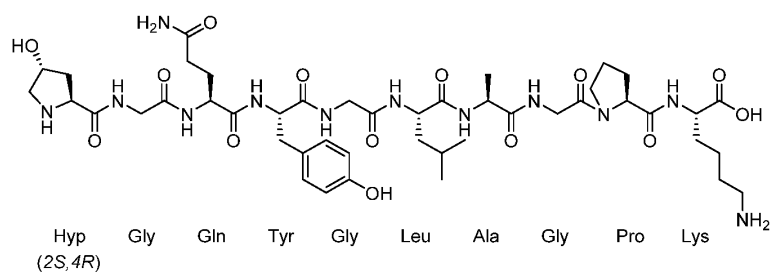
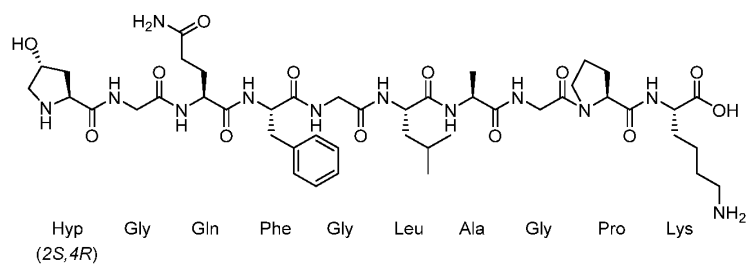
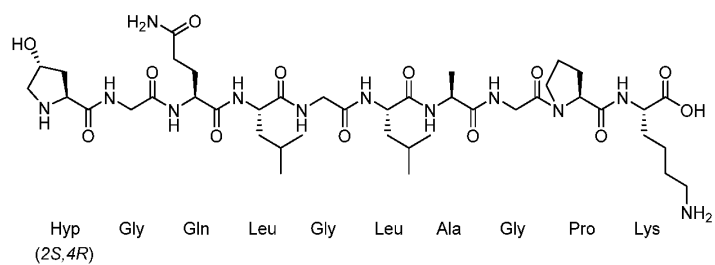
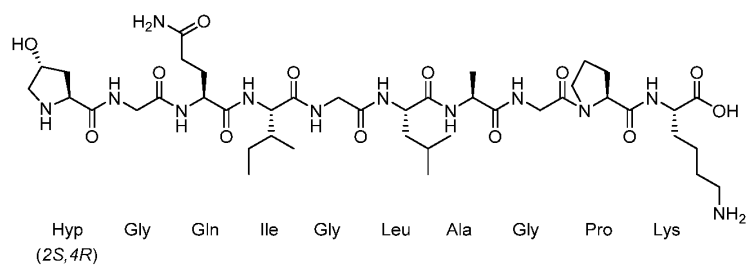
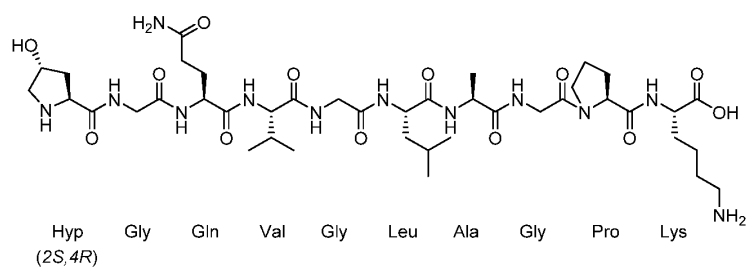
In certain embodiments, R^9 is $-\text{CH}_3$ or $-\text{H}$, preferably $-\text{H}$.

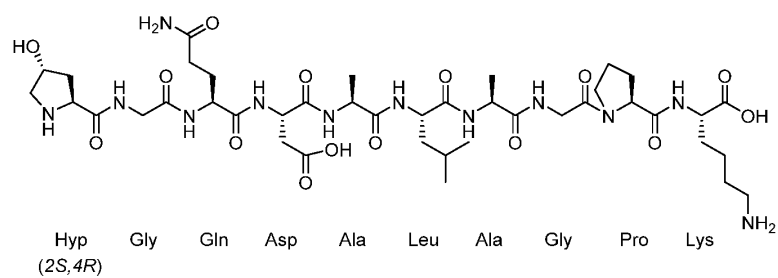
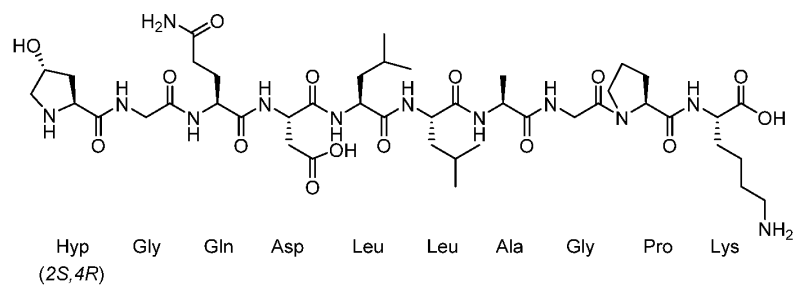
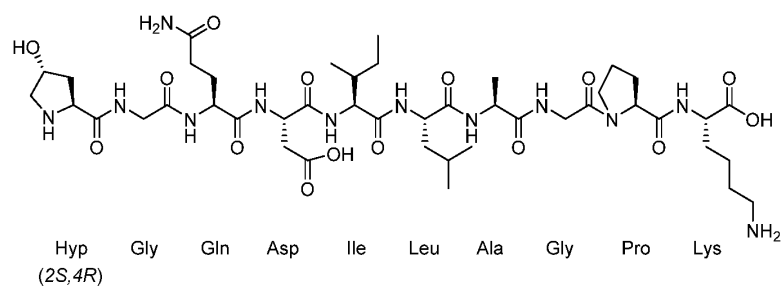
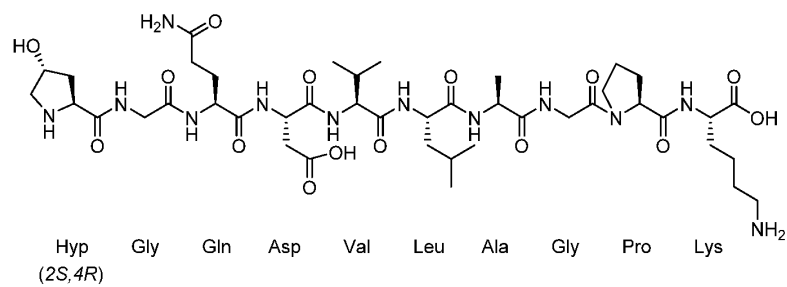
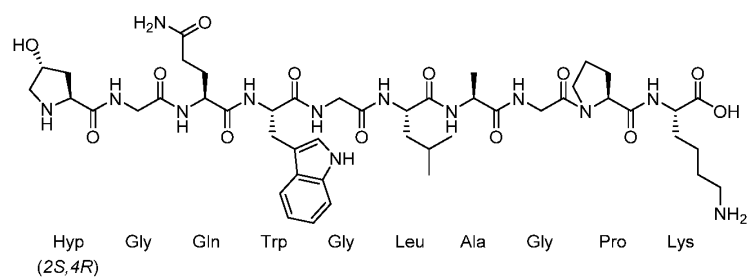
In certain embodiments, the compound comprises at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight D-amino acid residues.

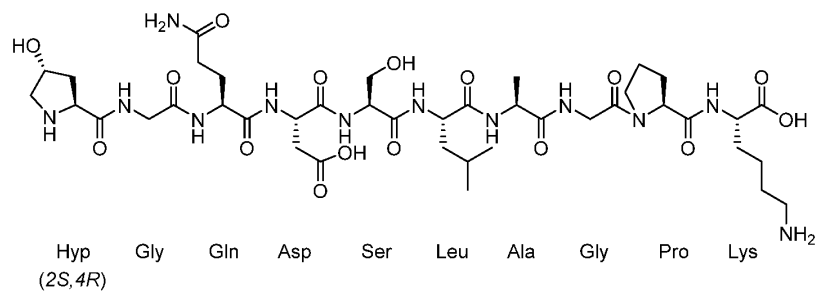
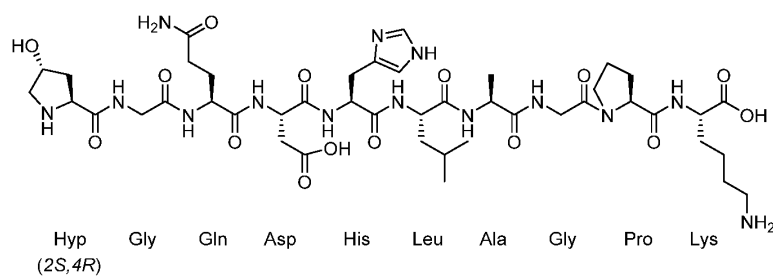
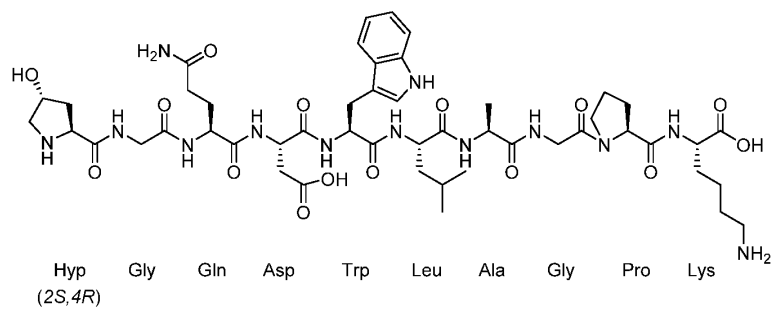
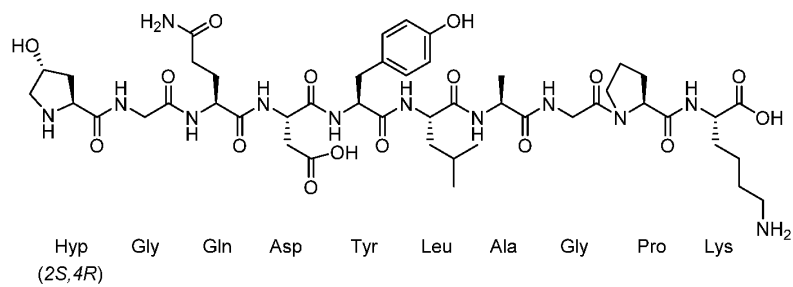
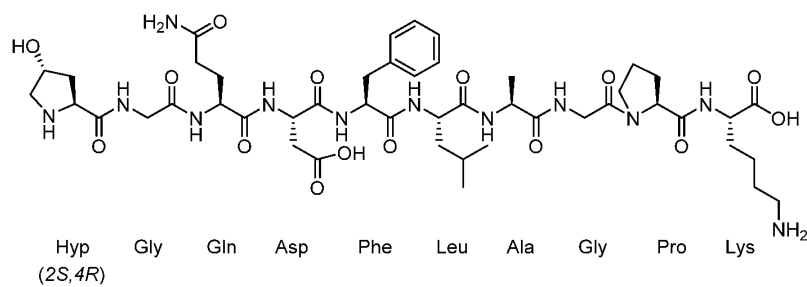
10 In certain embodiments, the invention provides a salt of a compound of formula (I), wherein the compound is selected from the following:

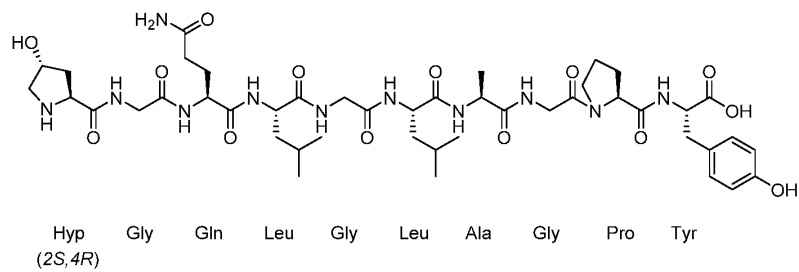
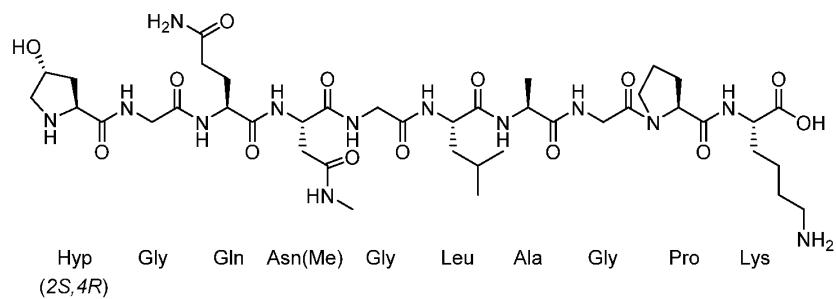
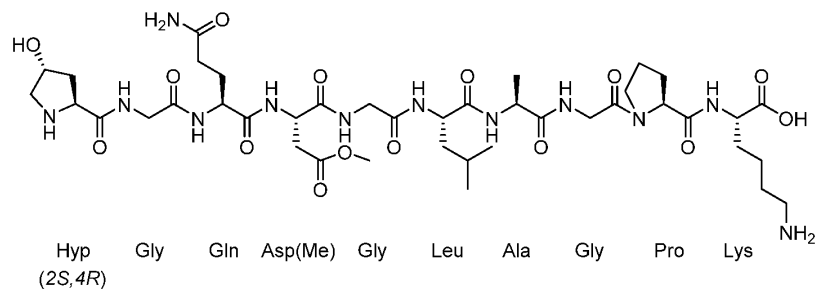
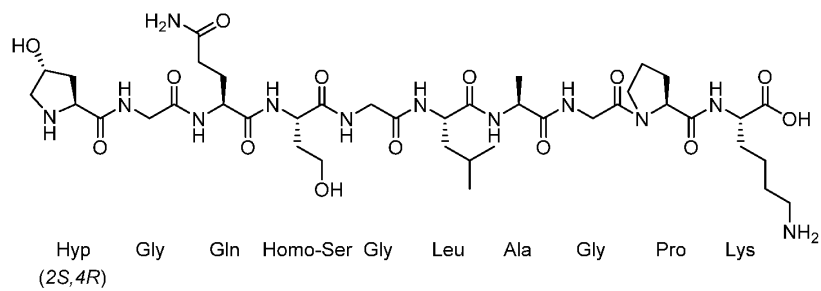
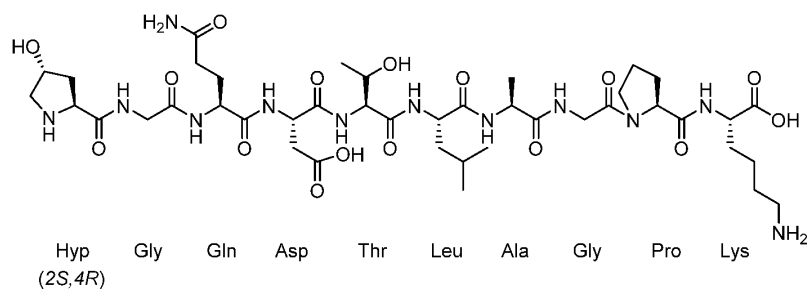


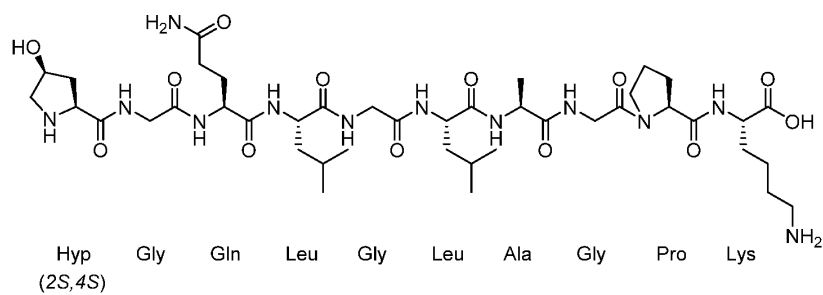
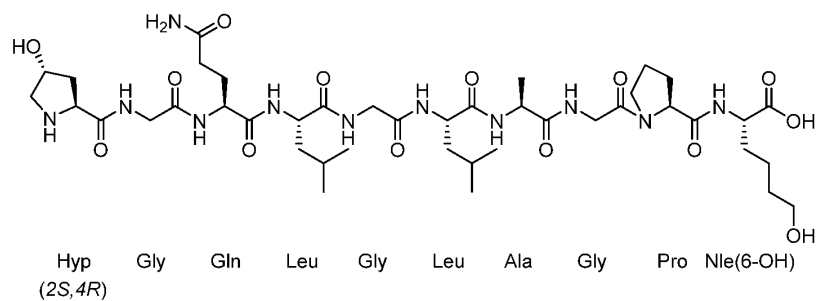
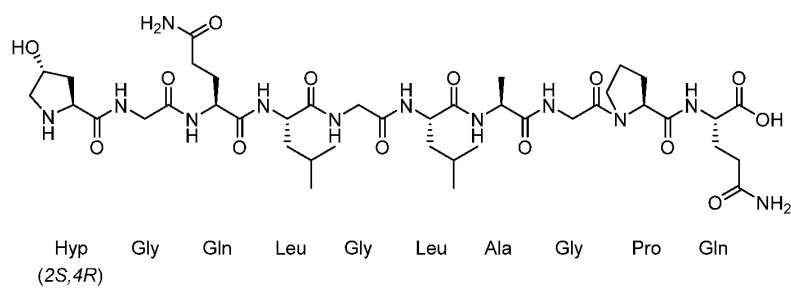
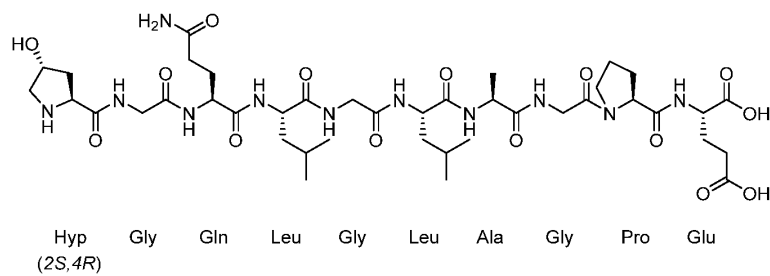
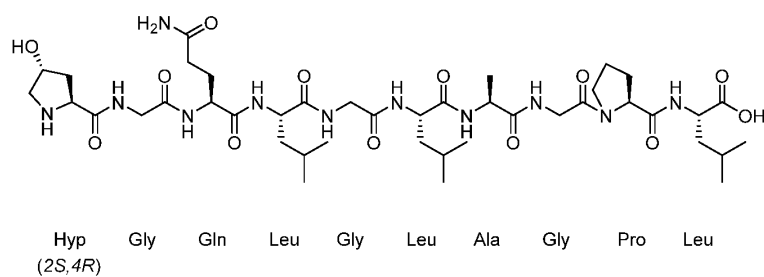


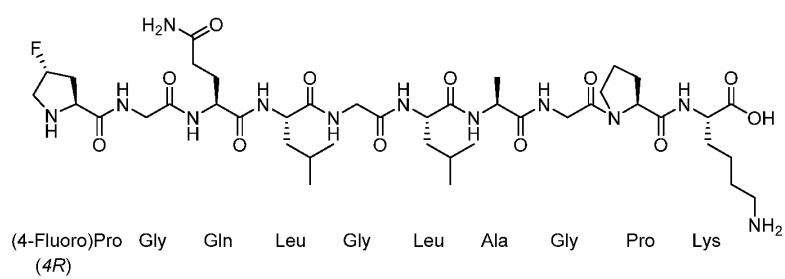
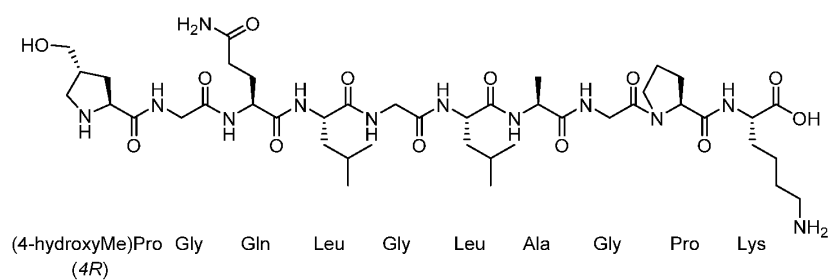
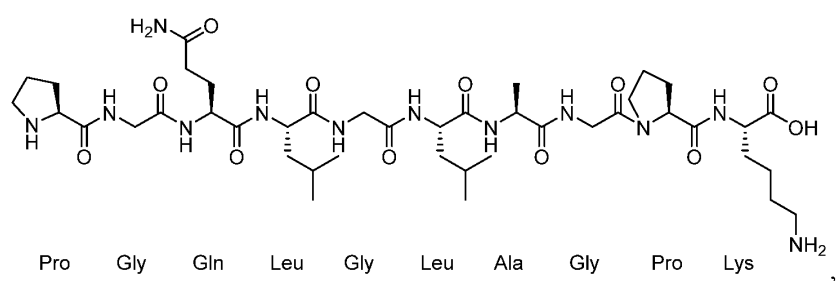
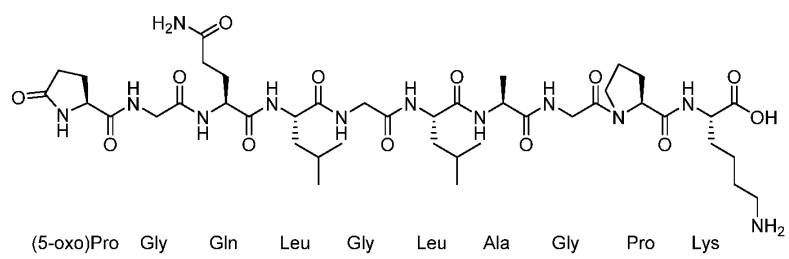
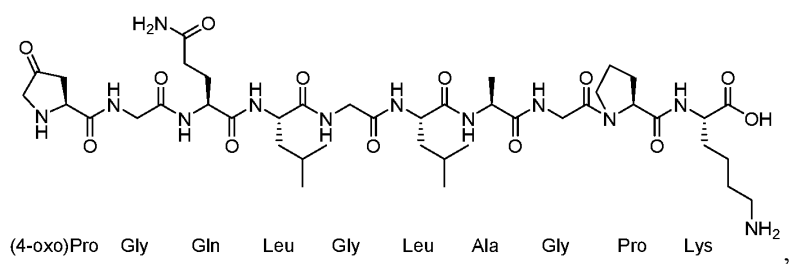


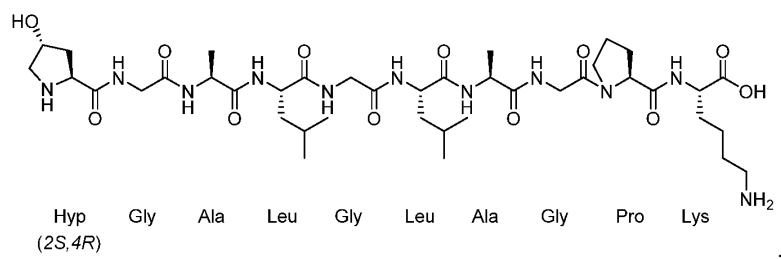
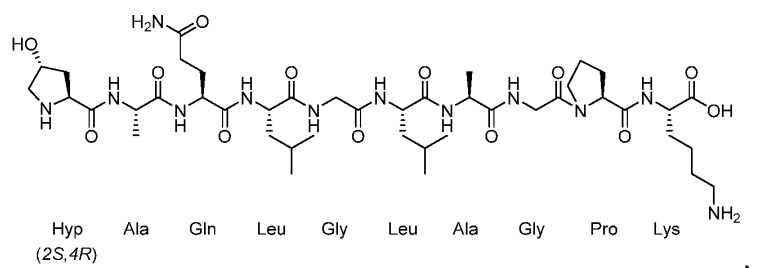
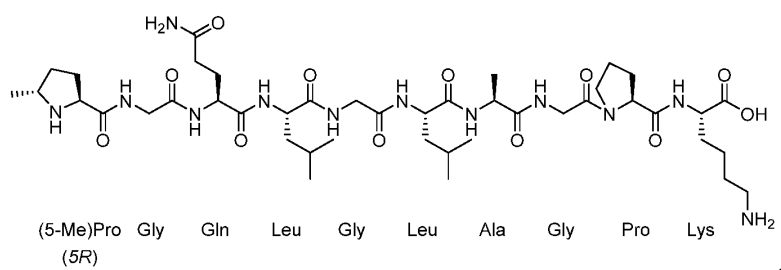
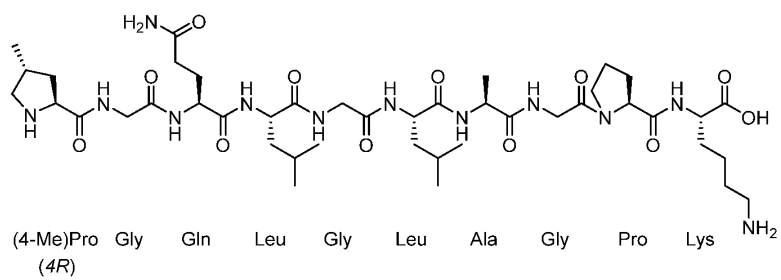
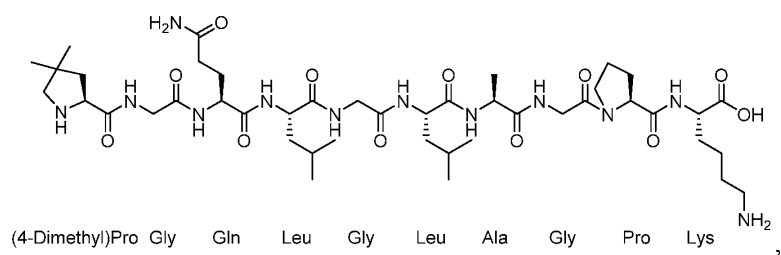


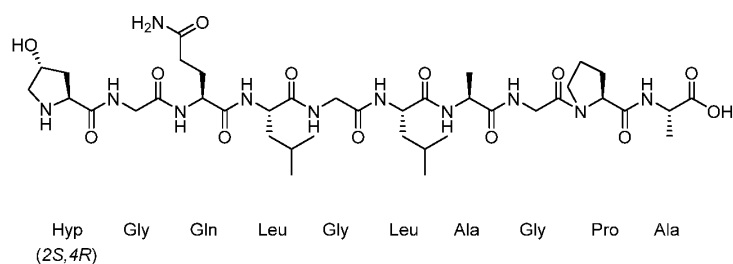
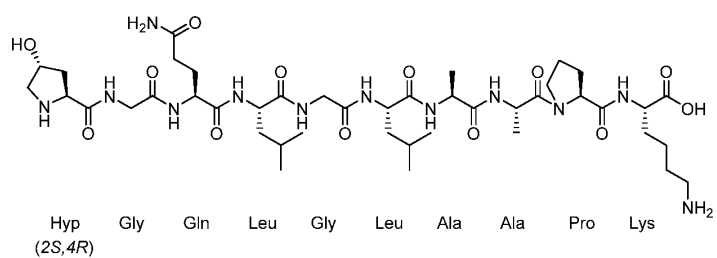
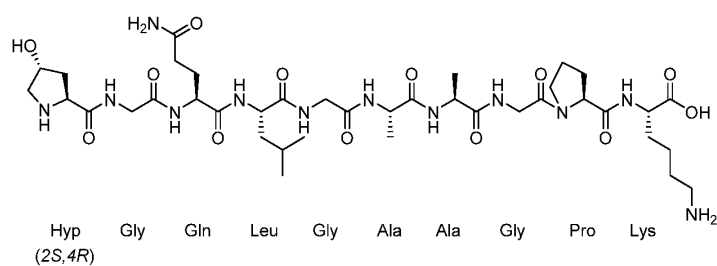
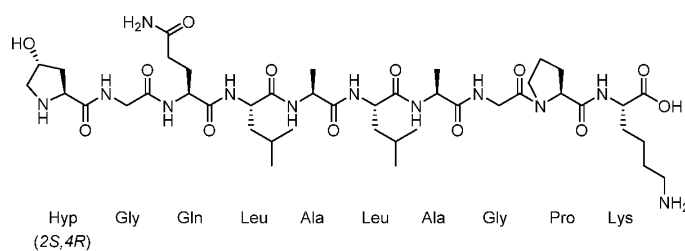
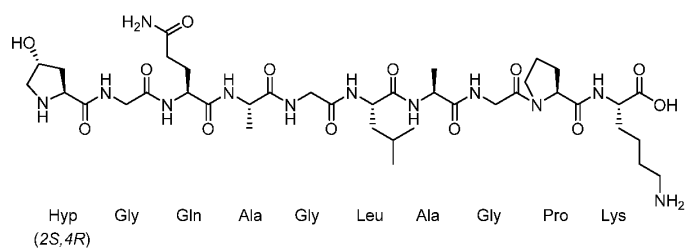




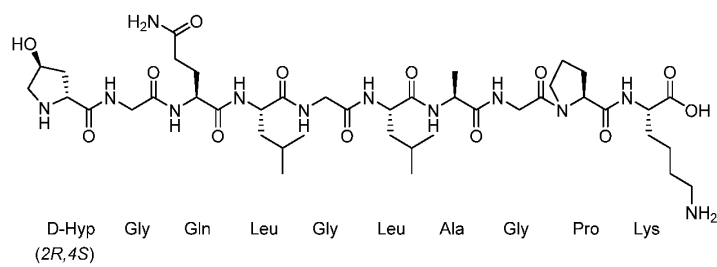


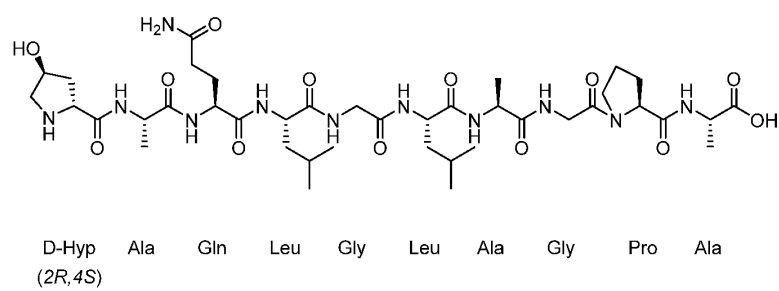
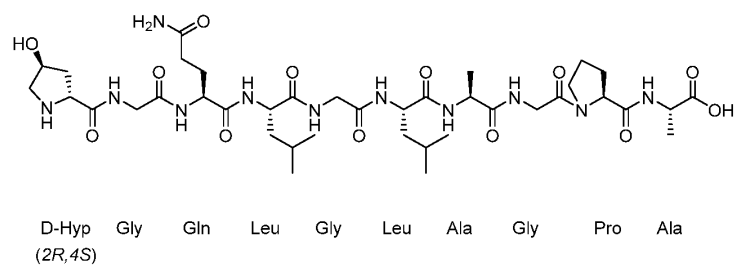
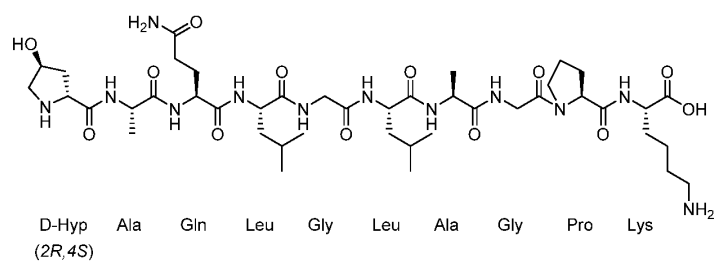
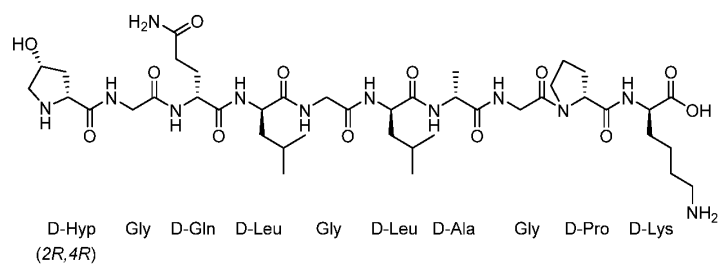
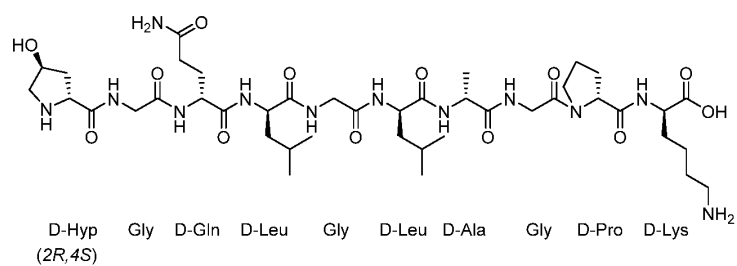


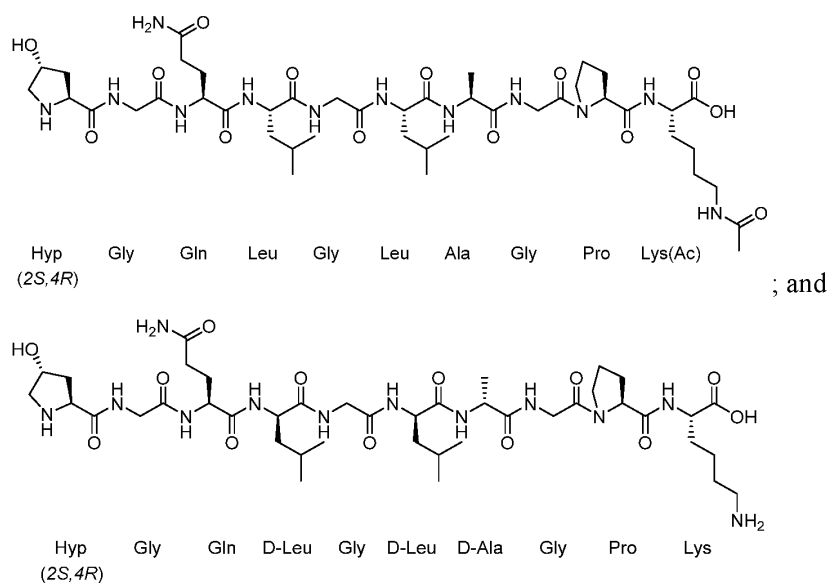




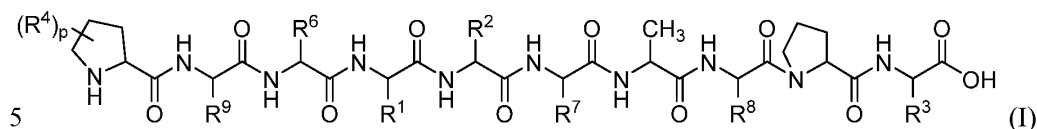
5







The present invention also provides a compound represented by Formula (I):



or a pharmaceutically acceptable salt thereof;

wherein:

R¹, R², and R³ are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, 10 cycloalkyl, heterocyclyl, or heterocyclylalkyl;

R⁴, independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclcyl, oxo, -OR^b, -CH₂OR^b, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

15 R⁶ is hydrogen or substituted or unsubstituted alkyl; and

R⁷, R⁸, and R⁹ are each independently hydrogen or alkyl;

wherein at least one of:

(a) at least one of R¹, R², and R³ is substituted or unsubstituted (C₂-C₁₀)haloalkyl;

(b) at least one of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl is

substituted with one or more substituents selected from $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-$

5 $C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$; and

at least one occurrence of R^a or R^c is heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl;

(c) the compound comprises at least one D-amino acid residue; or

(d) at least two occurrences of R^a ;

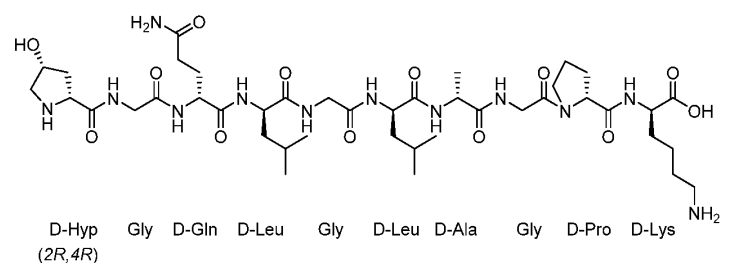
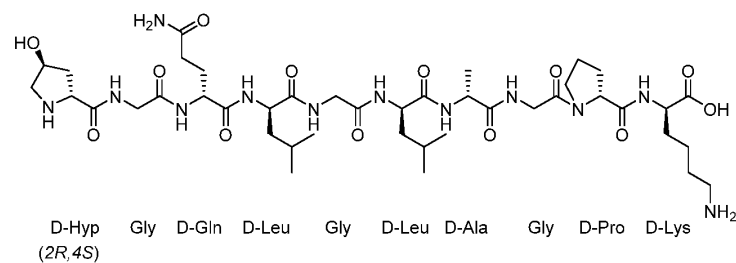
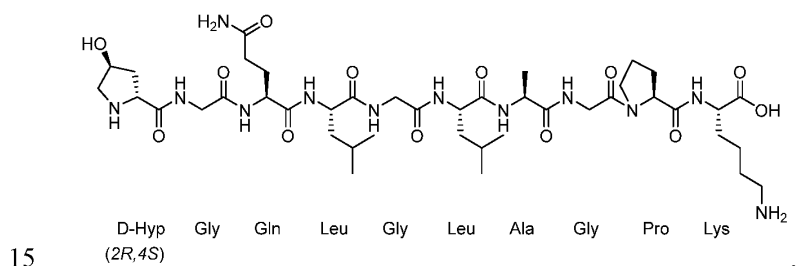
10 at least two occurrences of R^c ; or

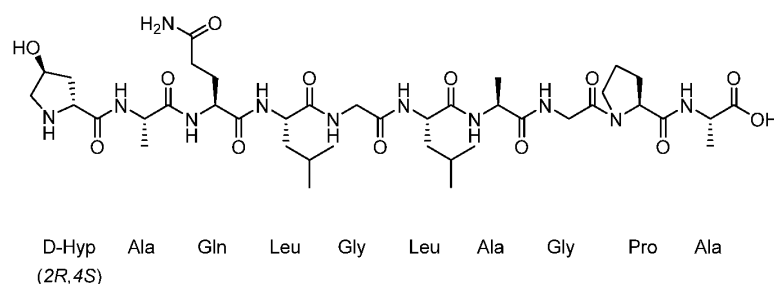
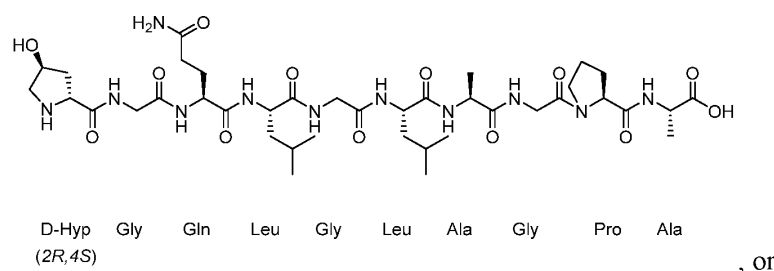
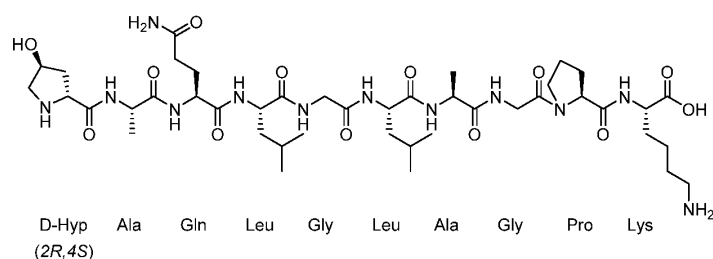
at least one occurrence of R^a and at least one occurrence of R^c ; and

at least one occurrence of R^a and/or R^c differs from the other occurrences;

and

wherein the compound is not:





In certain embodiments, at least one of R^1 , R^2 , and R^3 is substituted or unsubstituted
 5 (C₂-C₁₀)haloalkyl.

In certain embodiments, at least one of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is substituted with one or more substituents selected from $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$; and at least one occurrence of R^a or R^c is heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

10

In certain embodiments, the compound comprises at least one D-amino acid residue.
 15 In certain embodiments, the compound has:

at least two occurrences of R^a ;

at least two occurrences of R^c ; or

at least one occurrence of R^a and at least one occurrence of R^c ; and

at least one occurrence of R^a and/or R^c differs from the other occurrences.

In certain embodiments:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

5 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, $-OR^b$, hydroxyalkyl, $-CH_2OR^b$, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclalkyl;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl.

10 In some embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclalkyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, $-CN$, $-NO_2$, $=N-OH$, $-N_3$, $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, -
 15 $S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$;

R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

20 R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

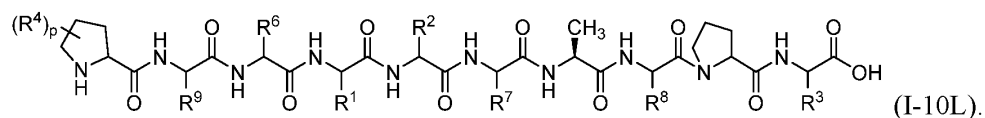
In more particular embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclalkyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected
 25 from halo, haloalkyl, oxo, $-R^a$, $-OR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, and $-(alkylene)-C(=O)N(R^a)_2$;

R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

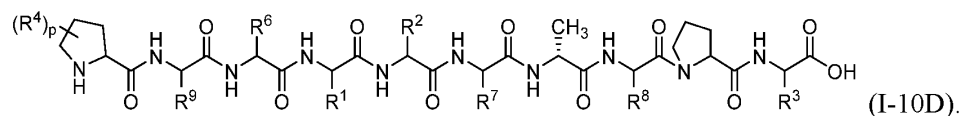
30 R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

In certain such embodiments, R^a , independently for each occurrence, is hydrogen, alkyl, aryl, arylalkyl, heterocyclalkyl, or heterocyclalkyl; and R^c , independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclalkyl, or heterocyclalkyl.

In certain embodiments, the compound has the structure of formula (I-10L):



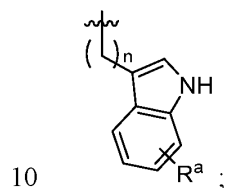
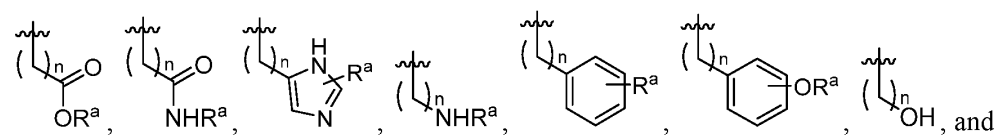
Alternatively, the compound may have the structure of formula (I-10D):



5 In certain embodiments, R^1 is substituted or unsubstituted (C_2 - C_{10})haloalkyl.

In certain embodiments, R^1 is substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

More specifically, R^1 may be selected from substituted or unsubstituted alkyl,

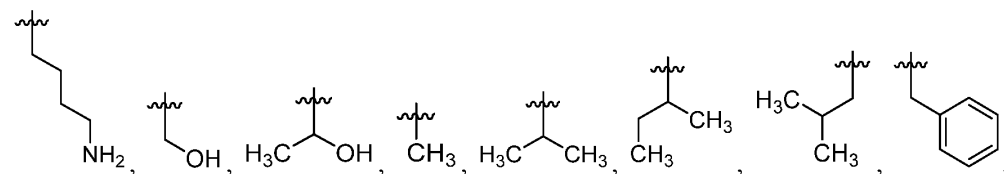
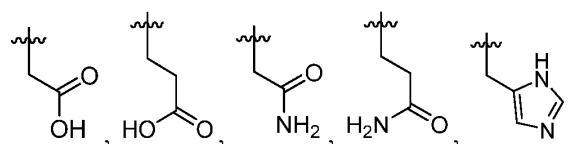


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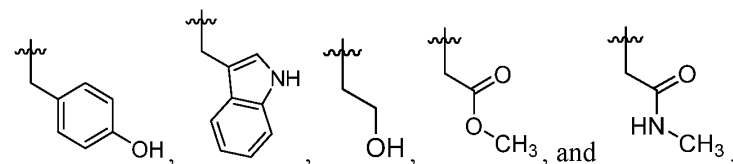
R^a is hydrogen or alkyl; and

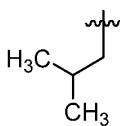
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

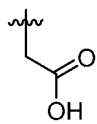
Exemplary R^1 groups include



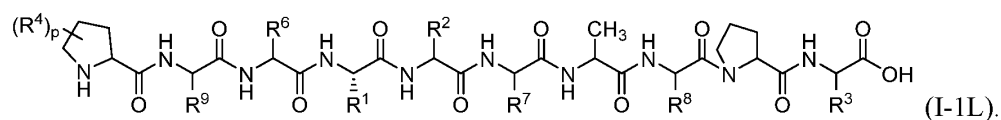
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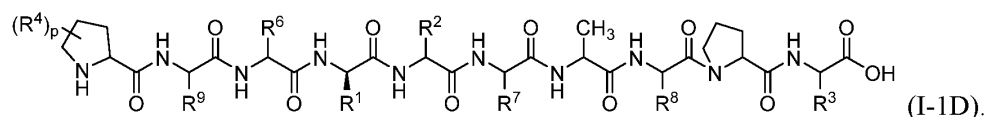
In some preferred embodiments, R^1 is . In alternative preferred

embodiments, R^1 is .

In certain embodiments, the compound has the structure of formula (I-1L):



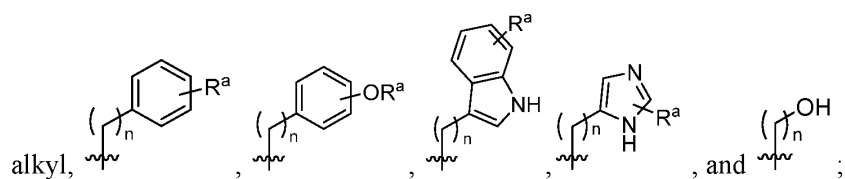
5 Alternatively, the compound may have the structure of formula (I-1D)



In certain embodiments, R^2 is substituted or unsubstituted (C_2 - C_{10})haloalkyl.

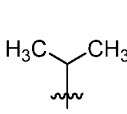
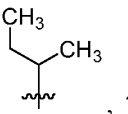
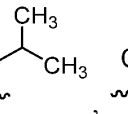
In certain embodiments, R^2 is H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

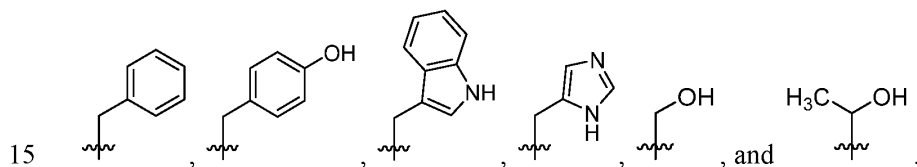
10 In some embodiments, R^2 is selected from hydrogen, substituted or unsubstituted



R^a is hydrogen or alkyl; and

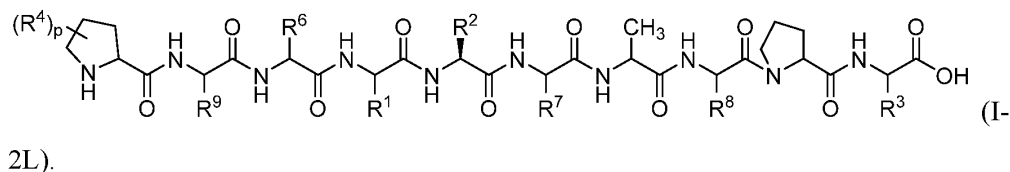
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

Exemplary R^2 groups include , , , , and .

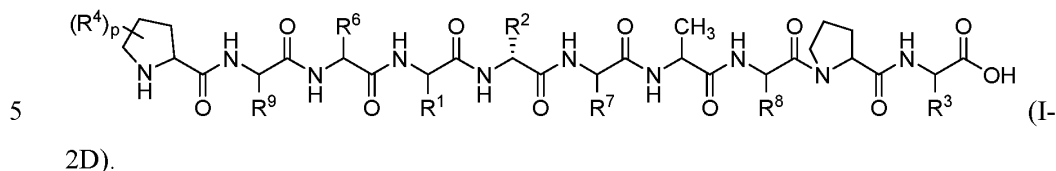


Preferably, R^2 is hydrogen.

In certain embodiments, the compound has the structure of formula (I-2L):



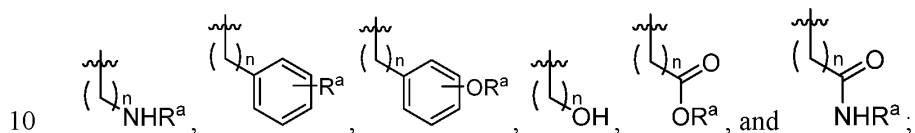
Alternatively, the compound may have the structure of formula (I-2D):



In certain embodiments, R³ is substituted or unsubstituted (C₂-C₁₀)haloalkyl.

In certain embodiments, R³ is substituted or unsubstituted alkyl or arylalkyl.

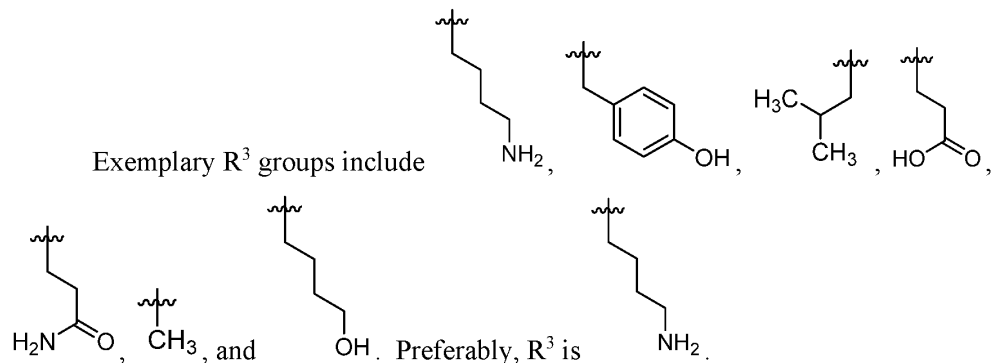
In some embodiments, R³ is selected from substituted or unsubstituted alkyl,



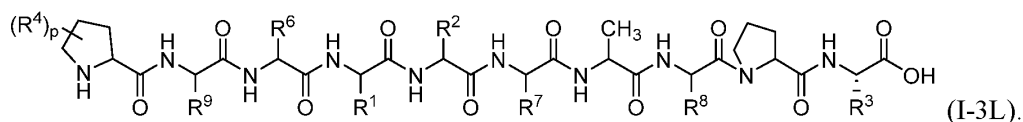
R^a is hydrogen or alkyl; and

n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

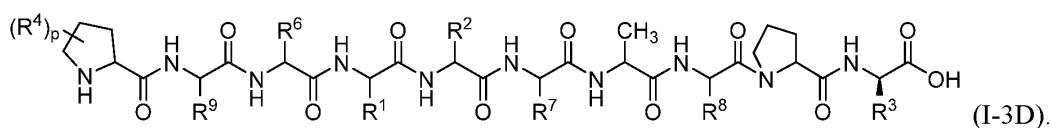
Exemplary R³ groups include



15 In certain embodiments, the compound has the structure of formula (I-3L):



Alternatively, the compound may have the structure of formula (I-3D):



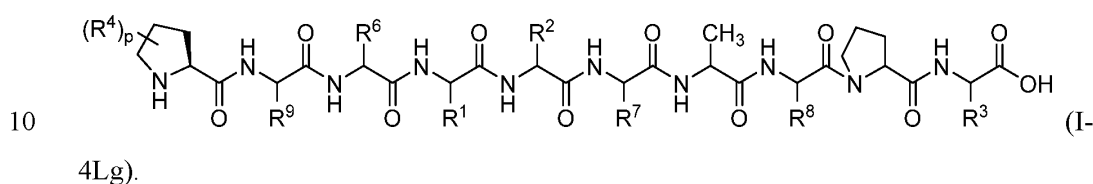
In certain embodiments, p is 1 or 2; and R⁴, independently for each occurrence, is selected from substituted or unsubstituted alkyl, -OR^b, -CH₂OR^b, halo, hydroxyl, and hydroxyalkyl.

In certain embodiments, p is 1 or 2; and R⁴, independently for each occurrence, is selected from -CH₃, halo, hydroxyl, and hydroxyalkyl.

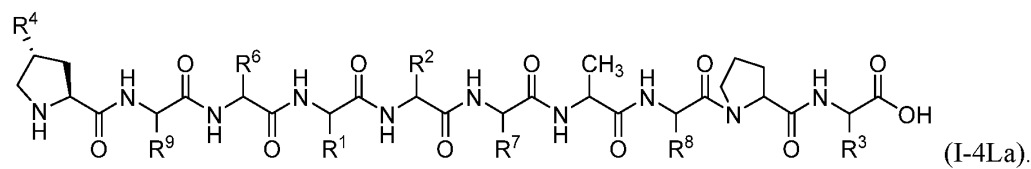
In certain preferred embodiments, R⁴ is hydroxyl. In alternative preferred embodiments, R⁴ is -CH₃.

In any of the above embodiments, p may be 1.

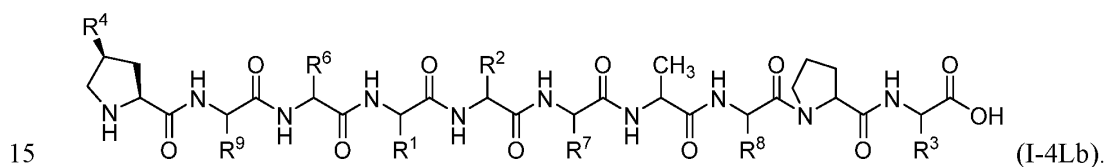
In certain embodiments, the compound has the structure of formula (I-4Lg):



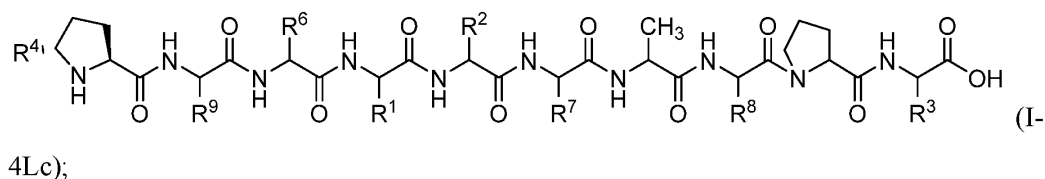
In certain embodiments, the compound has the structure of formula (I-4La):



In certain embodiments, the compound has the structure of formula (I-4Lb):

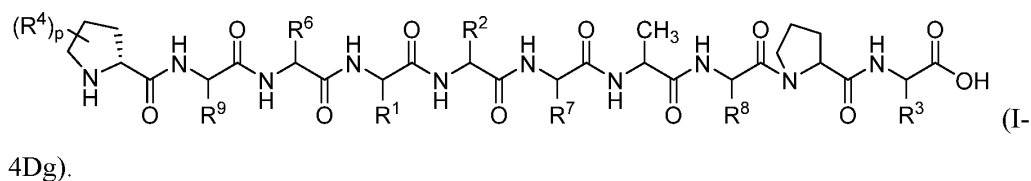


In certain embodiments, the compound has the structure of formula (I-4Lc):

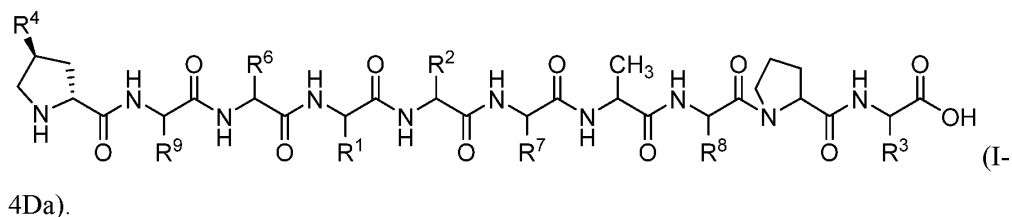


provided that R⁴ is not hydroxyl.

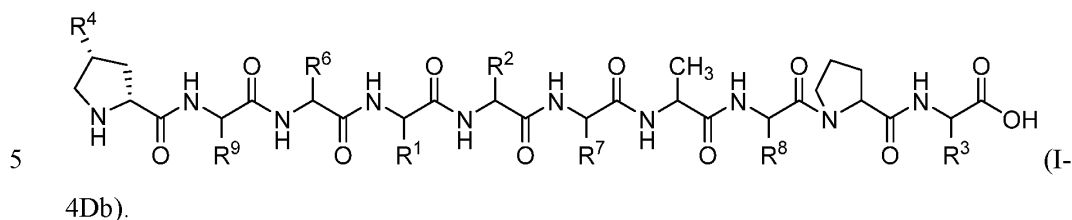
20 In certain embodiments, the compound has the structure of formula (I-4Dg):



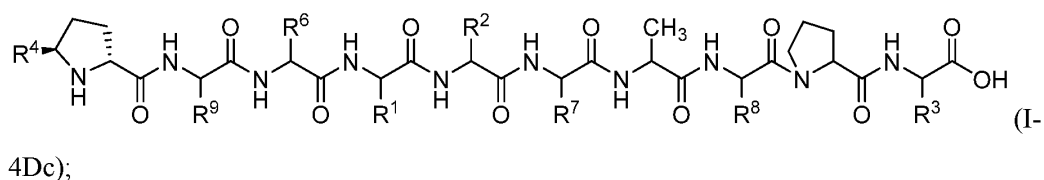
In certain embodiments, the compound has the structure of formula (I-4Da):



In certain embodiments, the compound has the structure of formula (I-4Db):



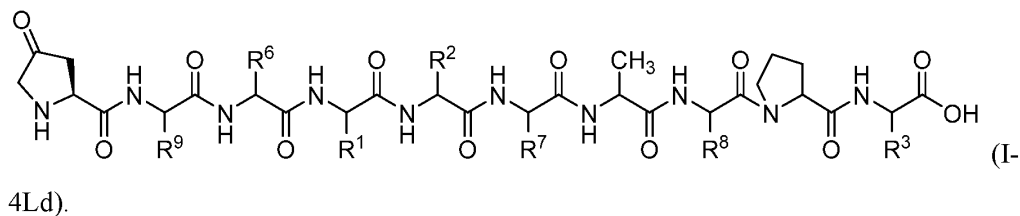
In certain embodiments, the compound has the structure of formula (I-4Dc):



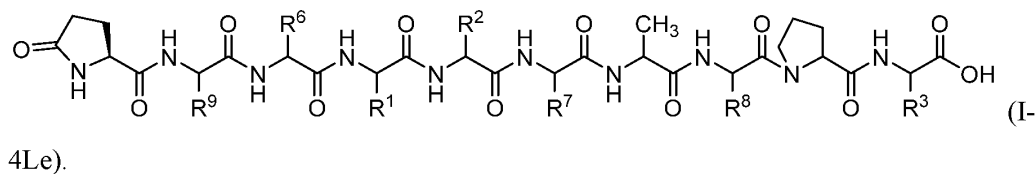
provided that R⁴ is not hydroxyl.

In certain embodiments, R⁴ is oxo.

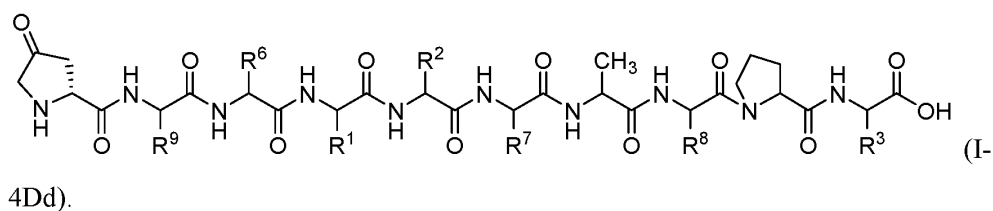
In certain embodiments, the compound has the structure of formula (I-4Ld):



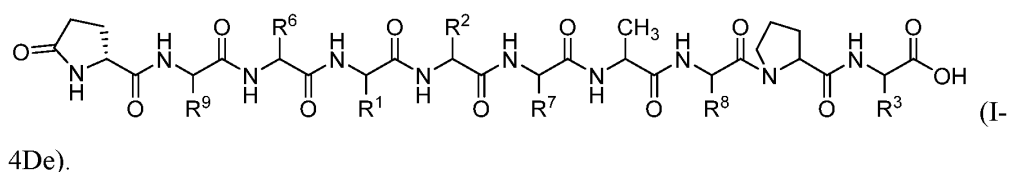
In certain embodiments, the compound has the structure of formula (I-4Le):



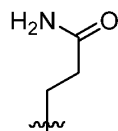
In certain embodiments, the compound has the structure of formula (I-4Dd):



In certain embodiments, the compound has the structure of formula (I-4De):

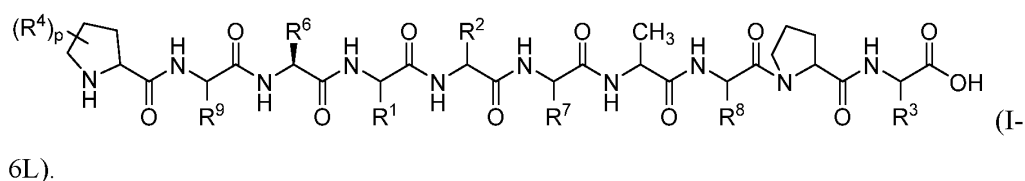


In certain embodiments, R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$. In certain embodiments, wherein R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$. For example, R^6 may be -

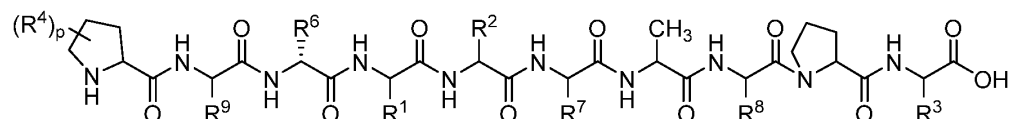


CH_3 . Alternatively, R^6 may be

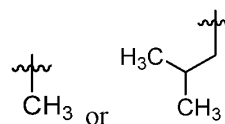
In certain embodiments, the compound has the structure of formula (I-6L):



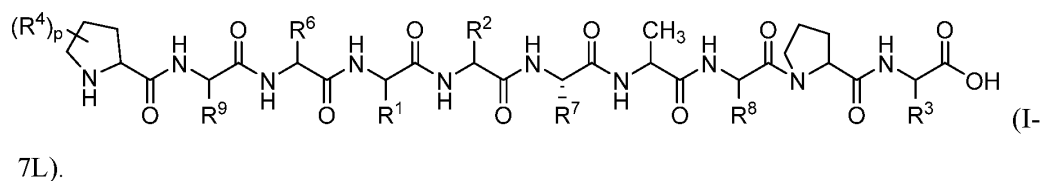
Alternatively, the compound may have the structure of formula (I-6D):



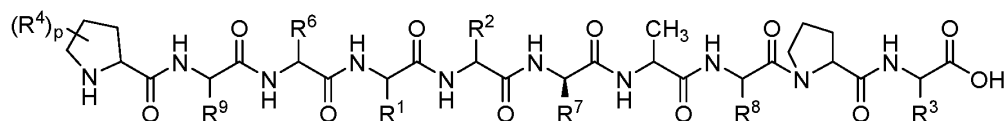
In certain embodiments, R^7 is (C_1-C_{10}) alkyl, preferably



In certain embodiments, the compound has the structure of formula (I-7L):

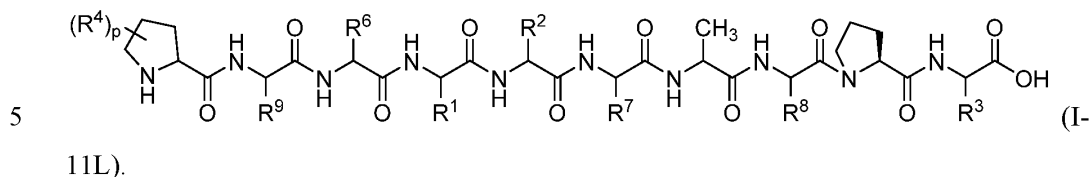


Alternatively, the compound may have the structure of formula (I-7D):

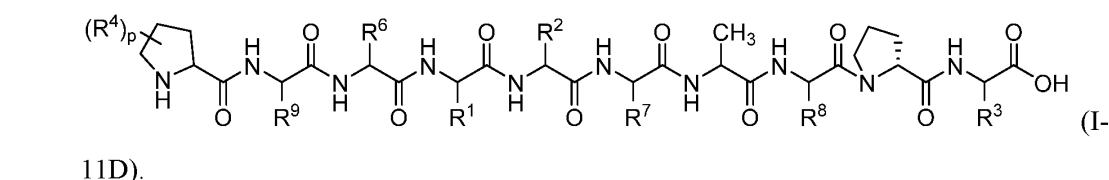


(I-7D).

In certain embodiments, the compound has the structure of formula (I-11L):



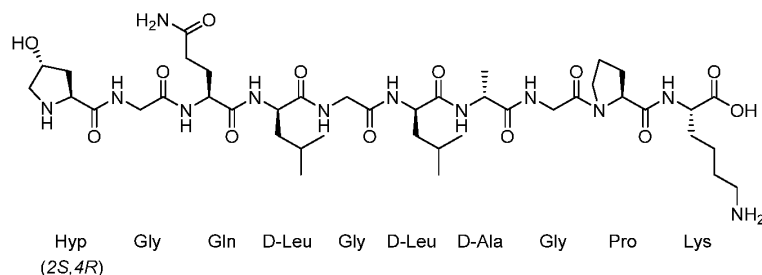
Alternatively, the compound may have the structure of formula (I-11D):



In certain embodiments, R⁸ is -CH₃ or -H, preferably -H.

In certain embodiments, R⁹ is -CH₃ or -H, preferably -H.

In certain embodiments, the compound is



, or a pharmaceutically

acceptable salt thereof.

15 In certain embodiments, the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys;

or a pharmaceutically acceptable salt and/or stereoisomer thereof;

wherein Xaa is selected from Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr,

Trp, homo-Ser, Asp(Me), and Asn(Me); and

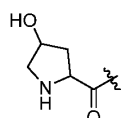
20 at least one amino acid residue in the peptide is a D-amino acid residue.

In certain such embodiments, at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

The peptide may be a variant of a collagen type II $\alpha 1$ -derived peptide. The collagen type II $\alpha 1$ may be isolated from the extracellular matrix derived from animal chondrocytes.

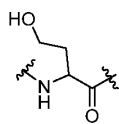
The term “peptide” used in the present invention refers to a compound in which two or more amino acids are linked by a peptide bond. Further, it is classified into dipeptide, tripeptide, tetrapeptide, and the like according to the number of constituent amino acids. An oligopeptide has about 10 or fewer peptide bonds, and a polypeptide has a plurality of peptide bonds. In addition, a peptide in the present invention includes a mutated peptide in which its amino acid residue is substituted.

The term “HyP” used in the present invention refers to an amino acid called hydroxyproline, in which a hydroxyl group (-OH) is bonded to the carbon atom at the 4-position of proline. HyP has a structure of $C_5H_9NO_3$ and may be depicted as follows:



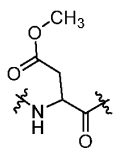
HyP may include all isomers. In addition, HyP may be an isomer represented by the stereochemistry of “2S,4R” unless otherwise specified.

The term “homo-Ser” used in the present invention is called homoserine and refers to an α -amino acid having a hydroxyl group in the side chain. Homo-Ser is an intermediate present in the biosynthesis of threonine and methionine in microorganisms and plants.



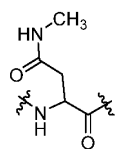
Homo-Ser may be depicted as follows:

The term “Asp(Me)” used in the present invention indicates an amino acid in which the hydrogen atom of the hydroxyl group (OH) bonded to the carbon atom at the 4-position of aspartic acid is substituted by a methyl group (CH_3). Asp(Me) may be depicted as

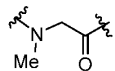


follows:

The term “Asn(Me)” used in the present invention indicates an amino acid in which the hydrogen atom of the amine group (NH_2) bonded to the carbon atom at the 4-position of asparagine is substituted by a methyl group (CH_3). Asn(Me) may be depicted as follows:



The term “(N-Me)Gly” used in the present invention indicates an amino acid in which the hydrogen atom of the amine group (NH₂) bonded to the carbon atom at the 2-position of glycine is replaced by a methyl group (CH₃). (N-Me)Gly may be depicted as follows:



5 In certain embodiments, the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys;
or a pharmaceutically acceptable salt and/or stereoisomer thereof;
wherein Xaa is selected from Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly;
and

10 at least one amino acid residue in the peptide is a D-amino acid residue.

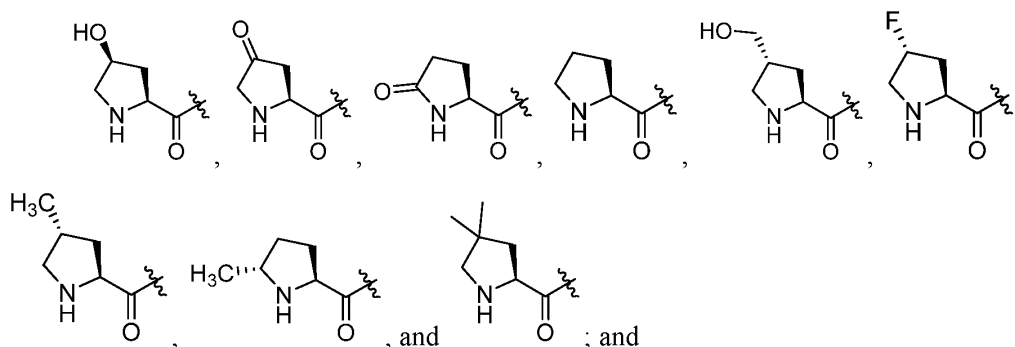
In certain such embodiments, at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

In certain embodiments, the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa;

15 or a pharmaceutically acceptable salt and/or stereoisomer thereof;
wherein Xaa is selected from Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH); and
at least one amino acid residue in the peptide is a D-amino acid residue.

In certain such embodiments, at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

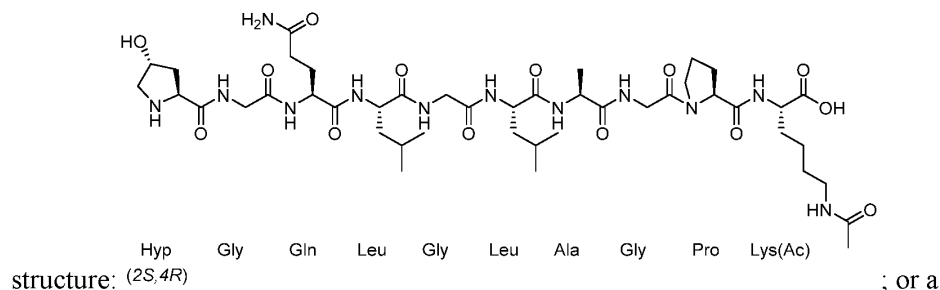
20 In certain embodiments, the compound is a peptide having an amino acid sequence represented by Xaa-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys;
or a pharmaceutically acceptable salt and/or stereoisomer thereof;
wherein Xaa is selected from:



25 , and
at least one amino acid residue in the peptide is a D-amino acid residue.

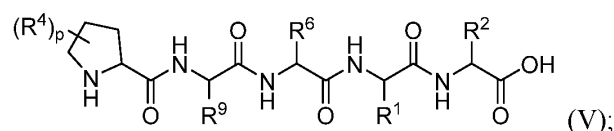
In certain such embodiments, at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

In certain embodiments, the invention provides a compound having the following



5 pharmaceutically acceptable salt thereof.

In certain embodiments, the invention provides a compound represented by Formula (V):



or a pharmaceutically acceptable salt thereof;

10 wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl;

15 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

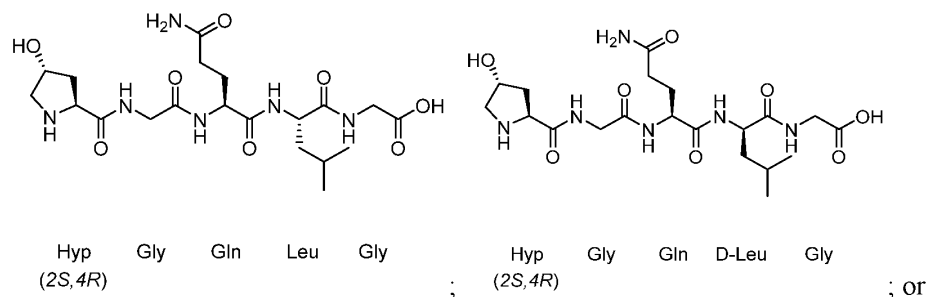
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

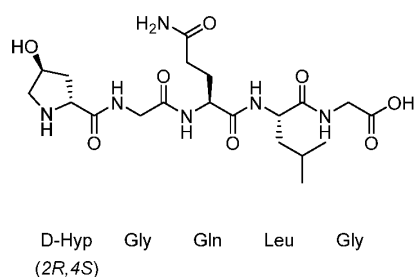
p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^9 is hydrogen or alkyl;

20 wherein the compound is not:





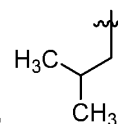
In certain embodiments, R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

R^4 for each occurrence is hydroxyl;

5 p is 1;

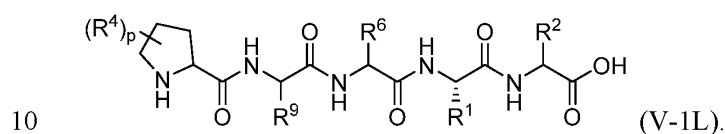
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

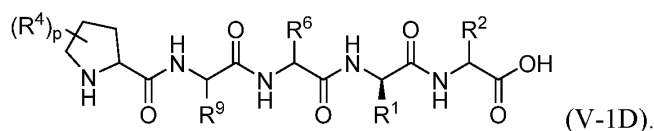


In certain embodiments, R^1 is substituted or unsubstituted alkyl, such as

In certain embodiments, the compound has the structure of formula (V-1L)



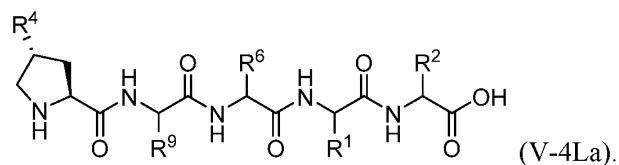
Alternatively, the compound may have the structure of formula (V-1D)



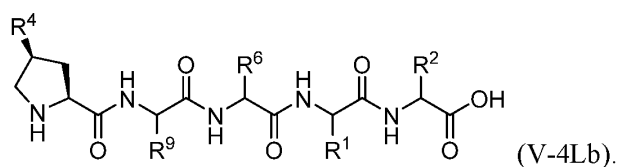
In certain embodiments, R^2 is H.

In certain embodiments, p is 1 and R^4 is hydroxyl.

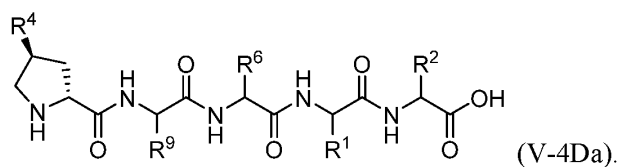
15 In certain embodiments, the compound has the structure of formula (V-4La):



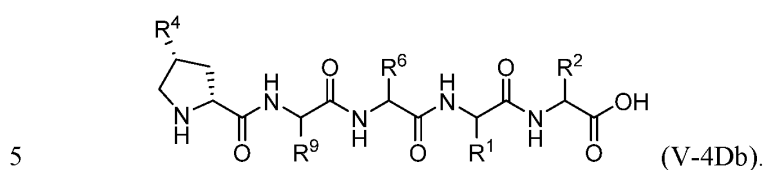
In certain embodiments, the compound has the structure of formula (V-4Lb):



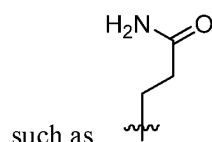
In certain embodiments, the compound has the structure of formula (V-4Da):



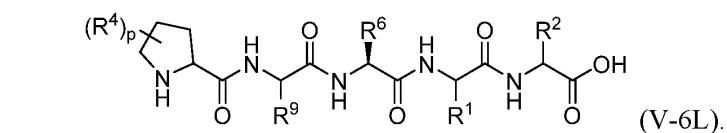
In certain embodiments, the compound has the structure of formula (V-4Db):



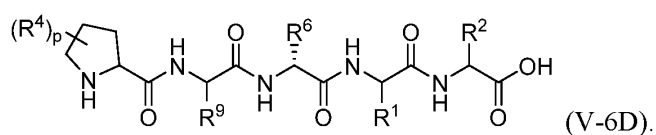
In certain embodiments, R^6 is alkyl substituted with one occurrence of $-C(=O)NH_2$,



In certain embodiments, the compound has the structure of formula (V-6L):

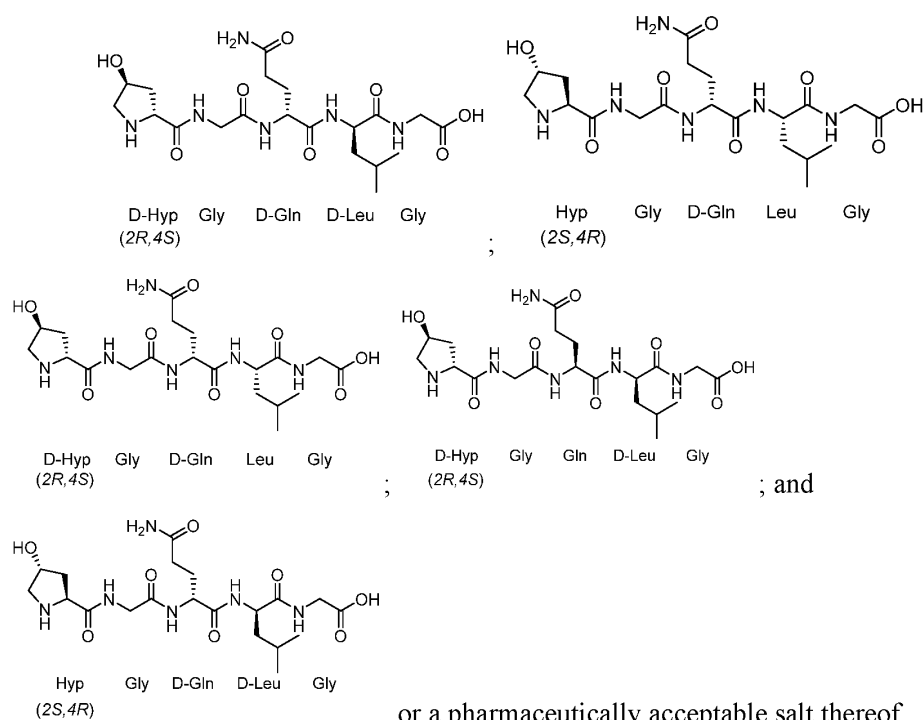


Alternatively, the compound may have the structure of formula (V-6D):



In certain embodiments, R^9 is $-H$.

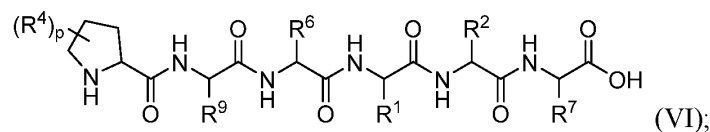
In certain embodiments, the compound is selected from the following:



, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the invention provides a compound represented by Formula

5 (VI):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy,
10 haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl,
heterocyclyl, or heterocyclylalkyl

R^4 , independently for each occurrence, is selected from substituted or unsubstituted
alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

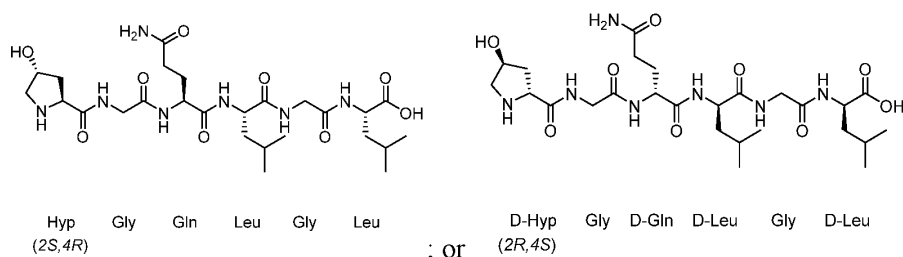
15 p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 is hydrogen or alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



In certain embodiments:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

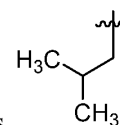
R^4 for each occurrence is hydroxyl;

5 p is 1;

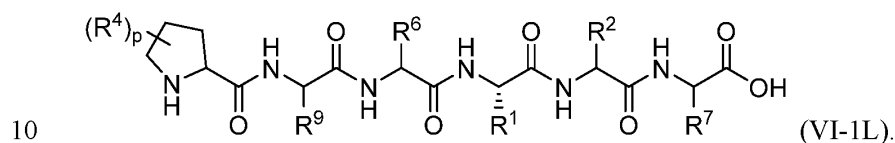
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

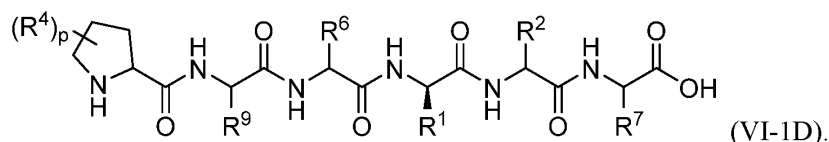
In certain embodiments, R^1 is substituted or unsubstituted alkyl, such as



In certain embodiments, the compound has the structure of formula (VI-1L)



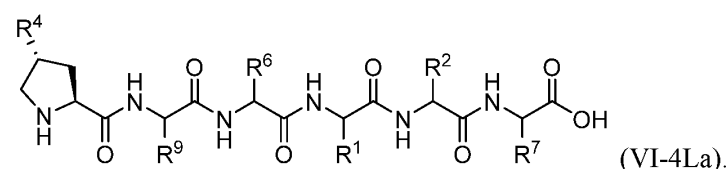
Alternatively, the compound may have the structure of formula (VI-1D)



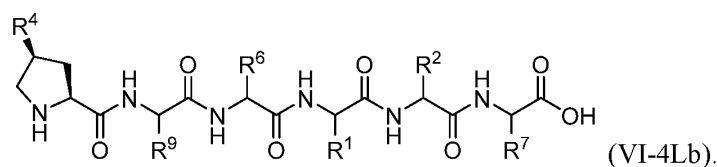
In certain embodiments, R^2 is H.

In certain embodiments, p is 1 and R^4 is hydroxyl.

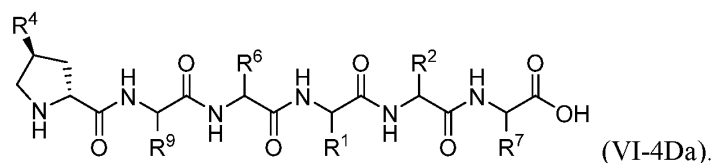
15 In certain embodiments, the compound has the structure of formula (VI-4La):



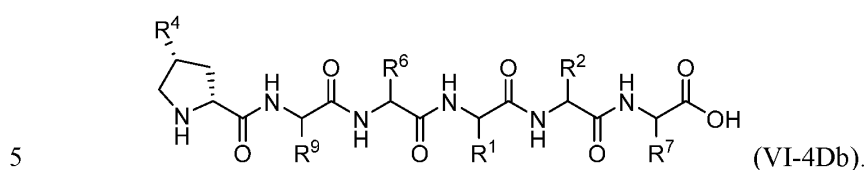
In certain embodiments, the compound has the structure of formula (VI-4Lb):



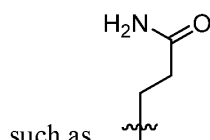
In certain embodiments, the compound has the structure of formula (VI-4Da):



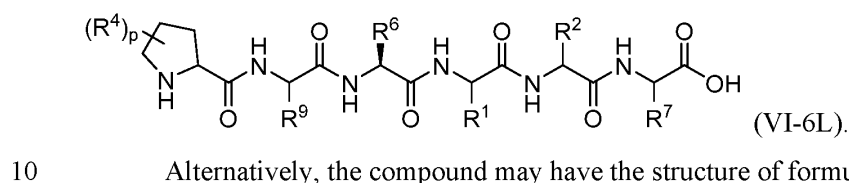
In certain embodiments, the compound has the structure of formula (VI-4Db):



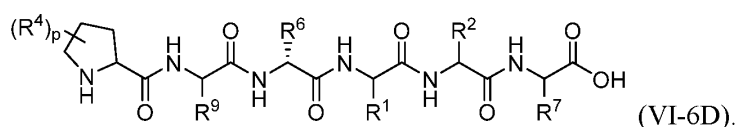
In certain embodiments, R^6 is alkyl substituted with one occurrence of $-C(=O)NH_2$,



In certain embodiments, the compound has the structure of formula (VI-6L):



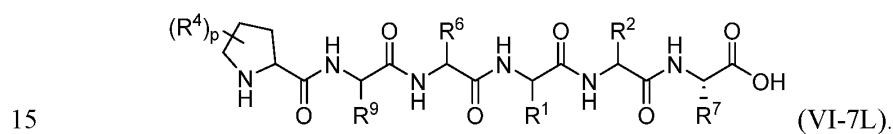
Alternatively, the compound may have the structure of formula (VI-6D):



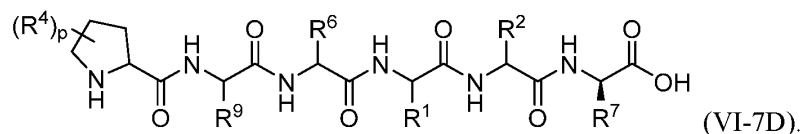
In certain embodiments, R^9 is $-H$.

In certain embodiments, R^7 is (C_1-C_{10}) alkyl, such as

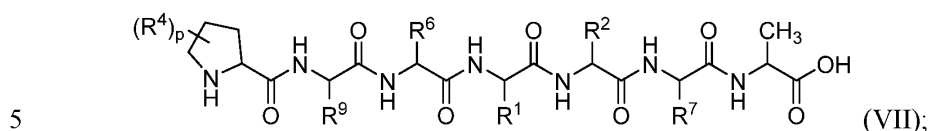
In certain embodiments, the compound has the structure of formula (VI-7L):



Alternatively, the compound may have the structure of formula (VI-7D):



In certain embodiments, the invention provides a compound represented by Formula (VII):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

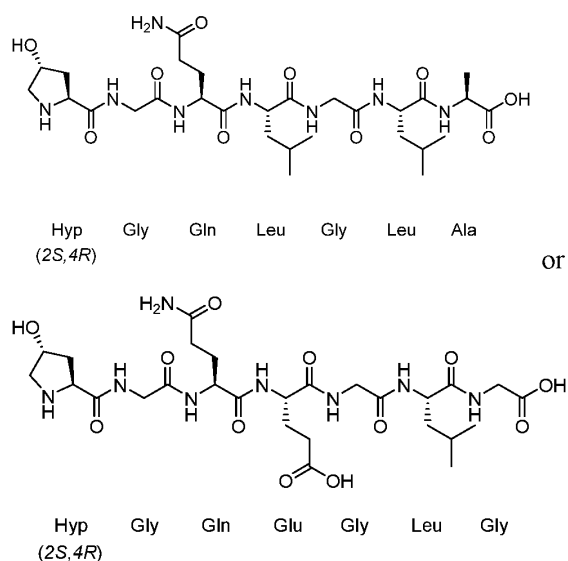
p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 is hydrogen or alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



In certain embodiments:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

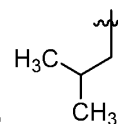
5 R^4 for each occurrence is hydroxyl;

p is 1;

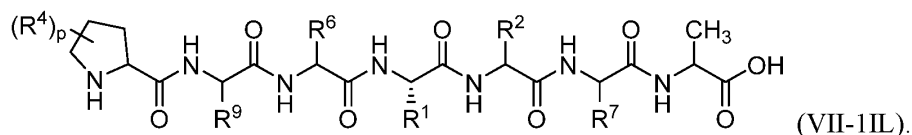
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

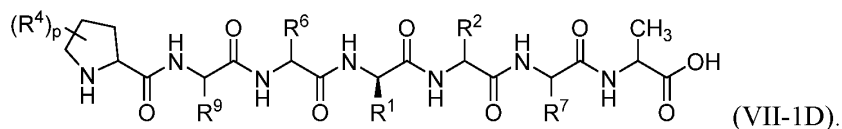
In certain embodiments, R^1 is substituted or unsubstituted alkyl, such as



10 In certain embodiments, the compound has the structure of formula (VII-1L)



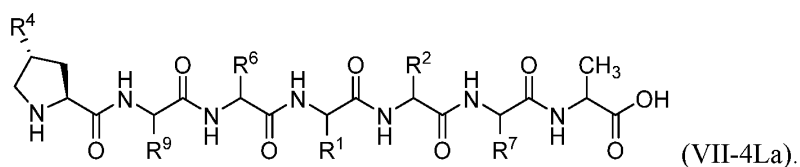
Alternatively, the compound may have the structure of formula (VII-1D)



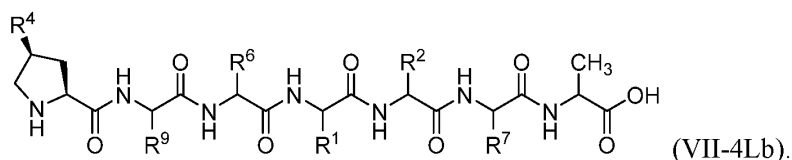
In certain embodiments, R^2 is H.

15 In certain embodiments, p is 1 and R^4 is hydroxyl.

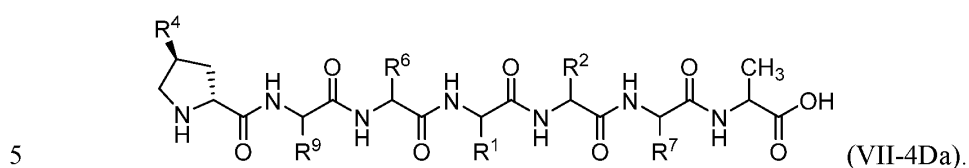
In certain embodiments, the compound has the structure of formula (VII-4La):



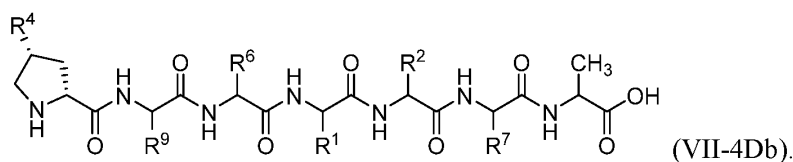
In certain embodiments, the compound has the structure of formula (VII-4Lb):



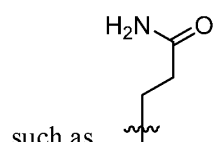
In certain embodiments, the compound has the structure of formula (VII-4Da):



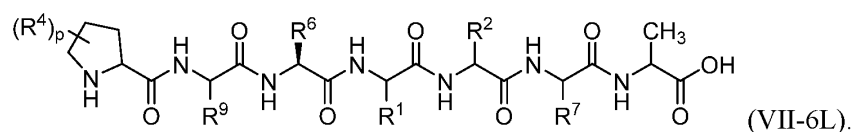
In certain embodiments, the compound has the structure of formula (VII-4Db):



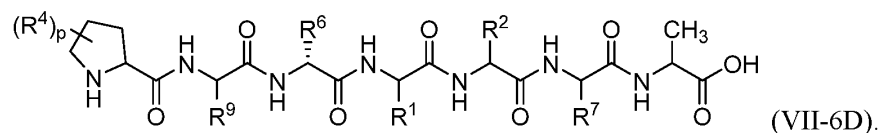
In certain embodiments, R⁶ is alkyl substituted with one occurrence of -C(=O)NH₂,



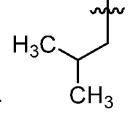
In certain embodiments, the compound has the structure of formula (VII-6L):



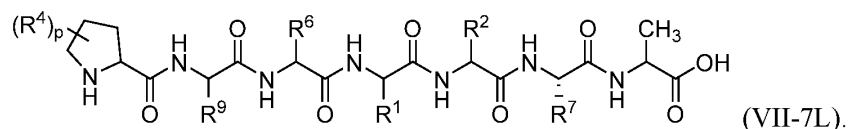
Alternatively, the compound may have the structure of formula (VII-6D):



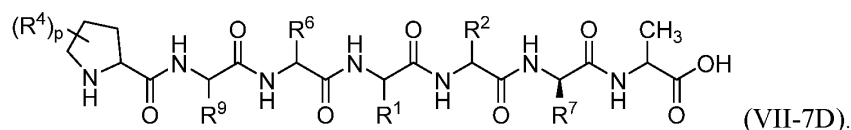
In certain embodiments, R⁹ is -H.

In certain embodiments, R^7 is (C₁-C₁₀)alkyl, such as  or .

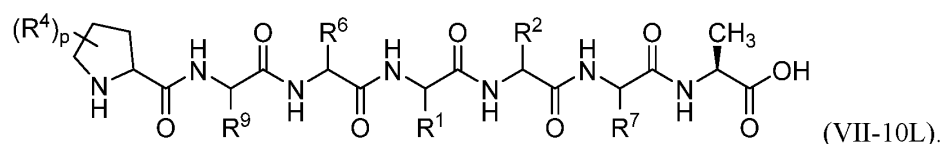
In certain embodiments, the compound has the structure of formula (VII-7L):



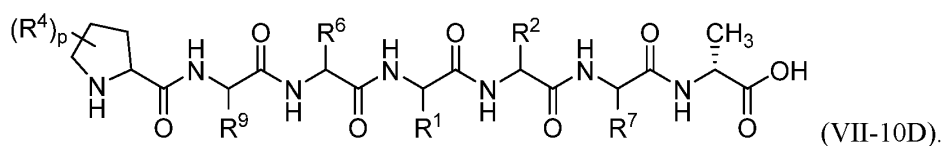
Alternatively, the compound may have the structure of formula (VII-7D):



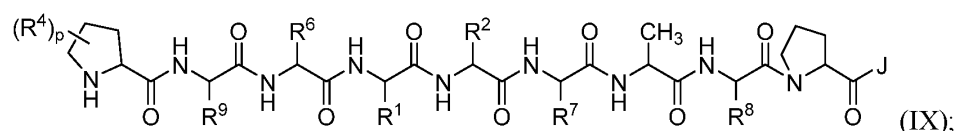
In certain embodiments, the compound has the structure of formula (VII-10L):



Alternatively, the compound may have the structure of formula (VII-10D):



The present invention also provides a compound represented by Formula (IX):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

J is OH or $-NR^xR^y$; and

- 5 R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

Exemplary compounds of Formula (IX) include YDE-100 through YDE-107.

In certain embodiments of the compounds of formula (IX):

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

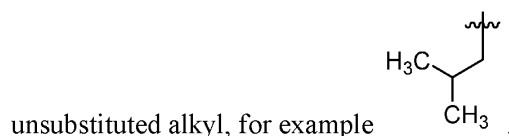
- 10 R^4 for each occurrence is hydroxyl;

p is 1;

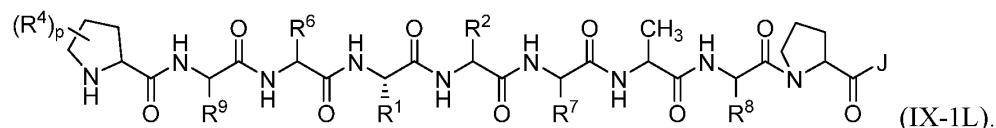
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

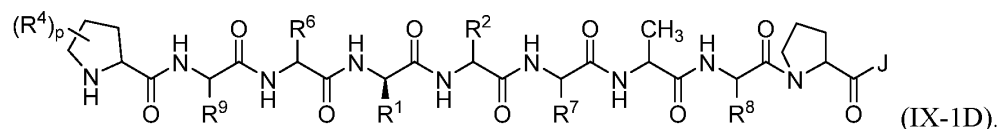
- 15 In certain embodiments of the compounds of formula (IX), R^1 is substituted or



In certain embodiments, the compound has the structure of formula (IX-1L):

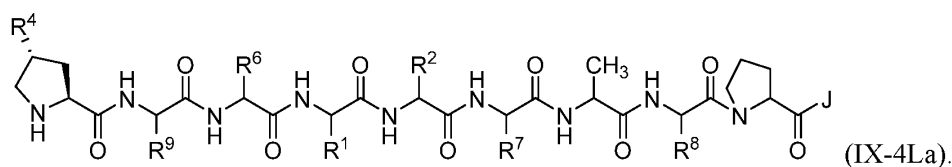


- Alternatively, in certain embodiments, the compound has the structure of formula
20 (IX-1D):

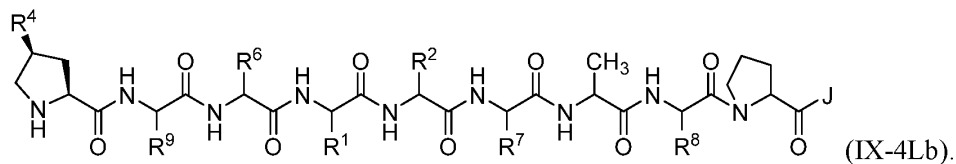


In certain embodiments, R^2 is H.

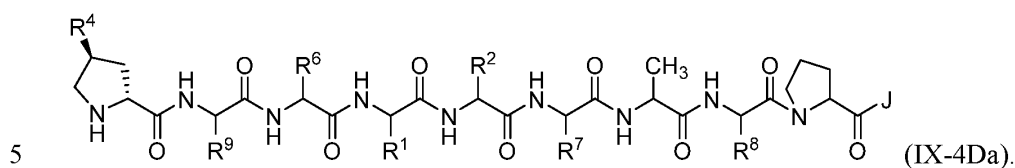
In certain embodiments, p is 1 and R^4 is hydroxyl. In certain embodiments, the compound has the structure of formula (IX-4La):



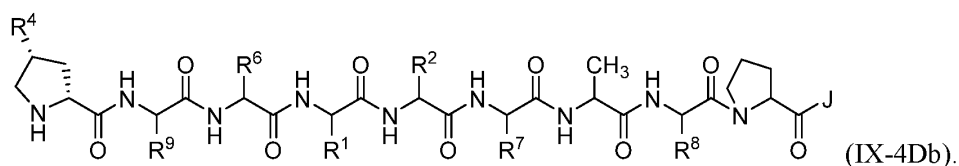
In certain embodiments, the compound has the structure of formula (IX-4Lb):



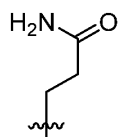
In certain embodiments, the compound has the structure of formula (IX-4Da):



In certain embodiments, the compound has the structure of formula (IX-4Db):

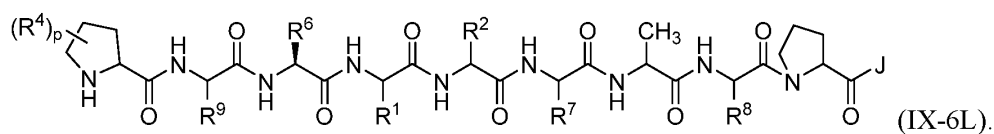


In certain embodiments, R^6 is alkyl substituted with one occurrence of $-C(=O)NH_2$,

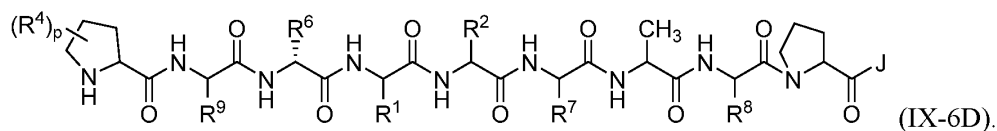


for example, R^6 may be

In certain embodiments, the compound has the structure of formula (IX-6L):

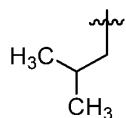


In certain embodiments, the compound has the structure of formula (IX-6D):

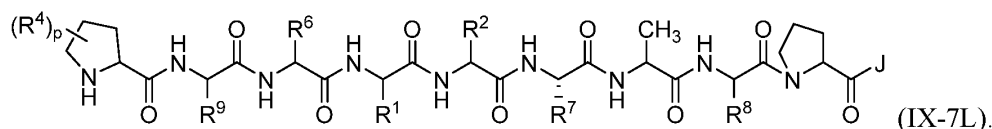


In certain embodiments, R^9 is $-H$.

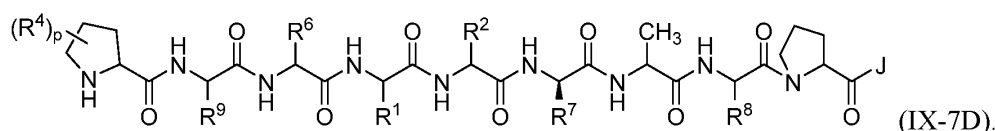
In certain embodiments, R^7 is (C₁-C₁₀)alkyl. For example, R^7 may be  or



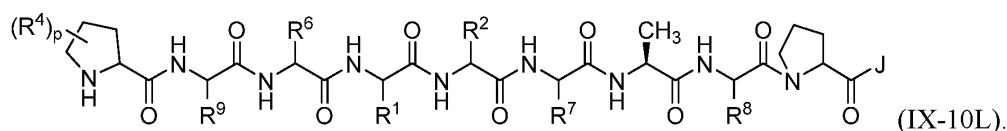
In certain embodiments, the compound has the structure of formula (IX-7L):



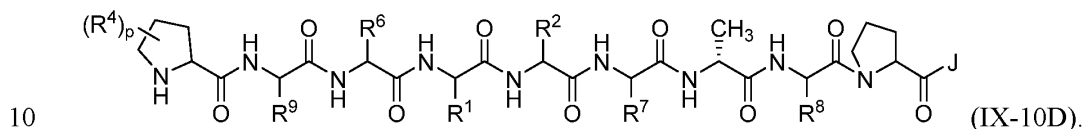
5 In certain embodiments, the compound has the structure of formula (IX-7D):



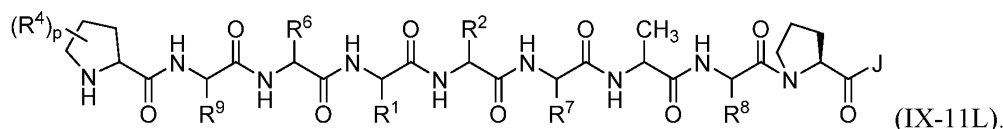
In certain embodiments, the compound has the structure of formula (IX-10L):



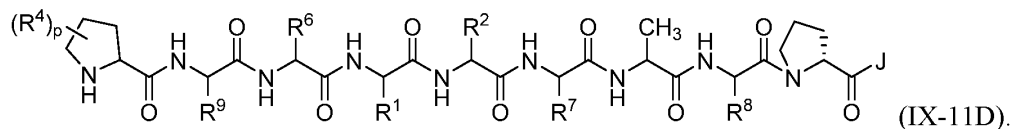
In certain embodiments, the compound has the structure of formula (IX-10D):



In certain embodiments, the compound has the structure of formula (IX-11L):



In certain embodiments, the compound has the structure of formula (IX-11D):

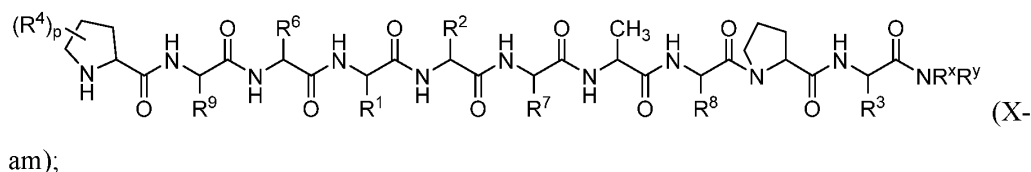


15 In certain embodiments, R^8 is $-CH_3$ or $-H$, preferably $-H$.

In certain embodiments, J is OH. Alternatively, in other embodiments, J is $-NR^xR^y$.

In certain such embodiments, R^x and R^y are each independently alkyl. Alternatively, R^x and R^y may be taken together with the intervening nitrogen atom form a ring.

In other embodiments, the present invention also provides a compound represented by Formula (X-am):



5 or a pharmaceutically acceptable salt thereof;

wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

10 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

15 R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

J is OH or $-NR^xR^y$; and

R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

20 Exemplary compounds of Formula (X-am) include YDE-93 and YDE-96.

In certain embodiments of the compound of Formula (X-am):

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

25 R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, $-OR^b$, hydroxyalkyl, $-CH_2OR^b$, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl.

30 In certain embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected

from halo, haloalkyl, oxo, -CN, -NO₂, =N-OH, -N₃, -R^a, -OR^a, -SR^a, -N(R^a)₂, -N(R^a)₃⁺,
 =NR^a, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -S(=O)₂R^c, -OS(=O)₂OR^a, -S(=O)₂OR^a, -
 S(=O)₂N(R^a)₂, -S(=O)R^c, -OP(=O)(OR^a)₂, -(alkylene)-C(=O)R^c, -C(=S)R^c, -C(=O)OR^a, -
 (alkylene)-C(=O)OR^a, -C(=S)OR^a, -C(=O)SR^a, -C(=S)SR^a, -(alkylene)-C(=O)N(R^a)₂, -
 5 C(=S)N(R^a)₂, and -C(-NR^a)N(R^a)₂; and

R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted
 alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl,
 arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

10 In further embodiments, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl,
 aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or
 heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected
 from halo, haloalkyl, oxo, -R^a, -OR^a, -N(R^a)₂, -N(R^a)₃⁺, -NHC(=O)R^c, -C(=O)R^c, -
 C(=O)N(R^a)₂, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, and -(alkylene)-C(=O)N(R^a)₂; and

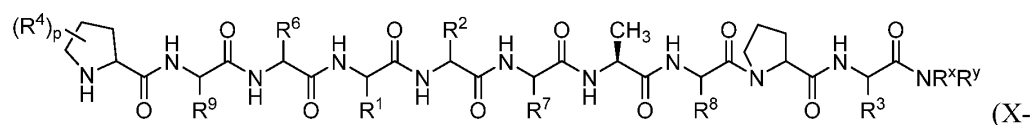
15 R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted
 alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl,
 arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

In still further embodiments, R^a, independently for each occurrence, is hydrogen,
 20 alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl; and

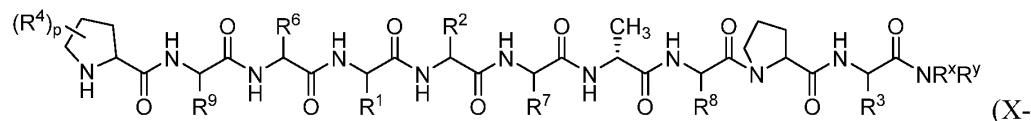
R^c, independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclyl, or
 heterocyclalkyl.

In certain embodiments, the compound has the structure of formula (X-am-10L):



25 am-10L).

In certain embodiments, the compound has the structure of formula (X-am-10D):

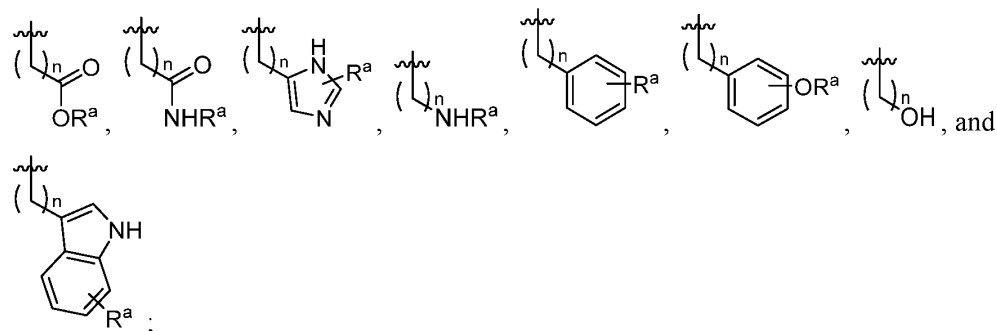


am-10D).

In certain embodiments, R¹ is substituted or unsubstituted (C₂-C₁₀)haloalkyl.

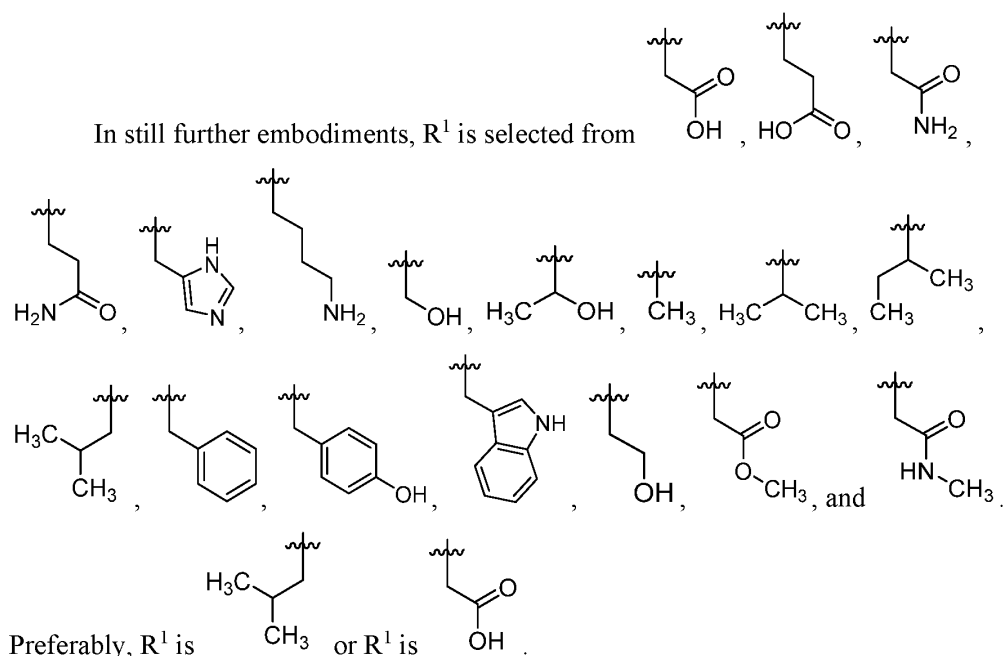
30 Alternatively, R¹ may be substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

In still further embodiments, R¹ is selected from substituted or unsubstituted alkyl,

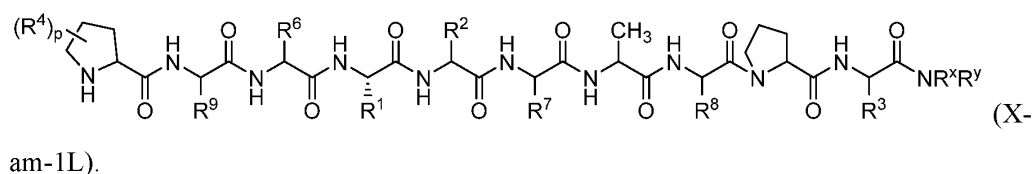


R^a is hydrogen or alkyl; and

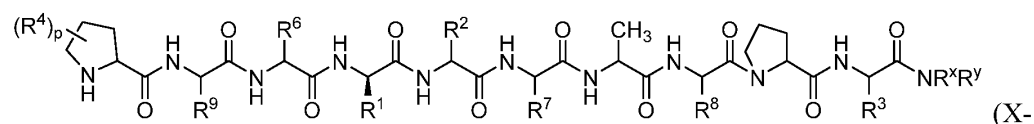
5 n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.



10 In certain embodiments, the compound has the structure of formula (X-am-1L):



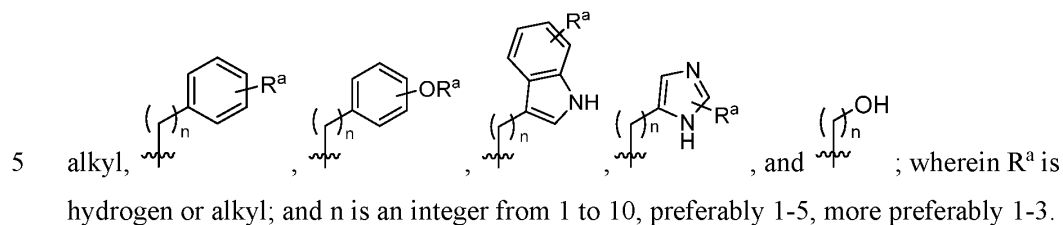
In certain embodiments, the compound has the structure of formula (X-am-1D):



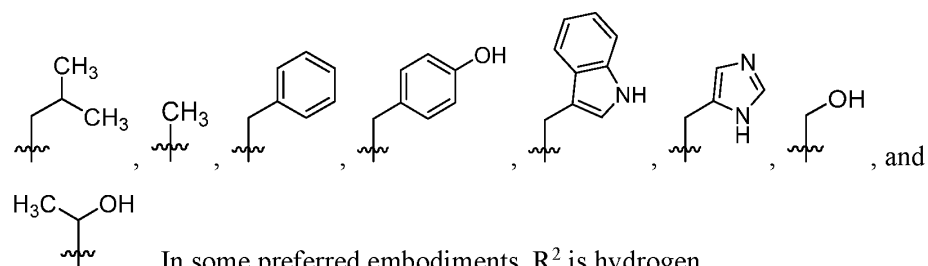
15 am-1D).

In certain embodiments, R² is substituted or unsubstituted (C₂-C₁₀)haloalkyl. Alternatively, R² may be H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclylalkyl.

In further embodiments, R² is selected from hydrogen, substituted or unsubstituted

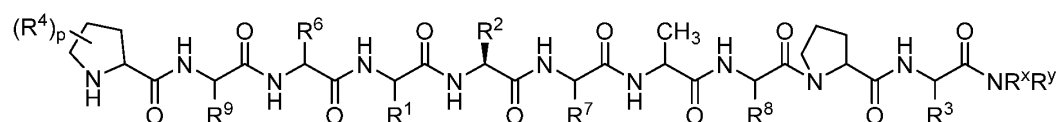


In other embodiments, R² may be selected from  ,  ,  ,



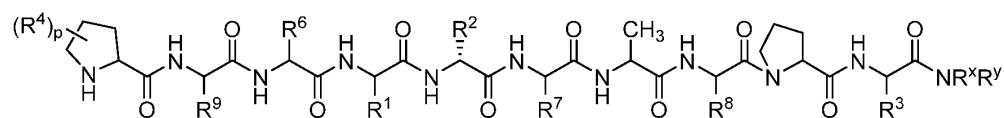
. In some preferred embodiments, R² is hydrogen.

10 In certain embodiments, the compound has the structure of formula (X-am-2L):



(X-am-2L).

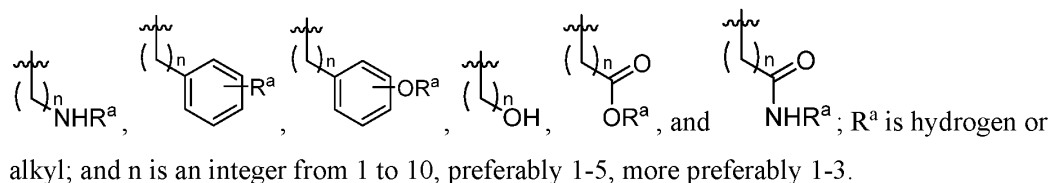
In certain embodiments, the compound has the structure of formula (X-am-2D):



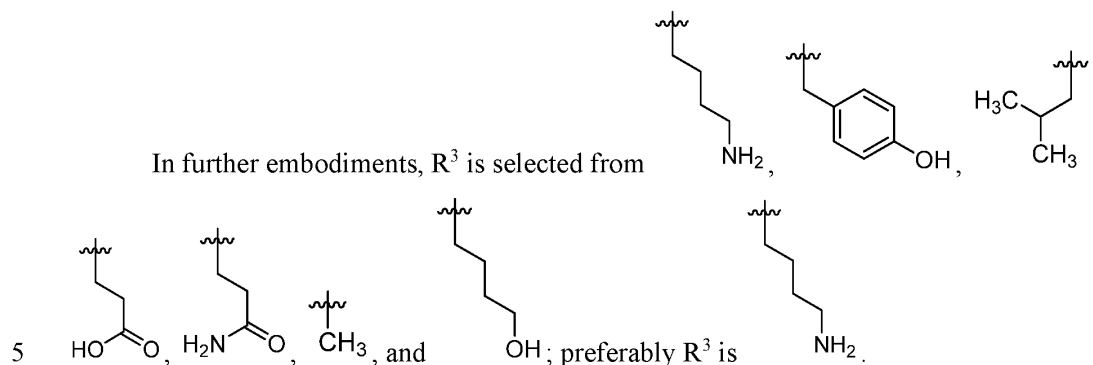
15 (X-am-2D).

In certain embodiments, R³ is substituted or unsubstituted (C₂-C₁₀)haloalkyl. Alternatively, R³ may be substituted or unsubstituted alkyl or arylalkyl.

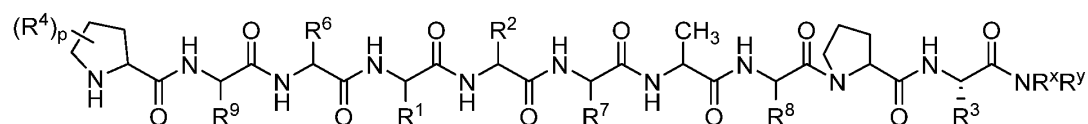
In certain embodiments, R^3 is selected from substituted or unsubstituted alkyl,



In further embodiments, R^3 is selected from

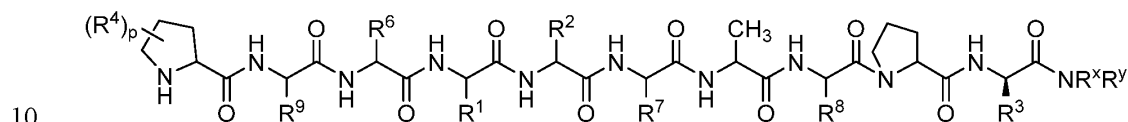


In certain embodiments, the compound has the structure of formula (X-am-3L):



(X-am-3L).

In certain embodiments, the compound has the structure of formula (X-am-3D):



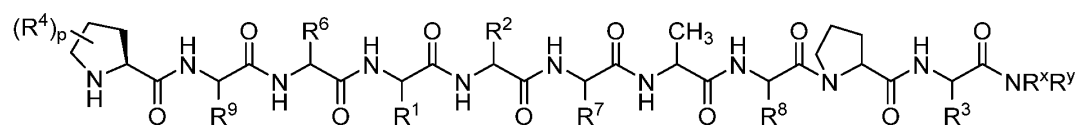
(X-am-3D).

In certain embodiments, p is 1 or 2; and R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl.

In further embodiments, p is 1 or 2; and R^4 , independently for each occurrence, is selected from $-CH_3$, halo, hydroxyl, and hydroxyalkyl. Preferably, R^4 is hydroxyl or R^4 is $-CH_3$.

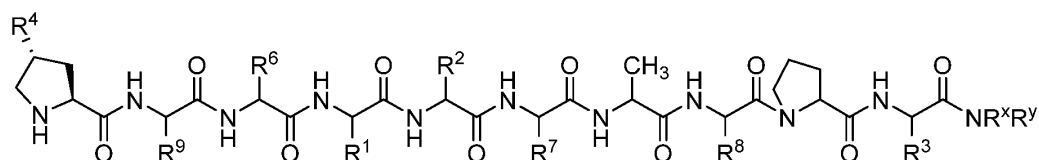
In certain embodiments, p is 1.

In certain embodiments, the compound has the structure of formula (X-am-4Lg):



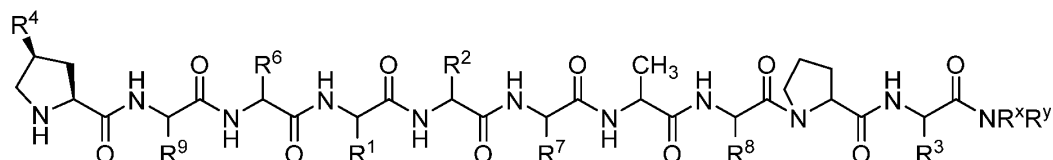
(X-am-4Lg).

In certain embodiments, the compound has the structure of formula (X-am-4La):



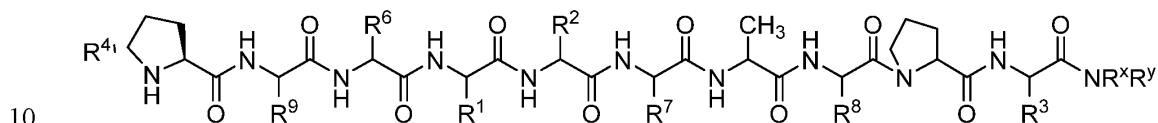
5 (X-am-4La).

In certain embodiments, the compound has the structure of formula (X-am-4Lb):



(X-am-4Lb).

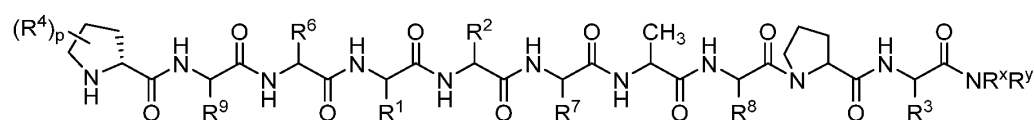
In certain embodiments, the compound has the structure of formula (X-am-4Lc):



(X-am-4Lc);

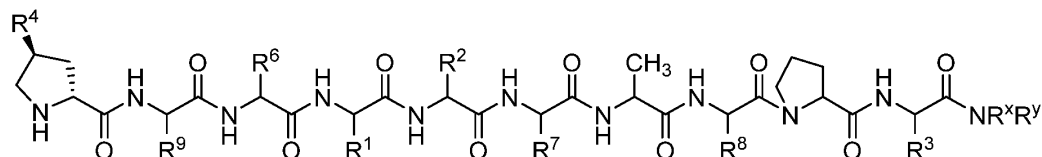
provided that R⁴ is not hydroxyl.

In certain embodiments, the compound has the structure of formula (X-am-4Dg):



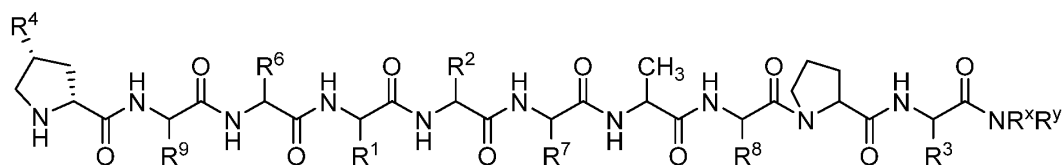
15 (X-am-4Dg).

In certain embodiments, the compound has the structure of formula (X-am-4Da):



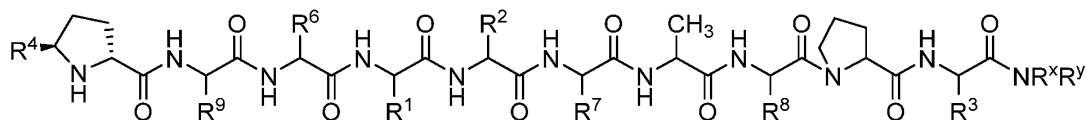
(X-am-4Da).

In certain embodiments, the compound has the structure of formula (X-am-4Db):



(X-am-4Db).

In certain embodiments, the compound has the structure of formula (X-am-4Dc):

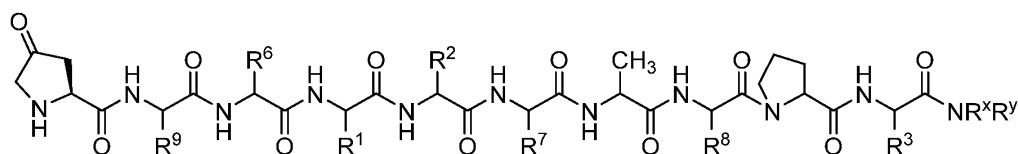


5 (X-am-4Dc);

provided that R⁴ is not hydroxyl.

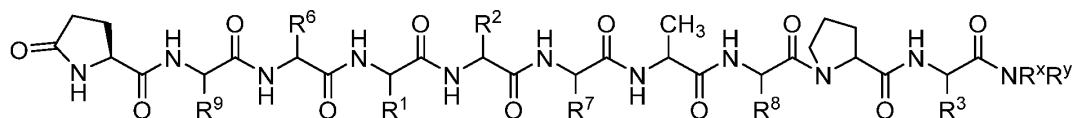
In certain embodiments, R⁴ is oxo.

In certain embodiments, the compound has the structure of formula (X-am-4Ld):



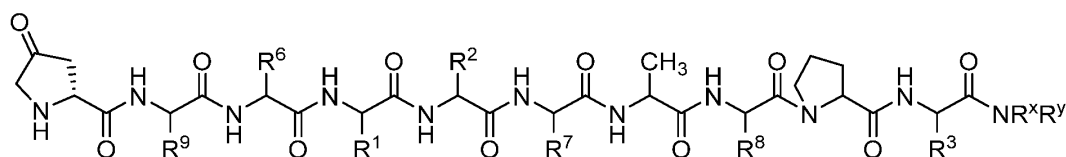
10 (X-am-4Ld).

In certain embodiments, the compound has the structure of formula (X-am-4Le):



(X-am-4Le).

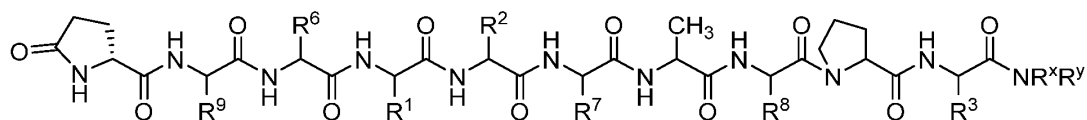
In certain embodiments, the compound has the structure of formula (X-am-4Dd):



15

(X-am-4Dd).

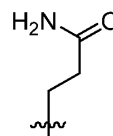
In certain embodiments, the compound has the structure of formula (X-am-4De):



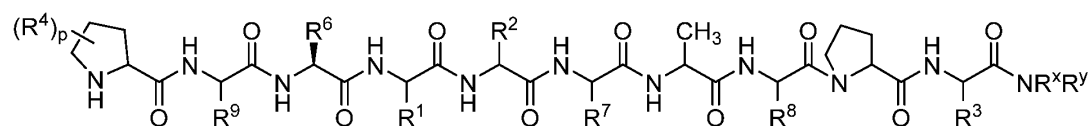
(X-am-4De).

In certain embodiments, R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$; preferably R^6 is alkyl optionally substituted

with one occurrence of $-C(=O)NH_2$. For example, R^6 may be $-CH_3$ or R^6 may be

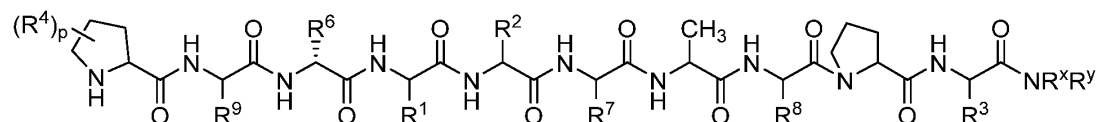


5 In certain embodiments, the compound has the structure of formula (X-am-6L):



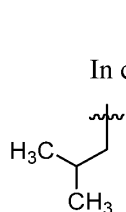
(X-am-6L).

In certain embodiments, the compound has the structure of formula (X-am-6D):

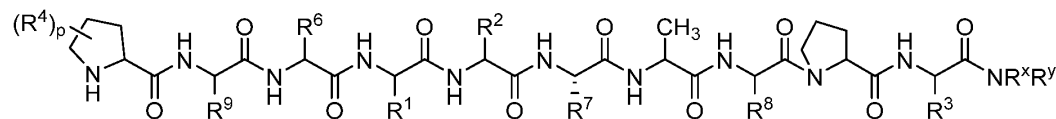


10 (X-am-6D).

In certain embodiments, R^7 is (C_1-C_{10}) alkyl. For example, R^7 may be

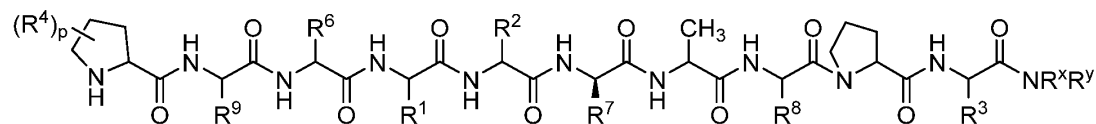


In certain embodiments, the compound has the structure of formula (X-am-7L):



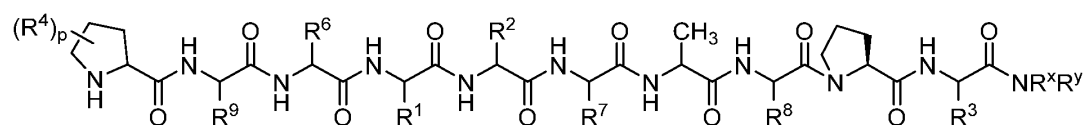
15 (X-am-7L).

In certain embodiments, the compound has the structure of formula (X-am-7D):



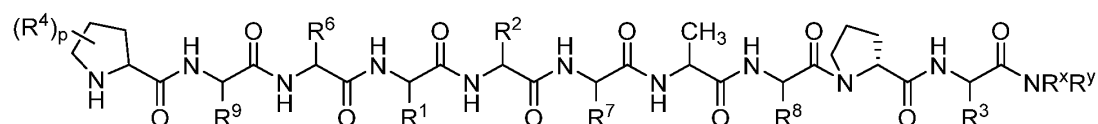
(X-am-7D).

In certain embodiments, the compound has the structure of formula (X-am-11L):



(X-am-11L).

In certain embodiments, the compound has the structure of formula (X-am-11D):



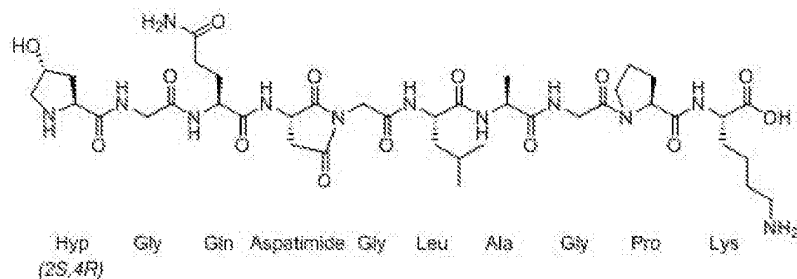
5 (X-am-11D).

In certain embodiments, R^8 is $-CH_3$ or $-H$, preferably $-H$.

In certain embodiments, R^9 is $-CH_3$ or $-H$, preferably $-H$.

In certain embodiments, R^x and R^y are each independently optionally substituted alkyl. In alternative embodiments, R^x and R^y are each independently optionally substituted
 10 alkoxyalkyl. In further alternative embodiments, R^x and R^y taken together with the intervening nitrogen atom form a ring.

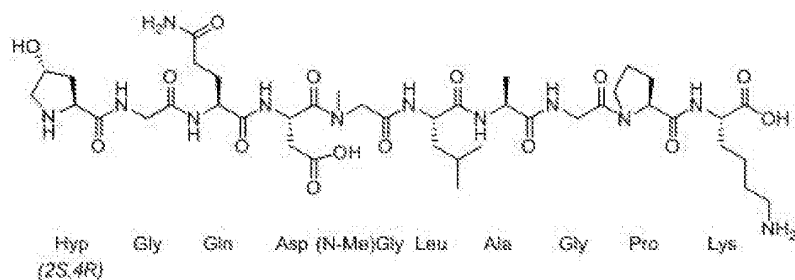
The invention also provides a salt of a compound represented by Formula 8:



[Formula 8];

and

15 a salt of a compound represented by Formula 10:



[Formula 10].

In certain embodiments, the compound may be a prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, a carboxylic acid present in the parent compound is presented as an ester, or an amino group is presented as an amide.

In certain such embodiments, the prodrug is metabolized to the active parent compound in vivo (e.g., the ester is hydrolyzed to the corresponding hydroxyl or carboxylic acid).

In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee.

The compounds of the invention have more than one stereocenter. Accordingly, the compounds of the invention may be enriched in one or more diastereomers. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de. In certain embodiments, the compounds of the invention have substantially one isomeric configuration at one or more stereogenic centers, and have multiple isomeric configurations at the remaining stereogenic centers.

In certain embodiments, the enantiomeric excess of a given stereocenter in the compound is at least 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, 92% ee, 94% ee, 95% ee, 96% ee, 98% ee or greater ee.

As used herein, single bonds drawn without stereochemistry do not indicate the stereochemistry of the compound. The compound of formula (I) provides an example of a compound for which no stereochemistry is indicated.

As used herein, hashed or bolded wedge bonds indicate absolute stereochemical configuration.

In certain embodiments, a therapeutic preparation of the compound of the invention may be enriched to provide predominantly one enantiomer of a compound. An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, *e.g.*, in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In certain embodiments, a therapeutic preparation may be enriched to provide predominantly one diastereomer of the compound of the invention. A diastereomerically

enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

Pharmaceutical Compositions

5 In certain embodiments, the invention provides a pharmaceutical composition comprising a salt or compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

 In certain embodiments, the pharmaceutical composition is formulated for topical administration to the eye, e.g., as eye drops.

10

 In certain embodiments at least 50%, 60%, 70%, 80%, or 90% of the compound is present as a salt. Preferably, at least 95% of the compound is present as a salt. Even more preferably, at least 99% of the compound is present as a salt.

 In certain embodiments, the present invention provides a pharmaceutical preparation
15 suitable for use in a human patient, comprising any salt or compound of the invention, and one or more pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein. In certain embodiments, the pharmaceutical preparations have a low enough pyrogen activity to be suitable for use in a human patient.

20 One embodiment of the present invention provides a pharmaceutical kit comprising a salt or compound of the invention, or a pharmaceutically acceptable salt thereof, and optionally directions on how to administer the compound.

 The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a
25 human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other
30 solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In certain preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial

barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a selfemulsifying drug delivery system or a selfmicroemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and

sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ (e.g., wheat germ), olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

5 Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

10 Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

15 Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

 Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

20 Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

 Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

25 The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

30 Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants,

such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by
5 dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also
10 contemplated as being within the scope of this invention. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are
15 compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial,
20 intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions,
25 dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the
30 pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by

the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinacious biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

- 5 The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular
10 compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

- A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical
15 composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective amount” is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of
20 the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those
25 skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

- In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon
30 the factors described above.

 If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of

the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry
5 and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent. As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously
10 administered therapeutic compound is still effective in the body (*e.g.*, the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within
15 one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds.

In certain embodiments, conjoint administration of compounds of the invention with one or more additional therapeutic agent(s) provides improved efficacy relative to each
20 individual administration of the compound of the invention (*e.g.*, a compound of formula I, V, VI, or VII) or the one or more additional therapeutic agent(s). In certain such embodiments, the conjoint administration provides an additive effect, wherein an additive effect refers to the sum of each of the effects of individual administration of the compound of the invention and the one or more additional therapeutic agent(s).

25 This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. The term “pharmaceutically acceptable salt” as used herein includes salts derived from inorganic or organic acids including, for example, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, phosphoric, formic, acetic, lactic, maleic, fumaric, succinic, tartaric, glycolic, salicylic,
30 citric, methanesulfonic, benzenesulfonic, benzoic, malonic, trifluoroacetic, trichloroacetic, naphthalene-2-sulfonic, oxalic, mandelic and other acids. Pharmaceutically acceptable salt forms can include forms wherein the ratio of molecules comprising the salt is not 1:1. For example, the salt may comprise more than one inorganic or organic acid molecule per

molecule of base, such as two hydrochloric acid molecules per molecule of compound of Formula I, V, VI, or VII. As another example, the salt may comprise less than one inorganic or organic acid molecule per molecule of base, such as two molecules of compound of Formula I, V, VI, or VII per molecule of tartaric acid.

5 In further embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-
10 methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

 The pharmaceutically acceptable acid addition salts can also exist as various
15 solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

 Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and
20 magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

 Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium
25 metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

30

Methods of Treatment

The present invention also provides methods of treating eye disease, comprising administering to a subject in need thereof salt of the invention, a compound of the invention, or a pharmaceutical composition comprising a salt or compound of the invention.

5 Specifically, the eye disease may be selected from retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, keratoconjunctival epithelium disorder, proliferative vitreoretinopathy, pigmentary retinopathy, diabetic retinopathy, retinopathy of prematurity, retinopathy of immaturity, proliferative retinopathy, ischemic retinopathy, epidemic keratoconjunctivitis, atopic keratitis, superior
10 limbic keratitis, pterygium keratitis sicca, phlyctenular keratoconjunctivitis, scleritis, corneal transplant rejection, choroidal neovascularization, neovascular glaucoma, ischemic optic neuropathy, retrolental fibroplasias, diabetic macula, neovascular iris disease, erythrosis, myopia, Von Hippel-Lindau syndrome, ocular histoplasmosis, central retinal vein occlusion, Sjogren syndrome and Stevens-Johnson syndrome. Preferably, the eye
15 disease may be selected from retinopathy, keratitis, macular degeneration, dry eye syndrome and keratoconjunctival epithelium disorder.

In certain preferred embodiments, the eye disease is selected from retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, heratoconjunctivitis sicca and keratoconjunctival epithelium disorder.

20 The pharmaceutical composition for treating an eye disease, which comprises a salt or compound of the invention as an active pharmaceutical ingredient, may further comprise at least one additive selected from the group consisting of a carrier, an excipient, a disintegrant, a sweetener, a coating agent, a swelling agent, a lubricant, a slip agent, a flavor, an antioxidant, a buffer, a bacteriostat, a diluent, a dispersant, a surfactant, and a
25 binder. Specifically, a formulation for parenteral administration may be a sterilized aqueous solution, a non-aqueous solution, a suspension, an emulsion, a lyophilized preparation, a suppository, or the like.

The dose of the salt or compound of the invention that is administered to the subject may be adjusted depending on such various factors as the kind of the disease, the severity
30 of the disease, the kinds and amounts of the active pharmaceutical ingredient and other ingredients contained in the pharmaceutical composition, the type of the formulation, the age, body weight, general health condition, sex, and diet of the patient, the time and the route of administration, the duration of treatment, and the drugs concurrently used.

However, for the desired effect, the effective amount of the salt or compound contained in the pharmaceutical composition may be 0.0001 µg/day to 100 µg/day. In such event, the administration may be carried out once a day, or divided into several doses. Specifically, the concentration of the salt or compound contained in the pharmaceutical composition may be 1000 µM to 0.001 µM. Also, the concentration of the salt or compound contained in the pharmaceutical composition may be 100 µM to 0.005 µM or 50 µM to 0.02 µM.

In addition, if necessary, the concentration of the salt or compound contained in the pharmaceutical composition may be 30 µM to 1 µM. Further, the concentration of the compound or the peptide contained in the pharmaceutical composition may be 0.01 µM to 1 µM.

In addition, the subject may be a mammal, particularly a human. The administration route may be appropriately selected by a person skilled in the art in consideration of the administration method, the volume and viscosity of the body fluid, and the like.

Specifically, the administration may be carried out through any one route selected from the group consisting of an application, intravenous, intraarterial, intraperitoneal, intramuscular, intrasternal, percutaneous, intranasal, inhalation, topical, rectal, oral, intraocular, and intradermal. Preferably, the administration comprises topical administration to the eye of the subject.

In particular, it may preferably be applied to the eye for use as an eye drop.

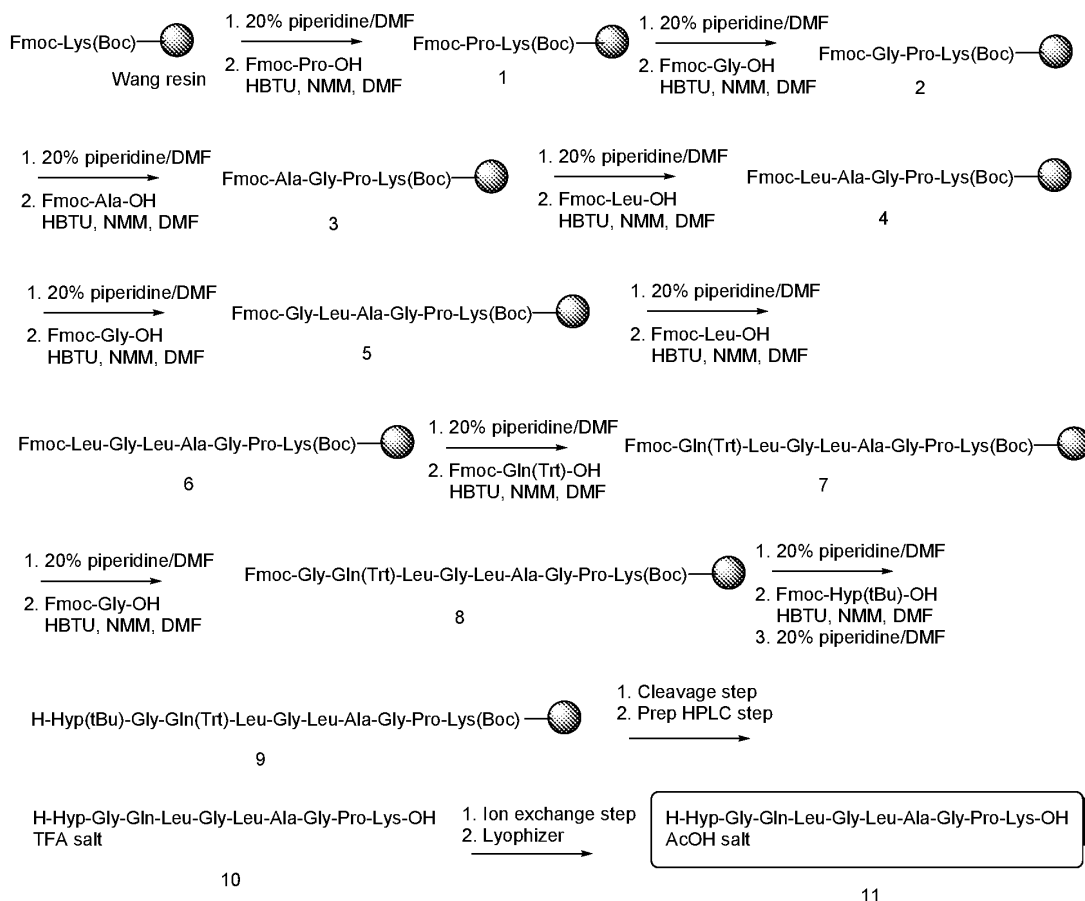
The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Examples

Example 1: Preparation of YDE derivatives

A protein analysis of the extracellular matrix derived from animal chondrocytes was performed in Baek's group of Center of Biomedical Mass Spectrometry (Diatech Korea Co., Ltd., Seoul, Korea). Proline-GQDGLAGPK (P-GQDGLAGPK), which is a part of the amino acid sequence of the collagen type II α1 protein, was obtained through the above protein analysis.

An exemplary protein synthesis for YDE-011 follows. The other compounds of the invention (e.g., YDE-001 – YDE-086) are made through an analogous procedure by, e.g., substituting in a different amino acid building block reagent in a desired step.



5 Exemplary procedure for YDE-011

Solid Phase Synthesis

Fmoc-Pro-Lys(Boc)- Wang Resin (1)

To a solid phase synthesis reactor equipped with filtration membrane was added Fmoc-Lys(Boc)-Wang Resin (1.75 g, 1 mmole) in DCM (30 mL) then swelled for 30 min then the resin was drained. To the resin, a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Pro-OH (3.37 g, 10 mmole) in DMF (25mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were added respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Gly-Pro-Lys(Boc)- Wang Resin (2)

To Fmoc-Pro-Lys(Boc)-Wang resin (1), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Gly-OH (3.0g, 10 mmole) in DMF (25 mL) and a solution of HBTU(3.8g, 10 mmole) and N-Methylmorpholine(2.0g, 20 mmole) in DMF (25mL) were added respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Ala-Gly-Pro-Lys(Boc)-Wang Resin (3)

To Fmoc-Gly-Pro-Lys(Boc)-Wang resin (2), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Ala-OH (3.1g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were added respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (4)

To Fmoc-Ala-Gly-Pro-Lys(Boc)-Wang resin (3), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Leu-OH (3.5g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (5)

To Fmoc-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin (4), 10 mL piperidine in DMF(40 mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Gly-OH (3.0g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (6)

To Fmoc-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin (5), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Leu-OH (3.5g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (7)

To Fmoc-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin (6), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Gln(Trt)-OH (6.1g, 10 mmole) in DMF (25 mL) and a solution of HBTU(3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL, 10eq) were respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

Fmoc-Gly-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (8)

To Fmoc-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin (7), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Gly-OH (3.0g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were added respectively. The reaction mixture was stirred for 1 h and the resin was drained. The resin was used to next step without further purification.

H-Hyp(tBu)-Gly-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (9)

To Fmoc-Gly-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin (8), a solution of piperidine (10 mL) in DMF (40mL) was added and stirred for 5 minutes then the resin was drained. The resin was washed for 6 times with DMF (50 mL). To the resin, a solution of Fmoc-Hyp(tBu)-OH(4.2g, 10 mmole) in DMF (25 mL) and a solution of HBTU (3.8g, 10 mmole) and N-Methylmorpholine (2.0g, 20 mmole) in DMF (25mL) were added and the reaction mixture was stirred for 1 h and the resin was drained. To Fmoc-Hyp(tBu)-Gly-

Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang resin, a solution of piperidine (10 mL) in DMF (40mL) was added. The reaction mixture was stirred for 5 minutes then the resin was drained. The resin was washed 6 times with DMF (50 mL).

Removal from Resin

5 H-Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys-OH TFA salt (10)

To the 1 mmole H-Hyp(tBu)-Gly-Gln(Trt)-Leu-Gly-Leu-Ala-Gly-Pro-Lys(Boc)-Wang Resin (9), 30 mL of cocktail solution (87.5% TFA/2.5% 1,2-ethanedithiol/2.5% H₂O/5.0% thioanisole) were added and the reaction mixture was stirred for 2 h and monitored the reaction mixture by HPLC. To filtered solution was added cold diethyl ether (500 mL) to
10 precipitate crude peptide. The precipitated peptide was filtered through a filtration apparatus and washed with 500 mL of diethyl ether. The crude peptide was dried under vacuum to give 105% (1g).

Purification step

H-Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys-OH TFA salt(10)

15 The crude compound was purified by Prep HPLC system

Salt exchange step

H-Hyp-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys-OH AcOH salt (11)

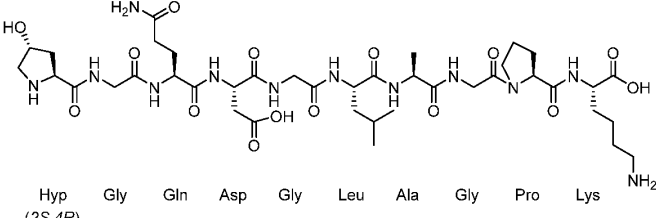
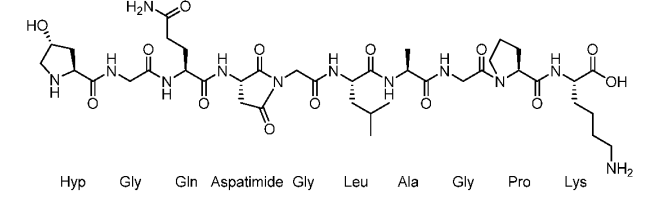
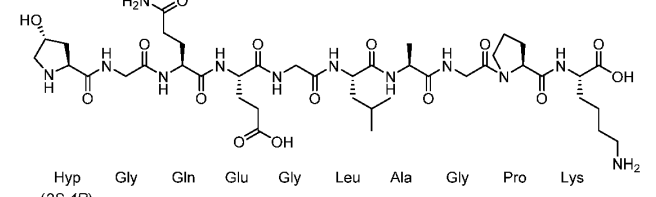
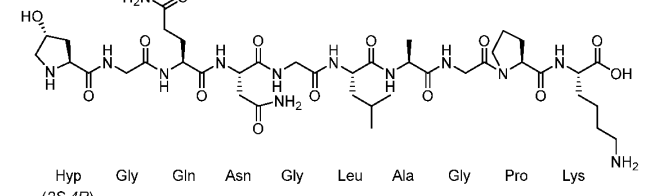
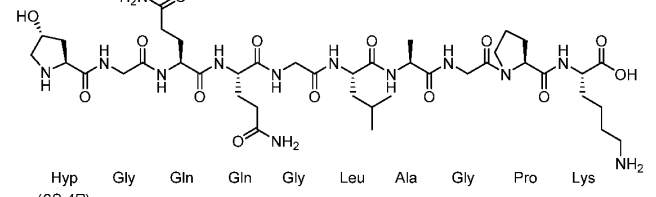
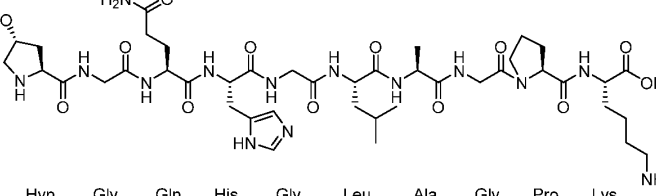
The Purified compound was exchanged from TFA salt to AcOH salt by Ion Exchange resin. The Ion exchanged peptide was dried by lyophilizer.

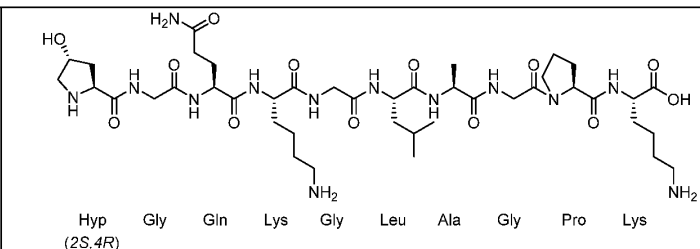
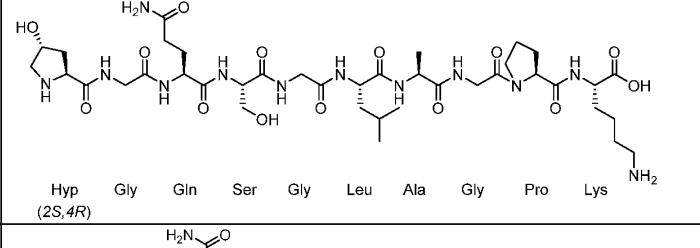
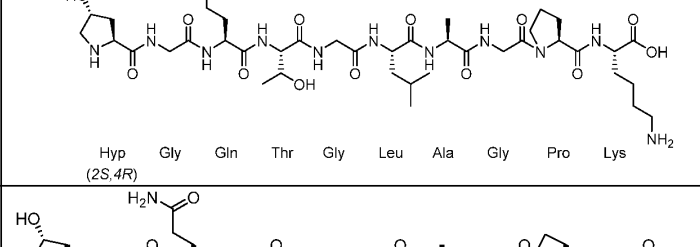
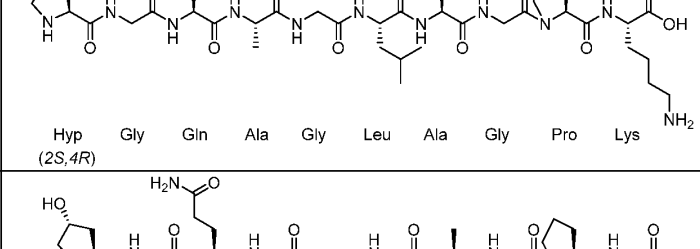
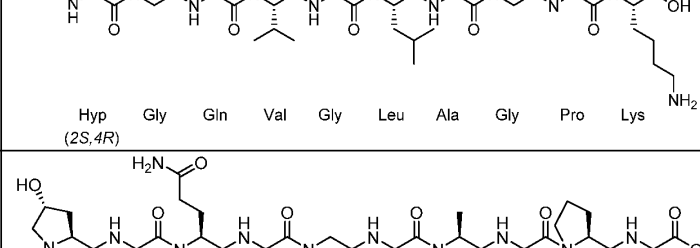
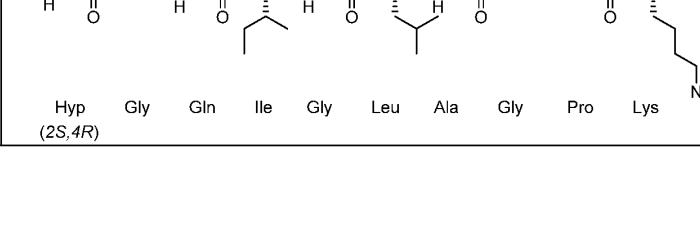
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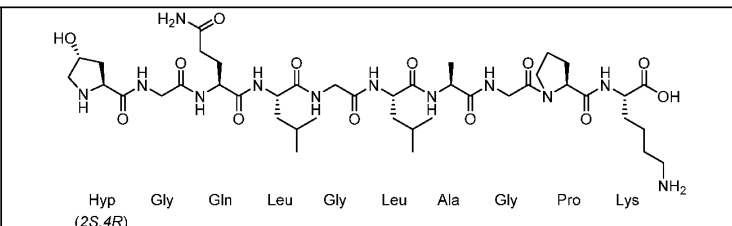
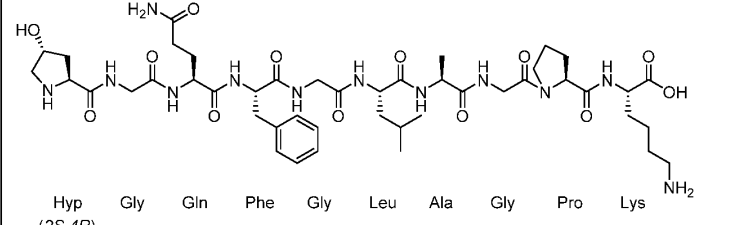
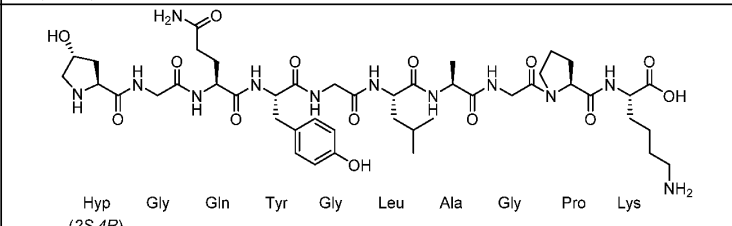
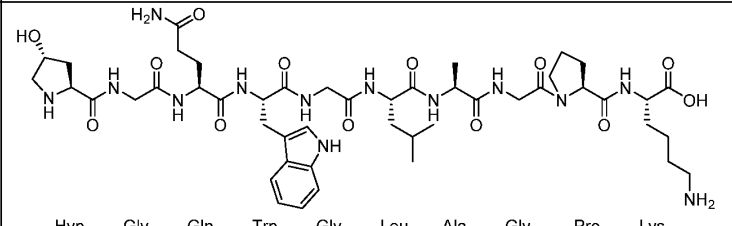
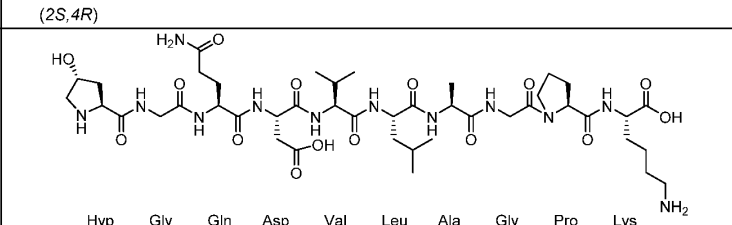
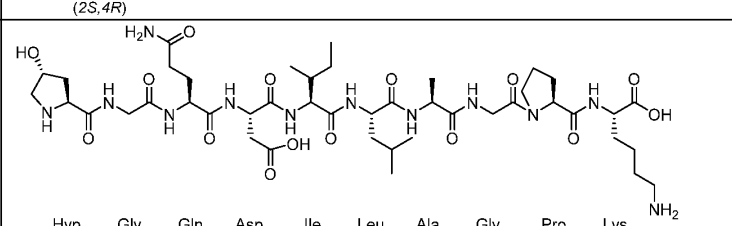
YDE-001 to YDE-092 peptides were synthesized by ANYGEN (Gwangju, Korea) in a manner analogous to the exemplary procedure shown above, by substituting one or more different amino acid residues into the peptide Proline-GQDGLAGPK (Fig. 1 and Table 1).

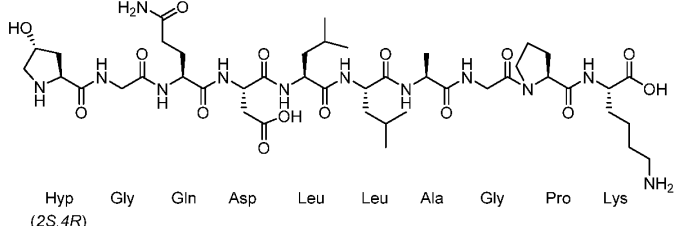
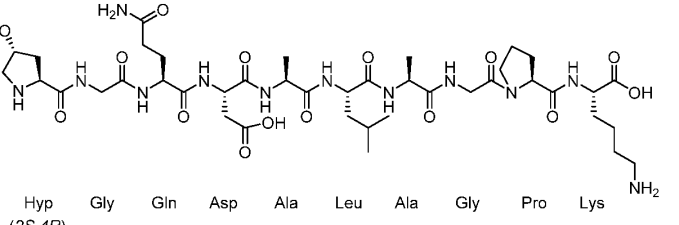
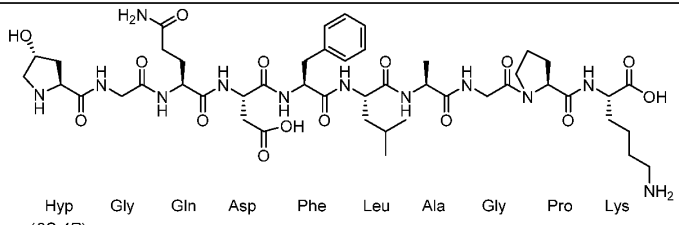
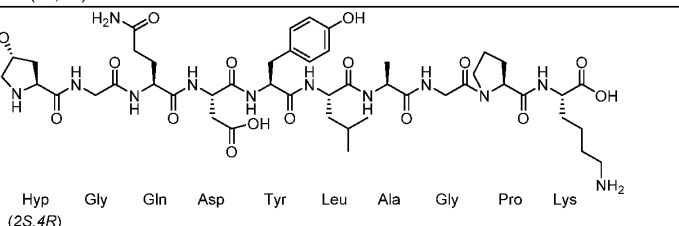
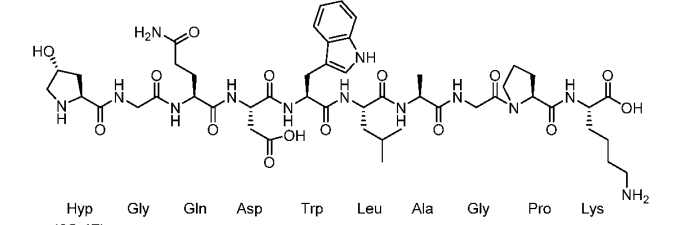
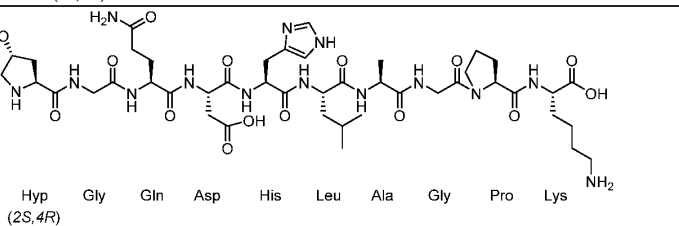
The process for synthesizing the YDE-001 to YDE-075 peptides and the purification
25 procedure thereof conducted by ANYGEN are depicted in Figs. 2 and 3.

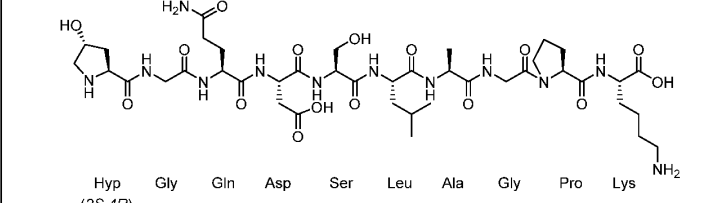
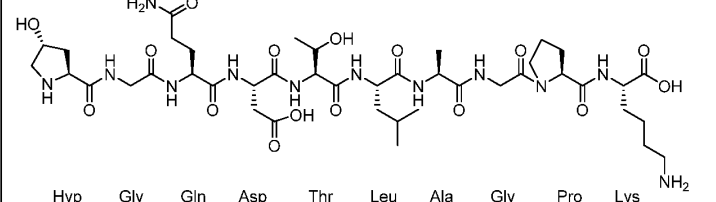
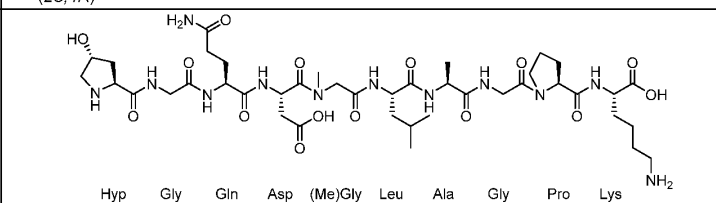
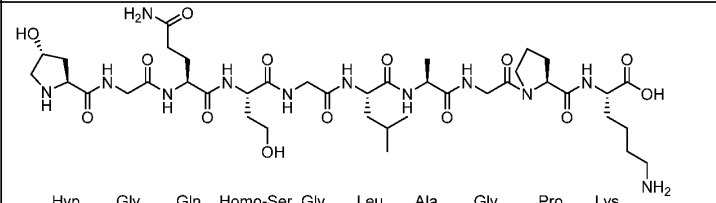
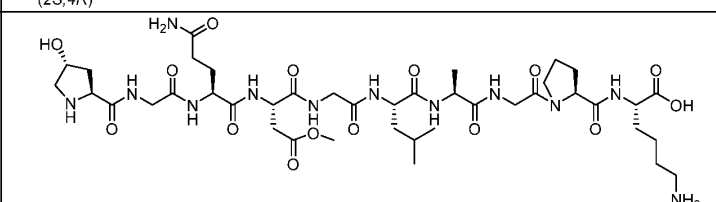
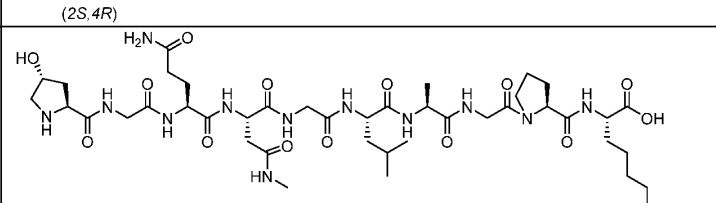
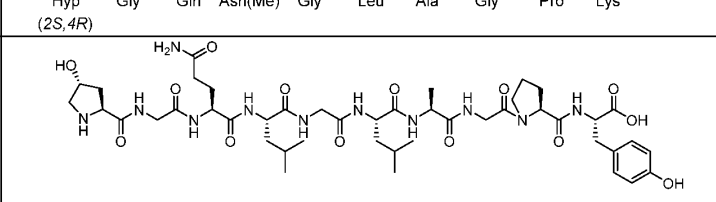
[Table 1]

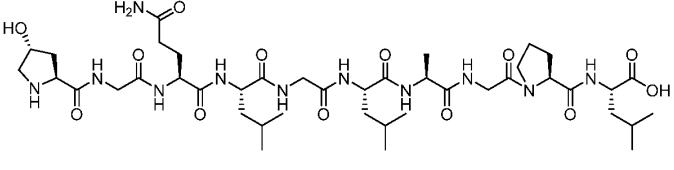
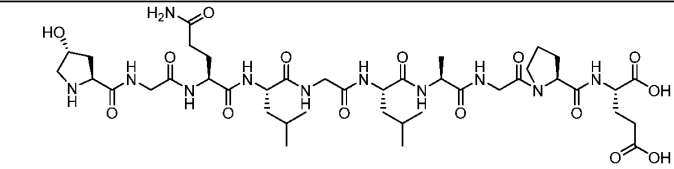
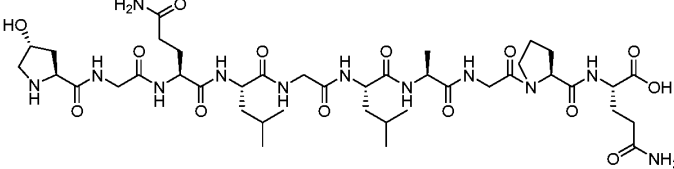
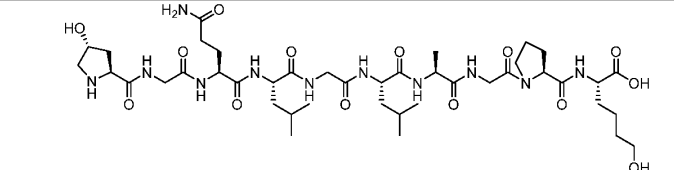
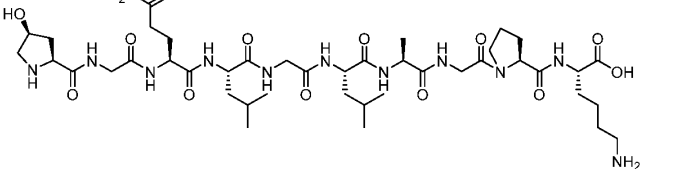
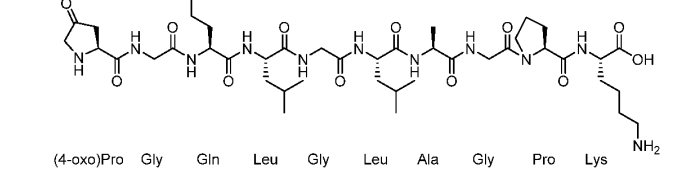
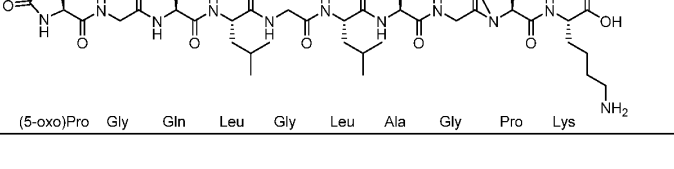
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YY-102	 Hyp Gly Gln Aspartimide Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 202
YDE-001	 Hyp Gly Gln Glu Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 1
YDE-002	 Hyp Gly Gln Asn Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 2
YDE-003	 Hyp Gly Gln Gln Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 3
YDE-004	 Hyp Gly Gln His Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 4

YDE-005	 Hyp Gly Gln Lys Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 5
YDE-006	 Hyp Gly Gln Ser Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 6
YDE-007	 Hyp Gly Gln Thr Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 7
YDE-008	 Hyp Gly Gln Ala Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 8
YDE-009	 Hyp Gly Gln Val Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 9
YDE-010	 Hyp Gly Gln Ile Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 10

YDE-011	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 11
YDE-012	 Hyp Gly Gln Phe Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 12
YDE-013	 Hyp Gly Gln Tyr Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 13
YDE-014	 Hyp Gly Gln Trp Gly Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 14
YDE-015	 Hyp Gly Gln Asp Val Leu Ala Gly Pro Lys (2<i>S</i>,4<i>R</i>)	SEQ ID NO: 15
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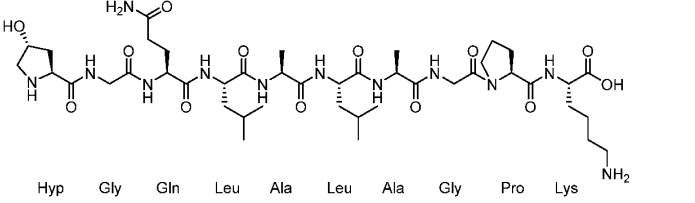
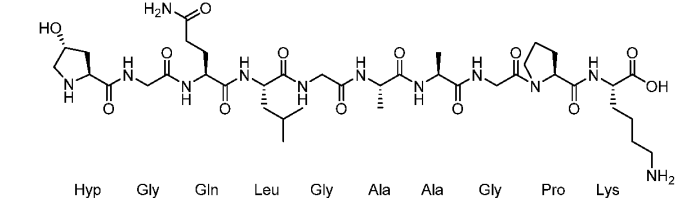
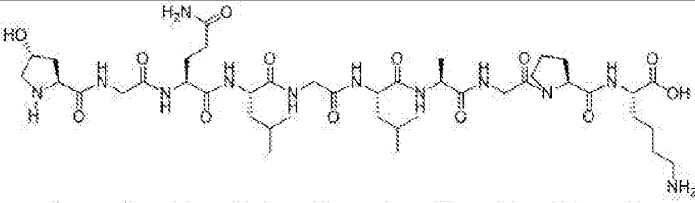
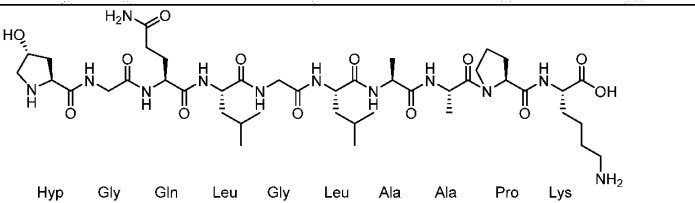
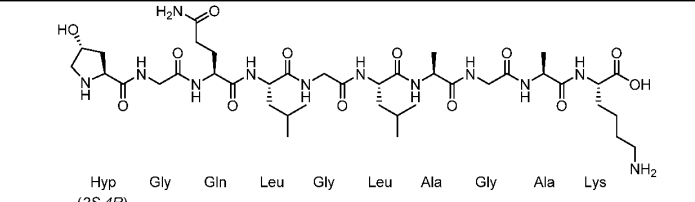
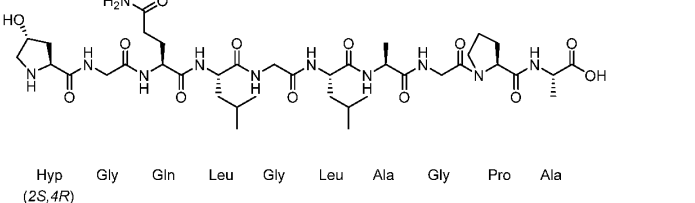
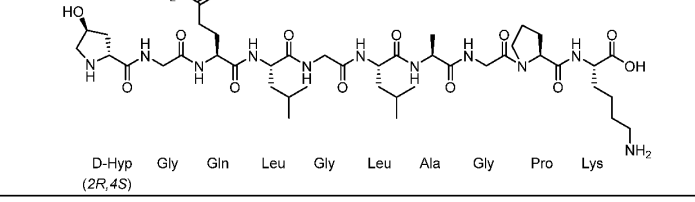
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YDE-019	 Hyp Gly Gln Asp Phe Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 19
YDE-020	 Hyp Gly Gln Asp Tyr Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 20
YDE-021	 Hyp Gly Gln Asp Trp Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 21
YDE-022	 Hyp Gly Gln Asp His Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 22

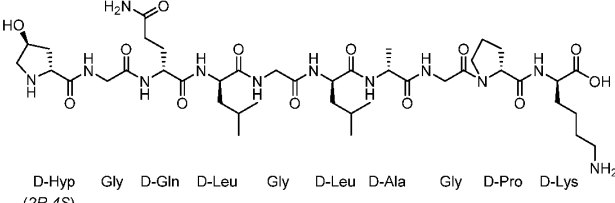
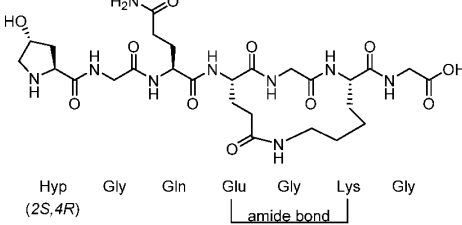
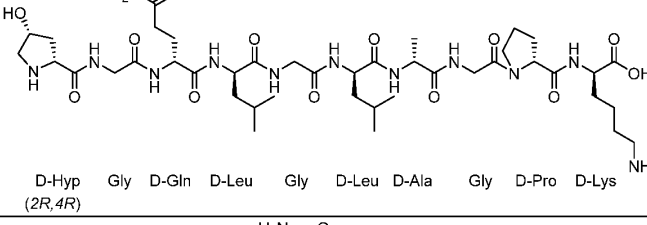
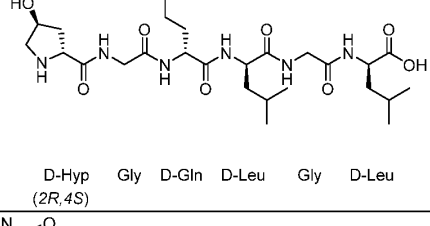
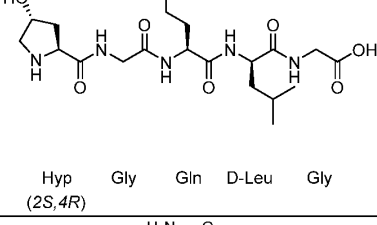
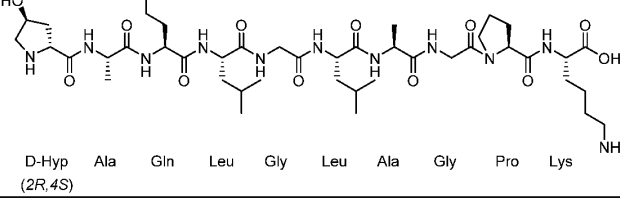
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YDE-025	 Hyp Gly Gln Asp (Me)Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 25
YDE-026	 Hyp Gly Gln Homo-Ser Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 26
YDE-027	 Hyp Gly Gln Asp(Me) Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 27
YDE-028	 Hyp Gly Gln Asn(Me) Gly Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 28
YDE-029	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Tyr (2S,4R)	SEQ ID NO: 29

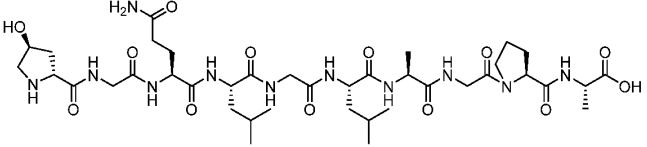
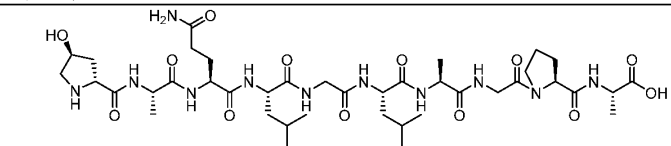
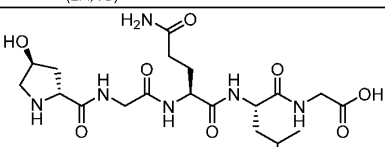
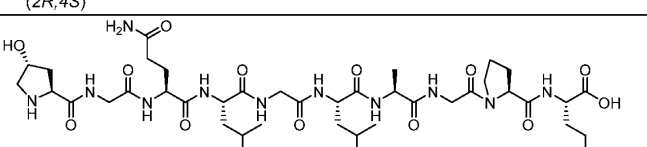
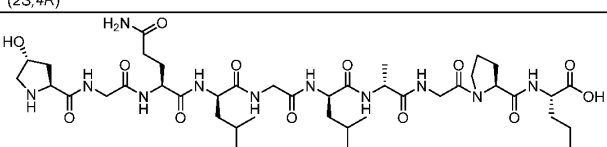
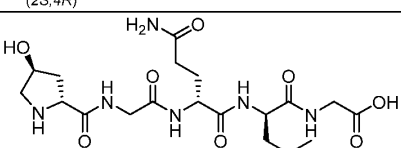
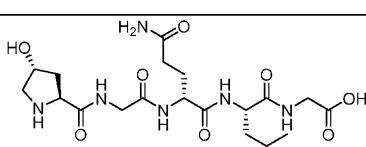
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YDE-032	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Gln (2S,4R)	SEQ ID NO: 32
YDE-033	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Nle(6-OH) (2S,4R)	SEQ ID NO: 33
YDE-034	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2S,4S)	SEQ ID NO: 34
YDE-035	 (4-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 35
YDE-036	 (5-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 36

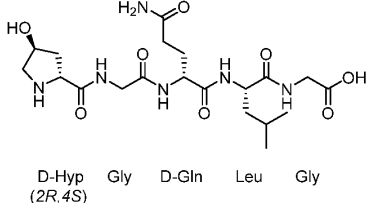
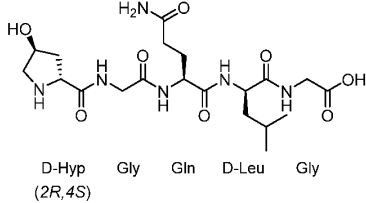
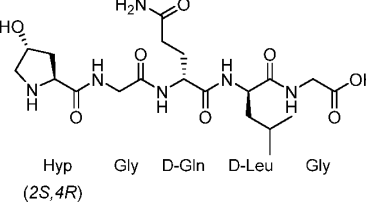
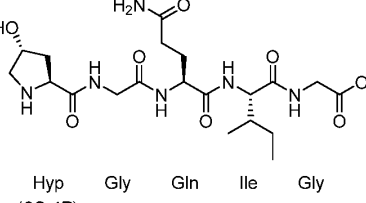
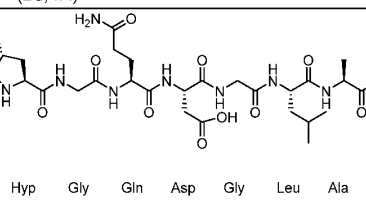
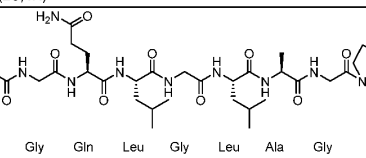
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YDE-038	(4-hydroxyMe)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (4R)	SEQ ID NO: 38
YDE-039	(4-Fluoro)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys (4R)	SEQ ID NO: 39
YDE-040	(4-Dimethyl)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 40
YDE-041	Hyp Gly Gln Leu Gly Leu Ala (2S,4R)	SEQ ID NO: 41
YDE-042	Hyp Gly Gln Leu Gly Leu (2S,4R)	SEQ ID NO: 42

YDE-043	Hyp Gly Gln Leu Gly (2S,4R)	SEQ ID NO: 43
YDE-044	(4-Me)Pro Gly Gln Leu Gly Leu Ala (4R)	SEQ ID NO: 44
YDE-045	(5-Me)Pro Gly Gln Leu Gly Leu Ala (5R)	SEQ ID NO: 45
YDE-047	Ala Gly Gln Leu Gly Leu Ala	SEQ ID NO: 47
YDE-048	Hyp Ala Gln Leu Gly Leu Ala (2S,4R)	SEQ ID NO: 48
YDE-049	Hyp Gly Ala Leu Gly Leu Ala (2S,4R)	SEQ ID NO: 49
YDE-050	Hyp Gly Gln Ala Gly Leu Ala (2S,4R)	SEQ ID NO: 8

YDE-051	 Hyp Gly Gln Leu Ala Leu Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 51
YDE-052	 Hyp Gly Gln Leu Gly Ala Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 52
YDE-053	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys	SEQ ID NO: 11
YDE-054	 Hyp Gly Gln Leu Gly Leu Ala Ala Pro Lys (2S,4R)	SEQ ID NO: 54
YDE-055	 Hyp Gly Gln Leu Gly Leu Ala Gly Ala Lys (2S,4R)	SEQ ID NO: 55
YDE-056	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala (2S,4R)	SEQ ID NO: 56
YDE-057	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys (2R,4S)	SEQ ID NO: 57

YDE-058	 D-Hyp Gly D-Gln D-Leu Gly D-Leu D-Ala Gly D-Pro D-Lys (2R,4S)	SEQ ID NO: 58
YDE-059	 Hyp Gly Gln Glu Gly Lys Gly (2S,4R) amide bond	SEQ ID NO: 59
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YDE-064	 D-Hyp Gly D-Gln D-Leu Gly D-Leu (2R,4S)	SEQ ID NO: 64
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YDE-073	 D-Hyp Gly Gln Leu Gly Leu Ala Gly Pro Ala (2R,4S)	SEQ ID NO: 73
YDE-074	 D-Hyp Ala Gln Leu Gly Leu Ala Gly Pro Ala (2R,4S)	SEQ ID NO: 74
YDE-075	 D-Hyp Gly Gln Leu Gly (2R,4S)	SEQ ID NO: 75
YDE-078	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys(Ac) (2S,4R)	SEQ ID NO: 78
YDE-080	 Hyp Gly Gln D-Leu Gly D-Leu D-Ala Gly Pro Lys (2S,4R)	SEQ ID NO: 80
YDE-081	 D-Hyp Gly D-Gln D-Leu Gly (2R,4S)	SEQ ID NO: 81
YDE-083	 Hyp Gly D-Gln Leu Gly (2S,4R)	SEQ ID NO: 83

YDE-084	 D-Hyp (2R,4S) Gly D-Gln Leu Gly	SEQ ID NO: 84
YDE-085	 D-Hyp (2R,4S) Gly Gln D-Leu Gly	SEQ ID NO: 85
YDE-086	 Hyp (2S,4R) Gly D-Gln D-Leu Gly	SEQ ID NO: 86
YDE-092	 Hyp (2S,4R) Gly Gln Ile Gly	SEQ ID NO: 92
YDE-094	 Hyp (2S,4R) Gly Gln Asp Gly Leu Ala	SEQ ID NO: 94
YDE-100	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro	SEQ ID NO: 100

Analysis of YDE derivatives

The YDE derivatives prepared in Example 1 were analyzed by HPLC. As a result, it was confirmed that the purities of YDE-001, YDE-002, YDE-003, YDE-004, YDE-005, YDE-006, YDE-007, YDE-008, YDE-009, YDE-010, YDE-011, YDE-012, YDE-013, YDE-014, YDE-015, YDE-016, YDE-017, YDE-018, YDE-019, YDE-020, YDE-021, YDE-022, YDE-023, YDE-024, YDE-025, YDE-026, YDE-027, YDE-028, YDE-029, YDE-030, YDE-031, YDE-032, YDE-033, YDE-034, YDE-035, YDE-036, YDE-037,

YDE-038, YDE-039, YDE-040, YDE-041, YDE-042, YDE-043, YDE-044, YDE-045, YDE-047, YDE-048, YDE-049, YDE-050, YDE-051, YDE-052, YDE-053, YDE-054, YDE-055, YDE-056, YDE-057, YDE-058, YDE-059, YDE-060, YDE-064, YDE-066, YDE-072, YDE-073, YDE-074, YDE-075, YDE-078, YDE-080, YDE-081, YDE-083, YDE-084, YDE-085, YDE-086, YDE-092, YDE-094, and YDE-100 synthesized were 98.3%, 98.9%, 98.7%, 98.5%, 99.1%, 99.4%, 98.0%, 99.6%, 99.6%, 99.2%, 98.1%, 98.3%, 96.1%, 98.9%, 95.1%, 98.6%, 96.9%, 99.5%, 98.0%, 98.1%, 98.8%, 98.2%, 97.2%, 98.6%, 98.8%, 98.7%, 99.2%, 98.7%, 98.1%, 97.5%, 96.5%, 97.4%, 98.7%, 97.8%, 95.5%, 97.5%, 97.2%, 96.9%, 99.3%, 98.0%, 99.4%, 96.4%, 95.1%, 98.6%, 97.4%, 98.8%, 97.4%, 95.8%, 98.9%, 96.9%, 98.8%, 97.7%, 95.0%, 97.9%, 96.3%, 97.8%, 99.2%, 98.6%, 95.9%, 99.2%, 99.0%, 95.1%, 95.0%, 97.4%, and 98.7%, respectively.

In addition, the YDE derivatives prepared in Example 1 were analyzed by Ion-Mass. As a result, it was confirmed that the molecular weights of YDE-001, YDE-002, YDE-003, YDE-004, YDE-005, YDE-006, YDE-007, YDE-008, YDE-009, YDE-010, YDE-011, YDE-012, YDE-013, YDE-014, YDE-015, YDE-016, YDE-017, YDE-018, YDE-019, YDE-020, YDE-021, YDE-022, YDE-023, YDE-024, YDE-025, YDE-026, YDE-027, YDE-028, YDE-029, YDE-030, YDE-031, YDE-032, YDE-033, YDE-034, YDE-035, YDE-036, YDE-037, YDE-038, YDE-039, YDE-040, YDE-041, YDE-042, YDE-043, YDE-044, YDE-045, YDE-047, YDE-048, YDE-049, YDE-050, YDE-051, YDE-052, YDE-053, YDE-054, YDE-055, YDE-056, YDE-057, YDE-058, YDE-059, YDE-060, YDE-064, YDE-066, YDE-072, YDE-073, YDE-074, YDE-075, YDE-078, YDE-080, YDE-081, YDE-083, YDE-084, YDE-085, YDE-086, YDE-092, YDE-094, and YDE-100 synthesized were 969.6, 954.8, 967.7, 977.1, 968.1, 926.9, 941.1, 910.7, 939.7, 953.0, 953.7, 987.8, 1003.8, 1025.9, 996.7, 1011.0, 1011.4, 968.7, 1044.4, 1061.4, 1084.5, 1035.0, 984.9, 999.1, 969.7, 942.0, 937.6, 967.3, 988.1, 960.6, 954.2, 991.1, 954.4, 990.7, 950.9, 937.6, 968.1, 955.4, 966.0, 709.3, 622.2, 486.8, 951.3, 951.3, 911.4, 967.5, 896.5, 911.0, 967.3, 911.2, 953.2, 967.2, 927.4, 896.4, 952.8, 953.4, 670.1, 953.3, 599.7, 486.5, 966.1, 895.8, 909.1, 486.4, 995.1, 953.1, 486.5, 486.5, 486.5, 486.5, 486.5, 673.2, and 823.9, respectively.

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Example 2: Preparation of YDE derivatives with modified C-terminus**Preparation of YDE peptides**

YDE peptides (YDE-093, YDE-096, and YDE-101 through YDE-107), derivatives of the amino acid sequence of the YDE-011, were obtained through the C-terminal modification of a YDE peptide such as YDE-011.

In order to prepare C-terminal modified peptide, Fmoc solid-phase peptide synthesis (SPPS) was conducted, based on a standard procedure described in WO 2018/225961 and further a C-terminal amidation reaction was carried out.

The peptides of the invention are made through an analogous procedure by, e.g., substituting in a different amino acid building block reagent in a desired step.

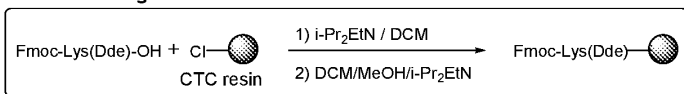
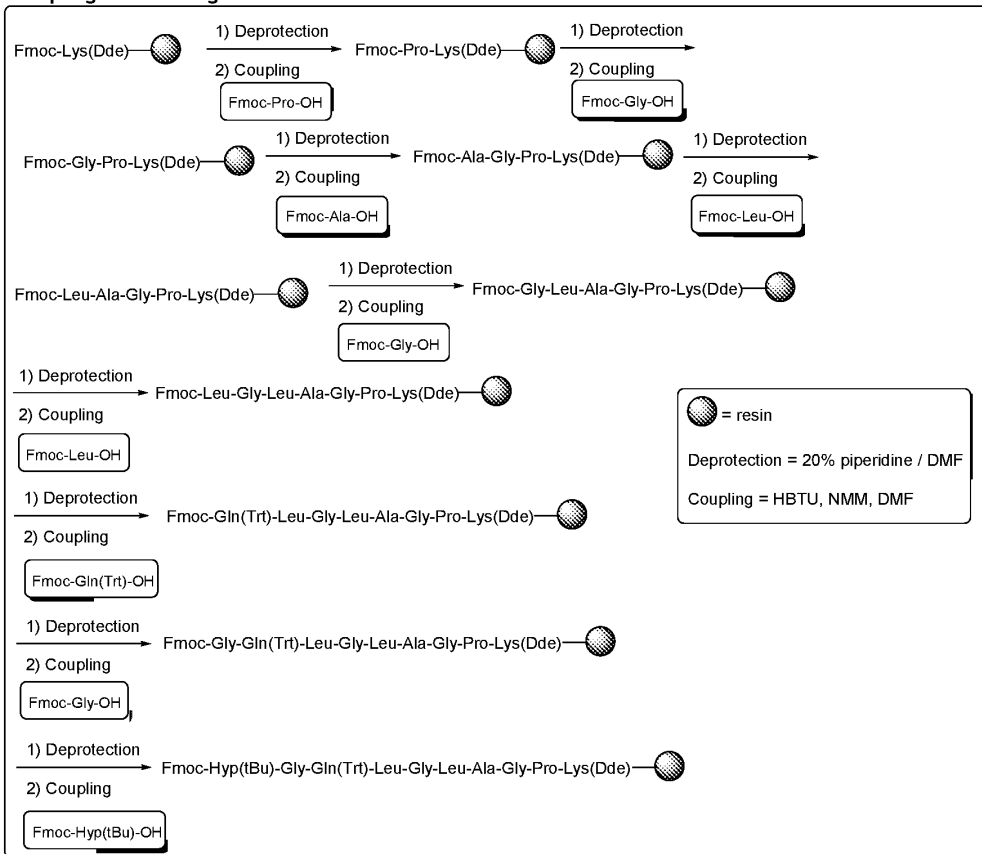
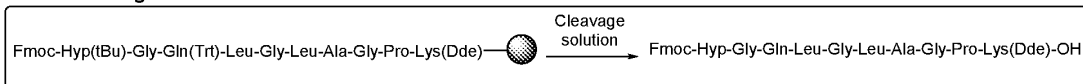
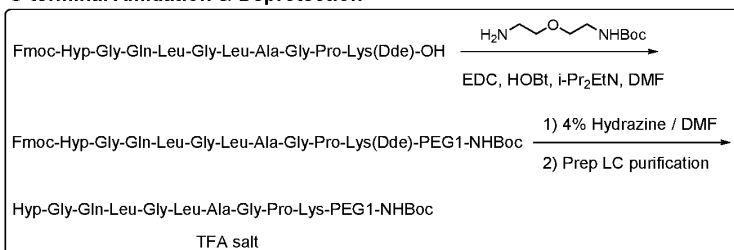
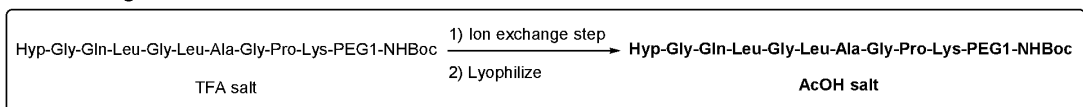
Exemplary Preparation of YDE-093

To prepare C-terminal amidated peptide YDE-093, a synthetic process was conducted as depicted in **Scheme A**, below. The Fmoc protected 10-mer peptide (Fmoc-Hyp-H-Gly-Gln-Leu-Gly-Ala-Leu-Gly-Pro-Lys(Dde)-OH) was prepared according to the procedure described in WO 2018/225961.

Based on the selected amino acid sequence, a chain reaction was conducted in this order as below:

- 1) Fmoc-Lys(Dde)-OH
- 2) Fmoc-Pro-OH
- 3) Fmoc-Gly-OH
- 4) Fmoc-Ala-OH
- 5) Fmoc-Leu-OH
- 6) Fmoc-Gly-OH
- 7) Fmoc-Leu-OH
- 8) Fmoc-Gln(Trt)-OH
- 9) Fmoc-Gly-OH
- 10) Fmoc-Hyp(tBu)-OH

Scheme A:

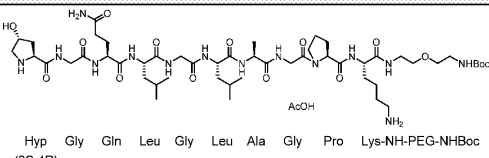
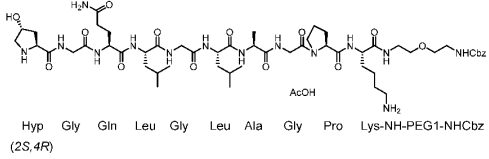
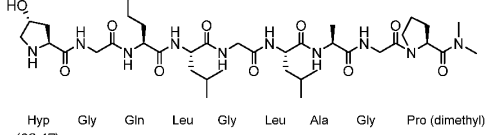
Resin Loading**Coupling the Building Blocks****Resin Cleavage****C-terminal Amidation & Deprotection****Salt Exchange**

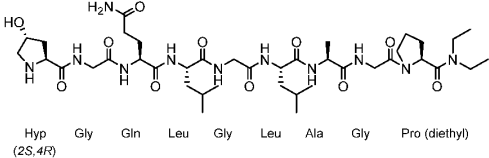
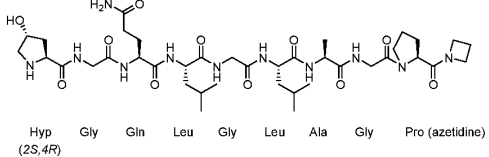
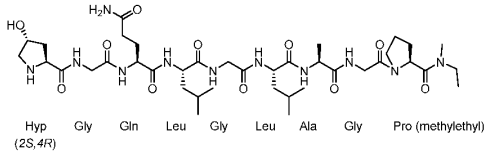
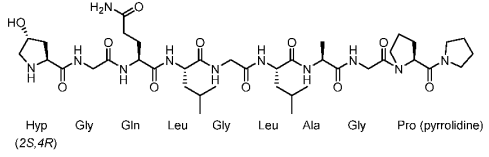
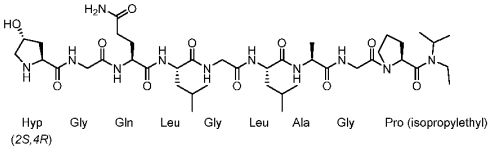
To a solution of Fmoc-Hyp-Gly-Gln-Leu-Gly-Ala-Leu-Gly-Pro-Lys(Dde)-OH (500 mg, 0.37 mmol) and tert-butyl (2-(2-aminoethoxy)ethyl)carbamate (91 mg, 0.44 mmol) in DMF (10mL) was added HOBt (76 mg, 0.56 mmol), EDCI (107 mg, 0.56 mmol) and i-Pr₂EtN (24 μ L, 0.136 mmol) at 0°C and stirred for 1 hour at same temperature. After 1 hour, the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. After the reaction was completed, the reaction mixture was poured into water (20mL) and extracted with DCM (20mL x 2). The combined organic layers were further washed with water (20mL x 2) and concentrated *in vacuo*. The residue was precipitation from diethyl ether to afford a desired Fmoc-protected peptide (400 mg, 71%) as a white solid.

Fmoc-Hyp-Gly-Gln-Leu-Gly-Ala-Leu-Gly-Pro-Lys(Dde)-PEG1-NHBoc (400 mg, 0.26 mmol) was put into a reaction vessel and 4% Hydrazine in DMF solution (10 mL) was added and stirred for 30 min, then diethyl ether (40 mL) was added to induce precipitation. Thereafter, the precipitates were collected by filtration, followed by washing twice with excess ether to afford the crude peptide YDE-093 (quantitative yield) as a white solid. The crude YDE-093 was purified by Preparative HPLC system. The purified peptide was exchanged from TFA salt to AcOH salt by ion exchange resin. The ion exchanged peptide was dried by lyophilizer.

YDE-093, YDE-096, and YDE-101 through YDE-107 are depicted in Table 1A below.

Table 1A:

No.	Chemical structure	SEQ ID NO.
YDE-093	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys-NH-PEG1-NHBoc (2S,4R)	SEQ ID NO: 93
YDE-096	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys-NH-PEG1-NHCbz (2S,4R)	SEQ ID NO: 96
YDE-101	 Hyp Gly Gln Leu Gly Leu Ala Gly Pro (dimethyl) (2S,4R)	SEQ ID NO: 101

YDE-102	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro (diethyl)	SEQ ID NO: 102
YDE-103	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro (azetidine)	SEQ ID NO: 103
YDE-105	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro (methylethyl)	SEQ ID NO: 105
YDE-106	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro (pyrrolidine)	SEQ ID NO: 106
YDE-107	 Hyp (2S,4R) Gly Gln Leu Gly Leu Ala Gly Pro (isopropylethyl)	SEQ ID NO: 107

Analysis of YDE peptides

The YDE peptides prepared in Example 2 were analyzed by HPLC. As a result, it was confirmed that the purities of YDE-093, YDE-096, YDE-101, YDE-102, YDE-103, YDE-105, YDE-106 and YDE-107 synthesized were 99.1%, 95.4%, 96.7%, 97.2%, 97.9%, 97.4%, 97.2% and 98.2%, respectively.

In addition, the YDE derivatives prepared in Example 2 were analyzed by Ion-Mass. As a result, it was confirmed that the molecular weights of YDE-093, YDE-096, YDE-101, YDE-102, YDE-103, YDE-105, YDE-106 and YDE-107 synthesized were 1139.0, 1173.6, 851.9, 880.1, 864.5, 866.1, 878.4 and 894.3, respectively.

Example 3: Evaluation of the eye protection effect on dry eye syndrome by the YDE derivatives

Preparation of rats with dry eye syndrome

In order to evaluate the eye protection effect on dry eye syndrome by YDE-001 to YDE-028 prepared in Example 1, a total of 320 Sprague-Dawley-type male rats (OrientBio,

Seungnam, Korea) were adapted for 7 days. Thereafter, dry eye syndrome was induced in 264 test rats through extraorbital lacrimal gland excision (hereinafter, ELGE). 8 test rats without the eye abnormality were subjected to a sham operation as a control group.

The rat was systemically anesthetized by inhaling a mixed gas of 2% to 3% of isoflurane (Hana Pharm. Co., Hwasung, Korea), 70% of N₂O, and 28.6% of O₂ using a rodent anesthesia machine (Surgivet, Waukesha, Wis., USA) and a ventilator (Model 687, Harvard Apparatus, Cambridge, UK). Thereafter, the extraorbital lacrimal gland located in the subdermal area above the masseter muscle and under the optic nerve was excised through a transverse incision in a size of 10 mm on the anterior part of the left ear tragus. The skin was sutured by a general method. The ELGE operation time did not exceed 5 minutes for each rat. After 6 days from the ELGE operation, it was checked through the Schirmer test by measuring the amount of tear secretion whether dry eye syndrome had been induced. Meanwhile, each rat of the control group with the sham operation was checked for the presence and location of the extraorbital lacrimal gland through a skin incision, and the skin was then sutured without the excision thereof (Fig. 4).

The average weight of the ELGE test group measured before the ELGE operation was 241.59 ± 13.56 g, and the average weight measured after 6 days from the ELGE operation was 297.38 ± 34.02 g. The average weight of the control group measured before the sham operation was 240.13 ± 25.63 g, and the average weight measured after 6 days from the sham operation was 297.38 ± 34.02 g (Fig. 5).

The average amount of tear secretion of the control group was 8.34 ± 0.73 mm³, and the average amount of tear secretion of the ELGE test group was 3.55 ± 0.70 mm³. 8 rats per group and a total of 32 groups were selected based on the average amount of tear secretion.

As a reference drug, 3% diquafosol sodium (Santen, Tokyo, Japan; hereinafter, DS), which is currently on the market, was used.

The present animal tests were conducted with a prior approval of the Animal Experimental Ethics Committee of Daegu Haany University (Approval No. DHU2017-003, January 12, 2017). All test animals were fasted for 18 hours before the ELGE operation and final sacrifice except for feeding water.

The 32 groups were summarized in Table 2.

[Table 2]

Group classification	32 groups in total; 8 rats per group
Sham control group	Group administered with physiological saline after the sham operation
ELGE control group	Group administered with physiological saline after the ELGE operation
Reference	Group administered with DS after the ELGE operation
YY-102	Group administered with a 0.3% YY-102 solution after the ELGE operation
YDE series	Group administered with any of 0.3% YDE-01 to YDE-28 solutions (28 groups in total)

In addition, in order to evaluate the eye protection effect on dry eye syndrome by YDE-029 to YDE-043 prepared in Example 1, a total of 200 Sprague-Dawley-type male rats (OrientBio, Seungnam, Korea) were adapted for 7 days. Dry eye syndrome was induced in 165 test rats through the ELGE. 8 test rats without the eye abnormality were subjected to the sham operation as a control group. The ELGE was carried out as described above.

The average weight of the ELGE test group measured before the ELGE operation was 264.09±11.53 g, and the average weight measured after 6 days from the ELGE operation was 316.13±15.77 g. The average weight of the control group measured before the sham operation was 263.50±9.24 g, and the average weight measured after 6 days from the sham operation was 315.25±10.85 g (Fig. 6).

The average amount of tear secretion of the control group was 10.90±1.69 mm³, and the average amount of tear secretion of the ELGE test group was 4.83±0.99 mm³. 8 rats per group and a total of 20 groups were selected based on the average amount of tear secretion.

As a reference drug, 3% DS, which is currently on the market, was used.

The present animal tests were conducted with a prior approval of the Animal Experimental Ethics Committee of Daegu Haany University (Approval No. DHU2017-050, June 08, 2017). All test animals were fasted for 18 hours before the ELGE operation and final sacrifice except for feeding water.

The 20 groups were summarized in Table 3.

[Table 3]

Group classification	20 groups in total; 8 rats per group
Sham control group	Group administered with physiological saline after the sham operation
ELGE control group	Group administered with physiological saline after the ELGE operation
Reference	Group administered with DS after the ELGE operation
YY-101	Group administered with a 0.3% YY-101 solution after the ELGE operation
YY-102	Group administered with a 0.3% YY-102 solution after the ELGE operation
YDE series	Group administered with any of 0.3% YDE-01 to YDE-28 solutions (15 groups in total)

Administration of the YDE derivatives

For YDE-001 to YDE-028, YY-102 and the 28 YDE-series were each dissolved in physiological saline at a concentration of 3 mg/ml and administered at a dose of 5 µl/eye at 9:30 am and 3:30 pm daily for 14 days after 7 days from the ELGE operation for a total of 28 times. The DS solution was dissolved in physiological saline at a concentration of 30 mg/ml and administered at a dose of 5 µl/eye twice a day for 14 days after 7 days from the ELGE operation for a total of 28 times. For the sham control and the ELGE control groups, the same stimulation as the administration was applied. In order to prevent excessive eye dryness, the same volume of physiological saline was applied in the same manner in place of the test substances.

Further, for YDE-029 to YDE-043, YY-102 and the 15 YDE-series were each dissolved in physiological saline at a concentration of 3 mg/ml and administered at a dose of 5 µl/eye at 9:30 am and 3:30 pm daily for 14 days after 7 days from the ELGE operation for a total of 28 times. The DS solution was dissolved in physiological saline at a concentration of 30 mg/ml and administered at a dose of 5 µl/eye twice a day for 14 days after 7 days from the ELGE operation for a total of 28 times. For the sham control and the ELGE control groups, the same stimulation as the administration was applied. In order to

prevent excessive eye dryness, the same volume of physiological saline was applied in the same manner in place of the test substances (Fig. 7).

Confirmation of the changes in the amount of tear secretion by the YDE

5 derivatives

After 6 days from the ELGE surgery, the changes in the amount of tear secretion were measured at day 7 and day 14 after the administration of YDE-001 to YDE-043. The amount of tear secretion was measured by the decrease in the travel distance of tears absorbed by cobalt chloride paper in a size of 1 x 15 mm (Toyo Roshi Kaisha, Japan).

10 The cobalt chloride paper was placed in the lateral canthus of a rat for 60 seconds to absorb tears (Fig. 9). The length of the area absorbed from the corner of the cobalt chloride paper was measured with an electronic digital caliper (Mytutoyo, Tokyo, Japan) (Fig. 8).

Fig. 9 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102 administered group, and E to AF are for the YDE-001 to YDE-028 administered groups in order.

15 As a result, it was confirmed that the amount of tear secretion was decreased after 6 days from the ELGE operation at days 7 and 14 after the application of physiological saline in the ELGE control group as compared with the sham control group. In the groups treated with YDE derivatives and the DS reference group, the amount of tear secretion was

20 increased as compared with the ELGE control group, except for the groups treated with a 3% solution of YDE-9, YDE-10, YDE-17, YDE-19, YDE-20, YDE-21, YDE-22, YDE-25, YDE-27, and YDE-28, which did not show any significant changes in the amount of tear secretion after the administration thereof for 14 days. Especially, the amount of tear secretion was increased by more than 20% in the groups treated with a 3% solution of

25 YDE-15, YDE-11, YDE-08, YDE-26, YDE-16, YDE-01, YDE-23, and YY-102 as compared with the DS reference group.

The specific amounts of tear secretion are shown in Fig. 10 and Table 4.

[Table 4]

No.	Tear Volumes (mm ³)	
	Day 7	Day 14
YY-101	7.66±0.61	6.00±0.69
YY-102	4.59±1.43	5.77±1.99
YDE-001	4.88±1.62	5.92±2.19

YDE-002	3.84±1.16	5.01±1.67
YDE-003	4.13±1.76	4.88±1.57
YDE-004	3.42±1.06	5.19±1.84
YDE-005	3.85±0.93	5.08±1.91
YDE-006	3.44±1.69	5.35±1.68
YDE-007	3.91±1.28	5.45±1.26
YDE-008	4.57±1.25	6.10±2.36
YDE-009	3.76±1.21	4.54±1.11
YDE-010	3.42±1.31	4.35±1.36
YDE-011	4.22±1.45	6.16±2.16
YDE-012	3.68±0.99	5.67±1.86
YDE-013	5.27±1.50	5.49±1.92
YDE-014	3.81±1.21	5.62±1.85
YDE-015	4.03±2.19	6.65±2.13
YDE-016	4.59±1.13	5.98±2.27
YDE-017	4.00±1.22	4.89±1.50
YDE-018	3.75±1.54	4.99±1.60
YDE-019	4.84±1.39	4.52±1.07
YDE-020	3.41±1.47	4.20±1.35
YDE-021	4.08±1.33	4.90±1.13
YDE-022	3.19±0.67	4.10±0.95
YDE-023	5.32±2.30	5.78±2.23
YDE-024	3.85±1.30	5.72±1.36
YDE-025	3.21±0.72	4.72±2.19
YDE-026	4.32±1.47	6.01±1.83
YDE-027	2.82±0.86	3.95±1.52
YDE-028	4.04±0.99	4.73±1.18

Fig. 11 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102 administered group, and E to S are for the YDE-029 to YDE-043 administered groups in order.

- As a result, it was confirmed that the amount of tear secretion was decreased after 6 days from the ELGE operation at days 7 and 14 after the application of physiological saline in the ELGE control group as compared with the sham control group. In the groups treated with YDE derivatives and the DS reference group, the amount of tear secretion was
- 5 increased as compared with the ELGE control group, except for the groups treated with a 3% solution of YDE-029, YDE-030, YDE-032, YDE-033, YDE-034, YDE-036, and YDE-41, which did not show any significant changes in the amount of tear secretion after the administration thereof for 14 days. Especially, the amount of tear secretion was increased by more than 20% in the groups treated with a 3% solution of YDE-040, YDE-043, and
- 10 YDE-042 in order as compared with the DS reference group.

The specific amounts of tear secretion are shown in Fig. 12 and Table 5.

[Table 5]

No.	Tear Volumes (mm ³)	
	Day 7	Day 14
YY-101	5.36±0.68	6.25±0.68
YY-102	5.77±1.01	6.60±0.64
YDE-029	5.33±1.43	6.03±1.71
YDE-030	5.69±1.79	6.65±2.17
YDE-031	5.63±1.97	5.91±0.85
YDE-032	5.58±0.80	5.03±0.93
YDE-033	4.99±1.20	4.54±1.16
YDE-034	6.16±1.01	6.43±1.86
YDE-035	4.96±0.96	6.25±0.79
YDE-036	4.95±1.05	5.13±1.03
YDE-037	4.98±0.66	5.80±0.90
YDE-039	6.04±1.01	6.44±1.96
YDE-040	5.77±1.05	8.63±1.53
YDE-041	5.01±1.26	6.25±2.15
YDE-042	6.30±1.08	7.97±1.48
YDE-043	5.90±1.06	8.16±1.42

Confirmation of the changes in the corneal damage by the YDE derivatives

After YDE-001 to YDE-028 were each administered to the eyes 14 times, the changes in the corneal permeability were checked.

In order to measure the corneal permeability, Zoletyl 50TM (Virbac Lab., Carros, France), an animal anesthetic, was intraperitoneally injected at a dose of 25 mg/kg. Thereafter, saline containing a 1% (v/v) fluorescent solution (fluorescein sodium salt, Tokyo Kasei Kogyo Co., Tokyo, Japan) was applied to the eyes at a dose of 5 µl/eye. The eyes thus treated were closed and fixed with a tape. After 1 hour, the remaining fluorescent solution was removed using a cotton swab (Fig. 12). After 12 hours to 24 hours, the corneal permeability was measured using a blue light tungsten lamp and an ophthalmic slit lamp table top model biomicroscope (Model SM-70N; Takagi Seiko Co., Nakano, Japan) (Fig. 13).

Fig. 14 shows the results of the test, wherein A is for the sham control group, B is for the ELGE control group, C is for the DS reference group, D is for the YY-102 administered group, and E to AF are for the YDE-001 to YDE-028 administered groups in order.

As a result, the permeability of the fluorescent dye was increased in the ELGE control group as compared with the sham control group. The permeability of the fluorescent dye was not decreased in the groups treated with a 3% solution of YDE-10, YDE-20, YDE-22, YDE-25, YDE-27, and YDE-28 as compared with the ELGE control group at day 14 after the administration. In the groups treated with YDE derivatives and the DS reference group, the corneal permeability of the fluorescent dye was decreased as compared with the ELGE control group, except for the groups treated with a 3% solution of YDE-10, YDE-20, YDE-22, YDE-25, YDE-27, and YDE-28. Especially, the permeability of the fluorescent dye was decreased by more than 20% in the groups treated with a 3% solution of YDE-15, YDE-11, YDE-08, YDE-26, YDE-16, YDE-01, YDE-23, and YY-102, as compared with the DS reference group.

The specific permeabilities of the fluorescent dye are shown in Fig. 15 and Table 6.

[Table 6]

No.	Permeability of fluorescent dye (%)
YY-101	27.53±5.62
YY-102	27.48±14.37
YDE-001	25.49±11.62
YDE-002	38.26±11.25
YDE-003	40.45±6.46
YDE-004	35.05±11.74
YDE-005	37.98±11.53
YDE-006	33.23±13.26
YDE-007	32.79±10.77
YDE-008	20.32±11.87
YDE-009	41.50±7.86
YDE-010	49.29±12.06
YDE-011	18.11±11.61
YDE-012	31.01±11.38
YDE-013	32.24±7.84
YDE-014	31.15±10.87
YDE-015	15.95±6.48
YDE-016	24.57±10.34
YDE-017	39.76±7.42
YDE-018	38.19±10.96
YDE-019	40.39±12.57
YDE-020	47.84±13.47
YDE-021	37.00±10.49
YDE-022	47.82±10.01
YDE-023	26.51±8.18
YDE-024	30.63±10.41
YDE-025	47.10±11.45
YDE-026	22.63±11.23
YDE-027	50.24±11.94
YDE-028	41.17±10.25

In addition, YDE-029 to YDE-043 were each administered to the eyes 14 times, and the changes in the corneal permeability were then checked. The measurement of the corneal permeability was carried out in the same manner as described above (Fig. 16).

As a result, the permeability of the fluorescent dye was increased in the ELGE control group as compared with the sham control group. The permeability of the fluorescent dye was not decreased in the groups treated with a 3% solution of YDE-29, YDE-32, YDE-33, YDE-36, and YDE-41 as compared with the ELGE control group at day 14 after the administration. In the groups treated with YDE derivatives and the DS reference group, the corneal permeability of the fluorescent dye was decreased as compared with the ELGE control group, except for the groups treated with a 3% solution of YDE-29, YDE-32, YDE-33, YDE-36, and YDE-41. Especially, the permeability of the fluorescent dye was decreased by more than 20% in the groups treated with a 3% solution of YDE-40, YDE-43, and YDE-42, as compared with the DS reference group.

The specific permeabilities of the fluorescent dye are shown in Fig. 17 and Table 7.

[Table 7]

No.	Permeability of fluorescent dye (%)
YY-101	33.80±11.11
YY-102	27.89±7.10
YDE-029	63.45±11.57
YDE-030	30.60±13.61
YDE-031	33.35±11.01
YDE-032	58.90±19.81
YDE-033	60.55±21.22
YDE-034	32.17±12.94
YDE-035	27.62±6.51
YDE-036	57.87±22.91
YDE-037	36.30±9.75
YDE-039	29.94±11.40
YDE-040	18.33±9.41
YDE-041	46.38±26.65
YDE-042	20.72±11.37
YDE-043	19.04±7.36

Example 4: Evaluation of the stability of the YDE derivatives

In order to confirm the stability of each test substance in an aqueous solution, 10 mg of each sample was dissolved in 1 ml of water to a concentration of 1 mg/ml, which was then charged to a glass vial, plugged with a rubber cap, sealed with an aluminum cap, and stored under long-term storage conditions (25°C, 75% RH). The stability of the test substance was evaluated by measuring the amount of related substances at the time of one week, two weeks, four weeks, eight weeks, and twelve weeks under the long-term storage conditions.

As a result, 66.5% of related substances was generated in YY-101 after two weeks. In contrast, 1.1% to 30.6% of related substances was generated in YDE-001 to YDE-028 after 12 weeks. The specific amounts are shown in Table 8.

[Table 8]

No.	Amount of related substances (%; after 12 weeks)
YY-101	66.51 (after 2 weeks)
YDE-001	3.92
YDE-002	4.93
YDE-003	6.86
YDE-004	2.11
YDE-005	2.97
YDE-006	3.67
YDE-007	3.76
YDE-008	4.42
YDE-009	4.71
YDE-010	4.39
YDE-011	3.83
YDE-012	3.57
YDE-013	5.92
YDE-014	6.72
YDE-015	13.05
YDE-016	11.33
YDE-017	11.88

YDE-018	25.39
YDE-019	13.43
YDE-020	21.54
YDE-021	21.33
YDE-022	19.23
YDE-023	30.66
YDE-024	20.59
YDE-025	5.17
YDE-026	10.15
YDE-027	12.74
YDE-028	1.15
YDE-029	2.77
YDE-030	2.74
YDE-031	34.82
YDE-032	6.16
YDE-033	5.6
YDE-034	1.25
YDE-035	3.89
YDE-036	8.77
YDE-037	2.88
YDE-039	2.19
YDE-040	3.58
YDE-041	3.04
YDE-042	3.98
YDE-043	3.43

Example 5: Evaluation of recovery of corneal damage by the YDE derivatives

In order to confirm whether the YDE derivatives could recover corneal damage, the cellular growth rate of human primary corneal epithelial cells was checked.

- 5 Specifically, primary corneal epithelial cells (ATCC, ATCC PCS-700-010) were seeded on a 96-well culture plate (Perkin Elmer, 6005680) containing the Corneal Epithelial Cell Basal Medium (ATCC, ATCC PCS-700-030) in the Corneal Epithelial Cell

Growth Kit (ATCC, ATCC PCS-700-040) in an amount of 5×10^3 cells per well, which was then cultured for 24 hours under the conditions of 37°C and 5% CO₂.

YDE-001 to YDE-075 were each dissolved in 100% DMSO (Sigma, D2660) to a concentration of 10 mM, which was then diluted with 100% DMSO to a concentration of the compound of 6, 1.9, 0.6, 0.2, 0.06, 0.02, 0.006, and 0.002 mM. 20 µl of the diluted YDE derivative was added to a 96-well microplate (Greiner Bio-One, 651201) containing 380 µl of the Corneal Epithelial Cell Basal Medium such that the concentration of DMSO was diluted to 5%.

After 24 hours, 20 µl of each of the YDE derivatives diluted in the 96-well microplate was added to the 96-well culture plate containing the cells. As a control group, hEGF (Sigma, E9644) was treated at the same concentration as the YDE derivatives. The cells treated with the YDE-derivatives or hEGF were cultured for 48 hours and 72 hours under the conditions of 37°C and 5% CO₂ (Figs. 18 to 25).

The cultured cells were treated with the CellTiter-Glo luminescent reagent (Promega, G7573) according to the manufacturer's instructions and reacted for 30 minutes at room temperature. Thereafter, the fluorescent signal (or luminescence signal) was checked using an Envision 2014 Multi-label plate reader. The measured values were normalized using a vehicle control (100% proliferation cell).

As a result, the cell proliferation was observed at concentrations of 0.3 µM or less in YY-101, YY-102, YDE-011, YDE-038, YDE-042, YDE-043, YDE-044, YDE-045, YDE-049, YDE-054, YDE-057, YDE-058, YDE-059, and YDE-060. Especially, a high cell proliferation rate was shown in YY-102, YDE-011, YDE-045, YDE-057, and YDE-060 (Figs. 26 to 43).

Incorporation by Reference

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

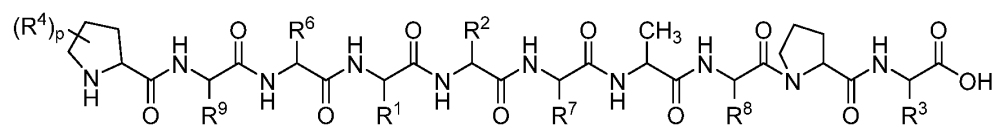
Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below.

- 5 The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. A salt of a compound represented by Formula (I):



(I)

wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

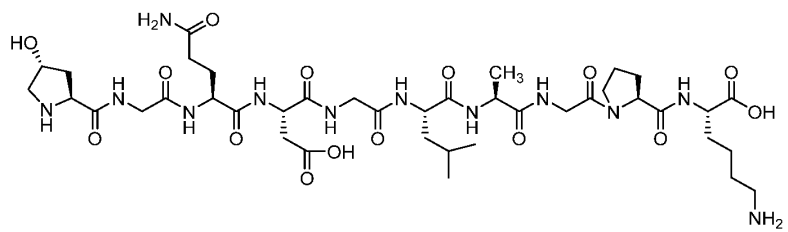
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

wherein the compound is not:



preferably wherein the compound comprises at least one D-amino acid residue.

2. The salt of claim 1, wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, $-OR^b$, hydroxyalkyl, $-CH_2OR^b$, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl.

3. The salt of claim 1 or 2, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, -CN, -NO₂, =N-OH, -N₃, -R^a, -OR^a, -SR^a, -N(R^a)₂, -N(R^a)₃⁺, =NR^a, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -S(=O)₂R^c, -OS(=O)₂OR^a, -S(=O)₂OR^a, -S(=O)₂N(R^a)₂, -S(=O)R^c, -OP(=O)(OR^a)₂, -(alkylene)-C(=O)R^c, -C(=S)R^c, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, -C(=S)OR^a, -C(=O)SR^a, -C(=S)SR^a, -(alkylene)-C(=O)N(R^a)₂, -C(=S)N(R^a)₂, and -C(-NR^a)N(R^a)₂;

R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

4. The salt of any one of claims 1-3, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, -R^a, -OR^a, -N(R^a)₂, -N(R^a)₃⁺, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, and -(alkylene)-C(=O)N(R^a)₂;

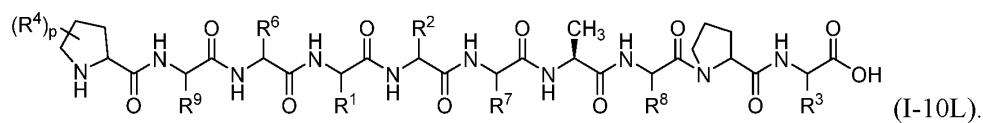
R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

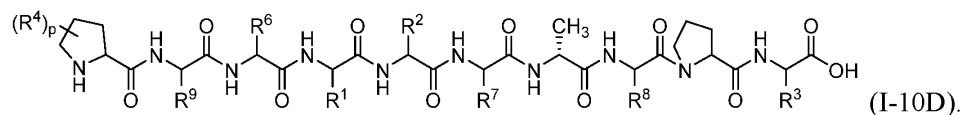
5. The salt of claim 4, wherein R^a, independently for each occurrence, is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl; and

R^c, independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl.

6. The salt of any one of claims 1-5, wherein the compound has the structure of formula (I-10L):

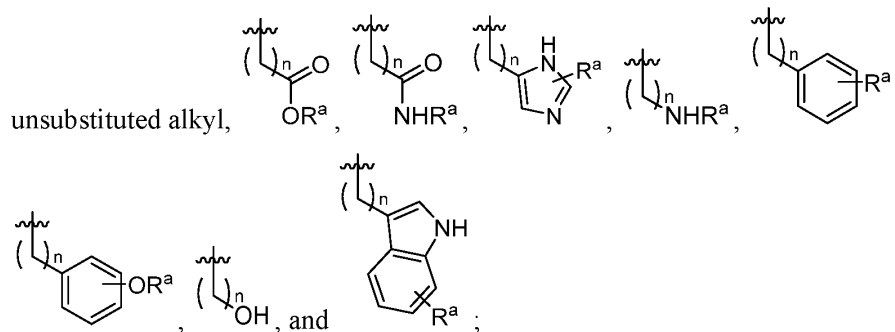


7. The salt of any one of claims 1-5, having the structure of formula (I-10D):



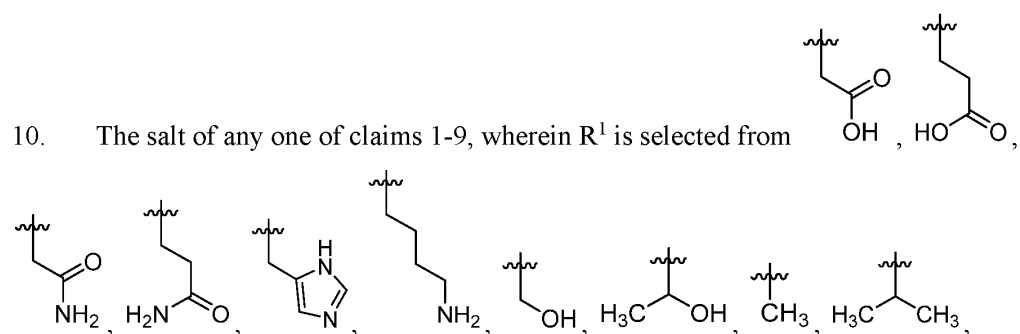
8. The salt of any one of claims 1-7, wherein R^1 is substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

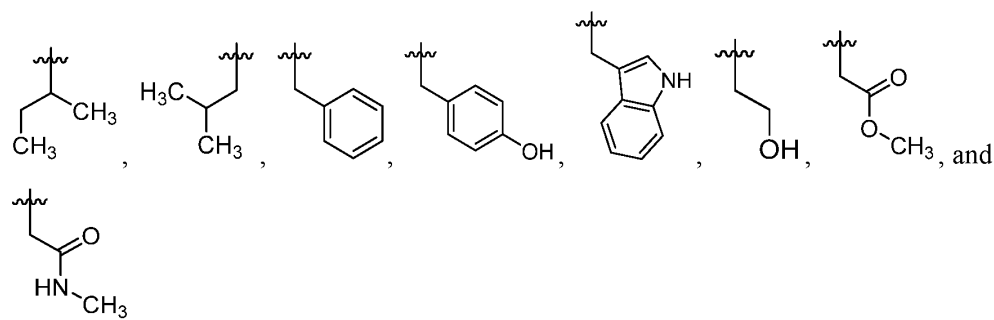
9. The salt of any one of claims 1-8, wherein R^1 is selected from substituted or



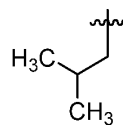
R^a is hydrogen or alkyl; and

n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

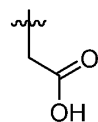




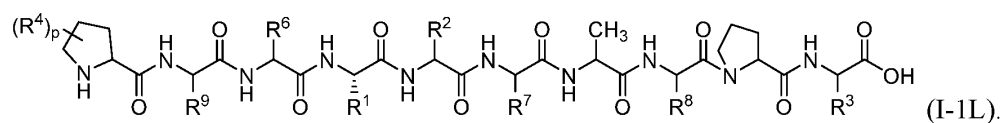
11. The salt of any one of claims 1-10, wherein R^1 is



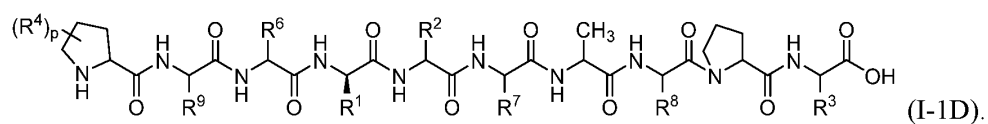
12. The salt of any one of claims 1-10, wherein R^1 is



13. The salt of any one of claims 1-12, wherein the compound has the structure of formula (I-1L)

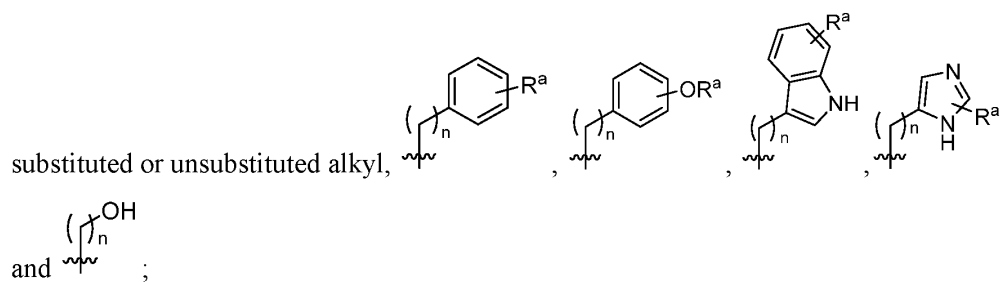


14. The salt of any one of claims 1-12, wherein the compound has the structure of formula (I-1D)



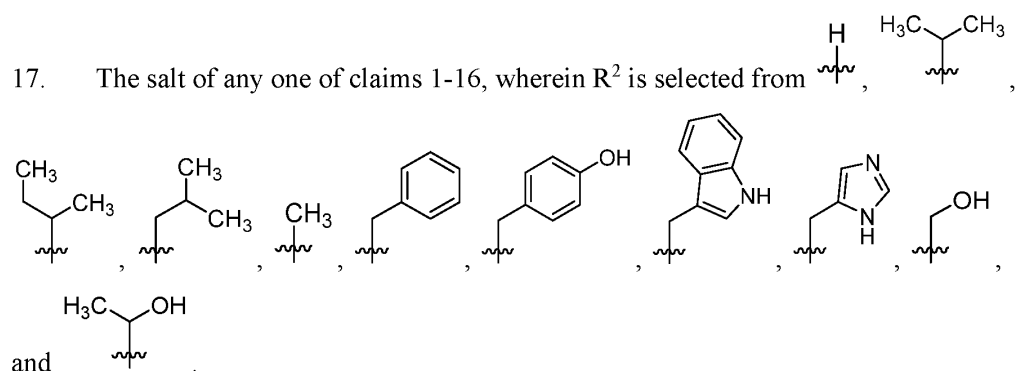
15. The salt of any one of claims 1-14, wherein R^2 is H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

16. The salt of any one of claims 1-15, wherein R^2 is selected from hydrogen,



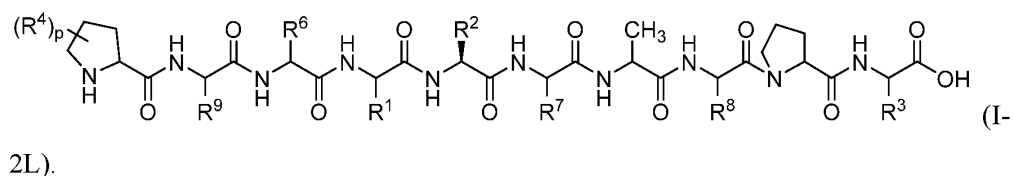
R^a is hydrogen or alkyl; and

n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

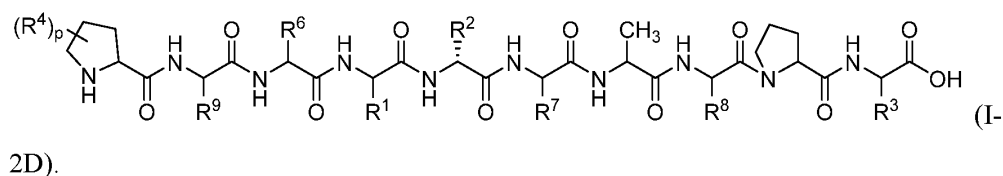


18. The salt of any one of claims 1-17, wherein R^2 is hydrogen.

19. The salt of any one of claims 1-18, wherein the compound has the structure of formula (I-2L):

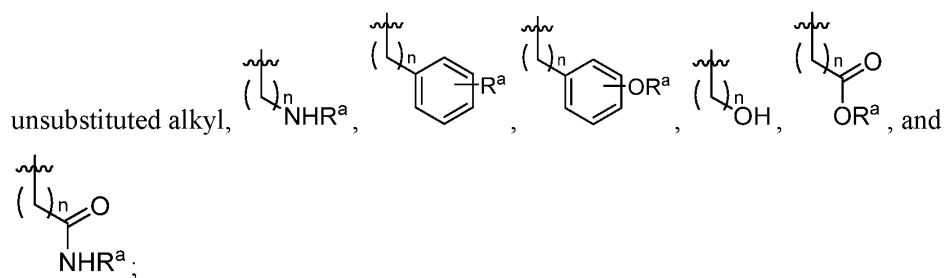


20. The salt of any one of claims 1-18, wherein the compound has the structure of formula (I-2D):



21. The salt of any one of claims 1-20, wherein R^3 is substituted or unsubstituted alkyl or arylalkyl.

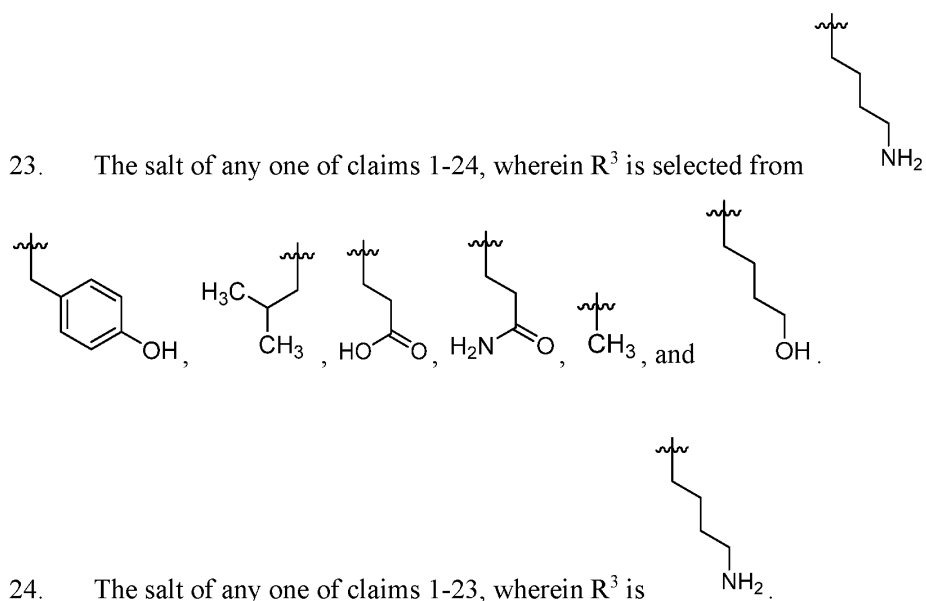
22. The salt of any one of claims 1-21, wherein R^3 is selected from substituted or



R^a is hydrogen or alkyl; and

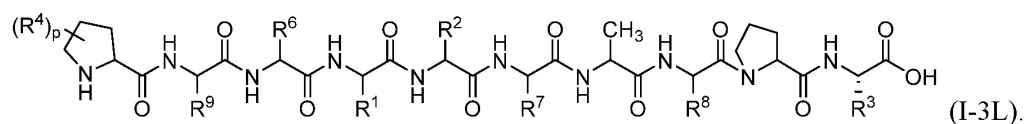
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

23. The salt of any one of claims 1-24, wherein R^3 is selected from

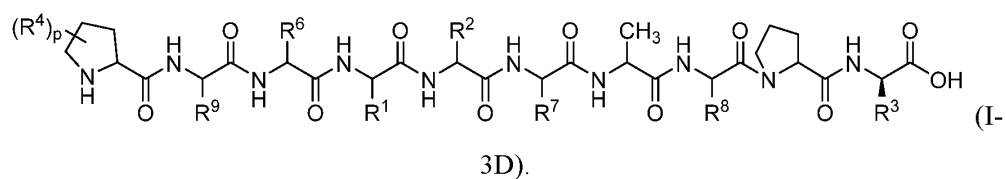


24. The salt of any one of claims 1-23, wherein R^3 is

25. The salt of any one of claims 1-24, wherein the compound has the structure of formula (I-3L):



26. The salt of any one of claims 1-24, wherein the compound has the structure of formula (I-3D):



27. The salt of any one of claims 1-26, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, $-OR^b$, $-\text{CH}_2OR^b$, halo, hydroxyl, and hydroxyalkyl.

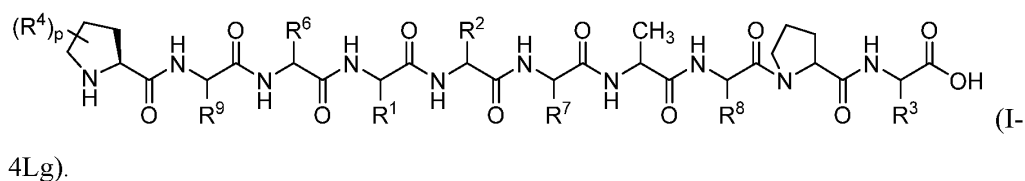
28. The salt of any one of claims 1-27, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from $-\text{CH}_3$, halo, hydroxyl, and hydroxyalkyl.

29. The salt of claim 28, wherein R^4 is hydroxyl.

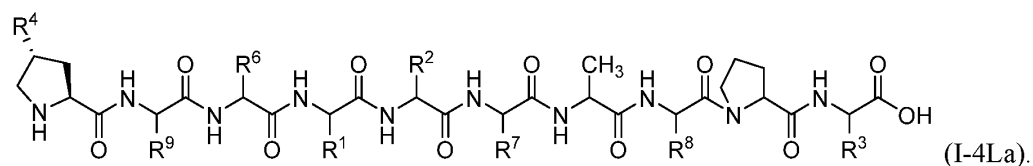
30. The salt of claim 28, wherein R^4 is $-\text{CH}_3$.

31. The salt of any one of claims 27-30, wherein p is 1.

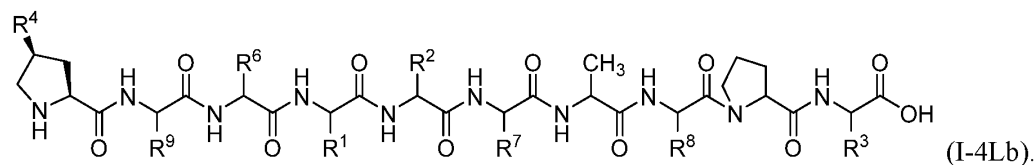
32. The salt of any one of claims 1-31, wherein the compound has the structure of formula (I-4Lg):



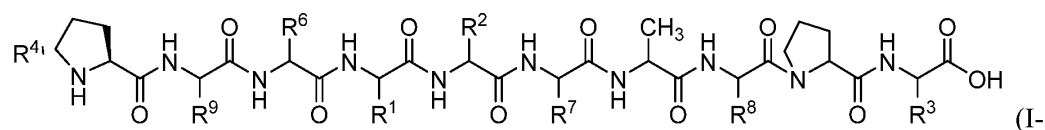
33. The salt of any one of claims 1-32, wherein the compound has the structure of formula (I-4La):



34. The salt of any one of claims 1-32, wherein the compound has the structure of formula (I-4Lb):

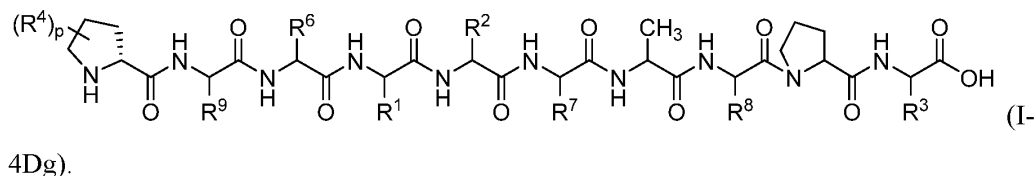


35. The salt of any one of claims 1-28, 30, and 31, wherein the compound has the structure of formula (I-4Lc):

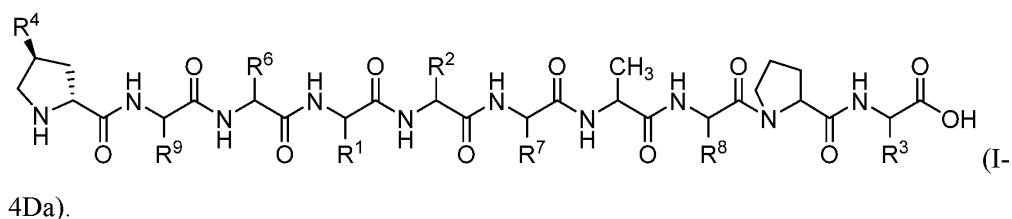


provided that R⁴ is not hydroxyl.

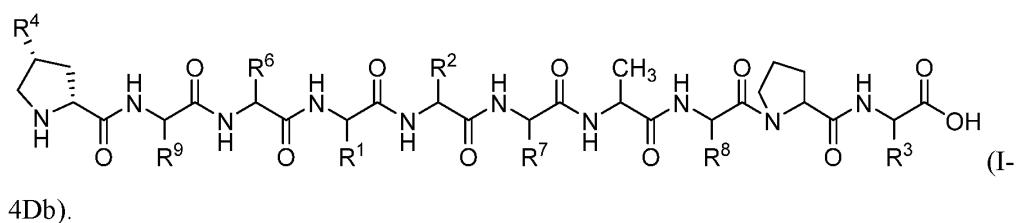
36. The salt of any one of claims 1-31, wherein the compound has the structure of formula (I-4Dg):



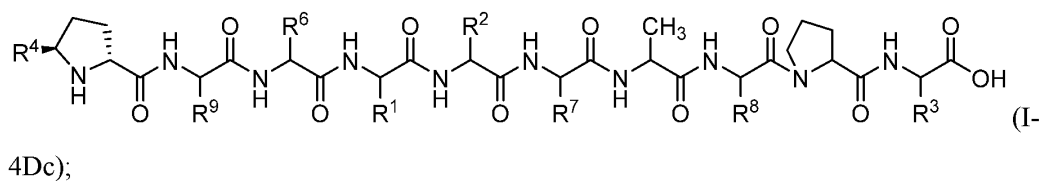
37. The salt of any one of claims 1-31 and 36, wherein the compound has the structure of formula (I-4Da):



38. The salt of any one of claims 1-31 and 36, wherein the compound has the structure of formula (I-4Db):



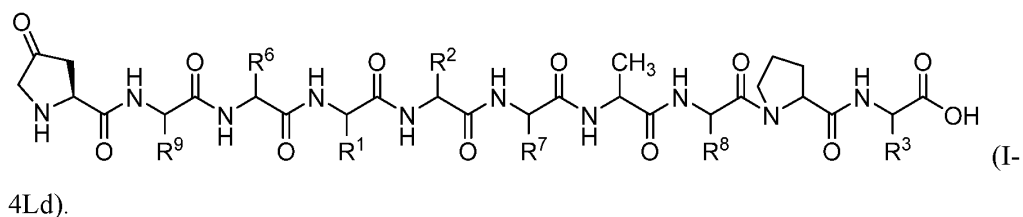
39. The salt of any one of claims 1-28, 30, 31, and 36, wherein the compound has the structure of formula (I-4Dc):



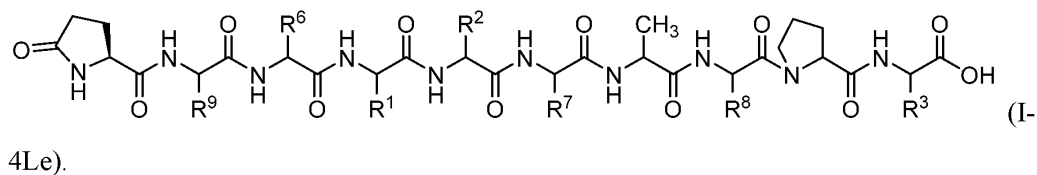
provided that R⁴ is not hydroxyl.

40. The salt of any one of claims 1-26, wherein R⁴ is oxo.

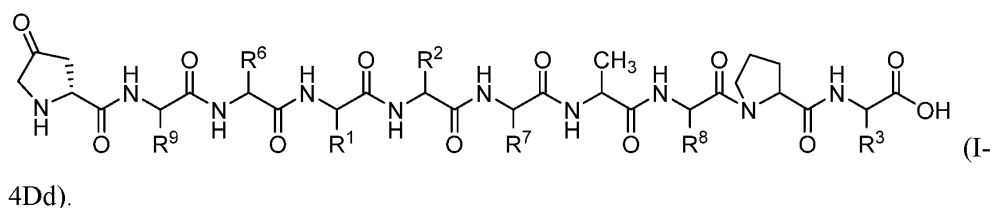
41. The salt of claim 40, wherein the compound has the structure of formula (I-4Ld):



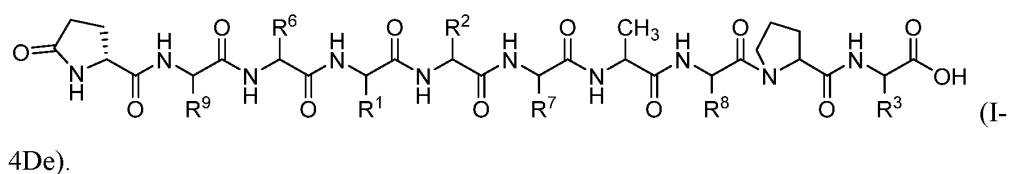
42. The salt of claim 40, wherein the compound has the structure of formula (I-4Le):



43. The salt of claim 40, wherein the compound has the structure of formula (I-4Dd):



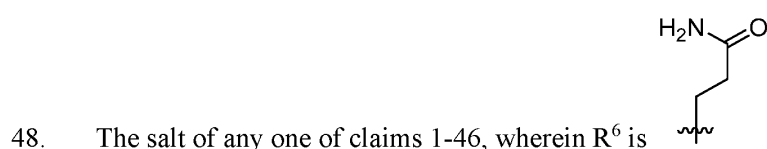
44. The salt of claim 40, wherein the compound has the structure of formula (I-4De):



45. The salt of any one of claims 1-44, wherein R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$.

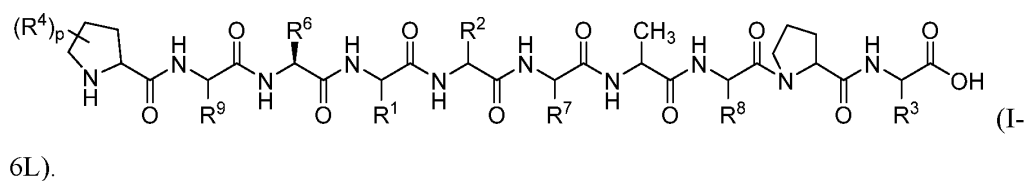
46. The salt of any one of claims 1-45, wherein R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$.

47. The salt of any one of claims 1-46, wherein R^6 is $-CH_3$.

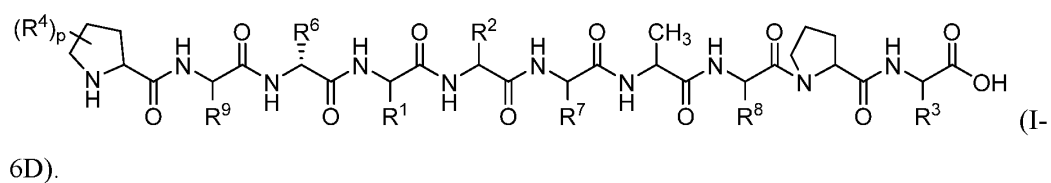


48. The salt of any one of claims 1-46, wherein R^6 is $-CH_3$.

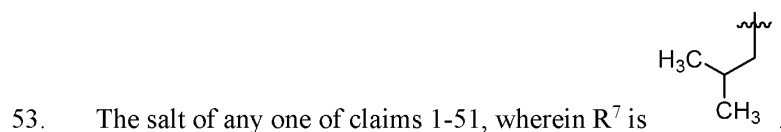
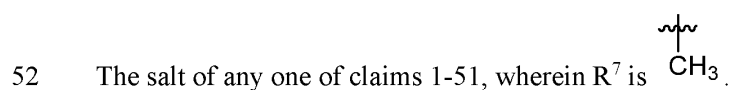
49. The salt of any one of claims 1-48, wherein the compound has the structure of formula (I-6L):



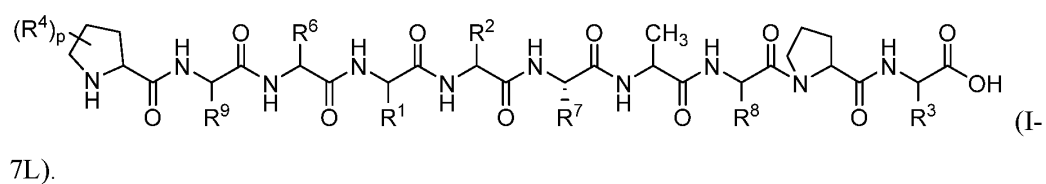
50. The salt of any one of claims 1-48, wherein the compound has the structure of formula (I-6D):



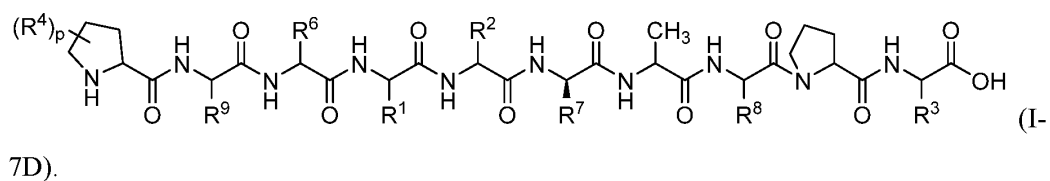
51. The salt of any one of claims 1-50, wherein R^7 is (C₁-C₁₀)alkyl.



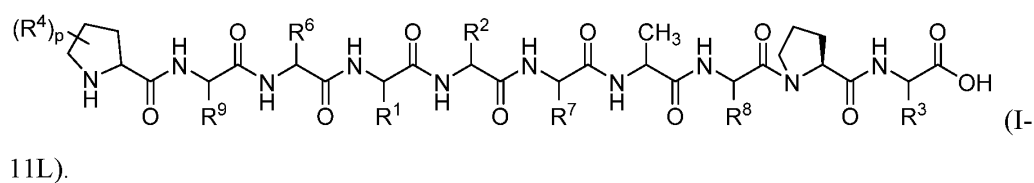
54. The salt of any one of claims 1-53, wherein the compound has the structure of formula (I-7L):



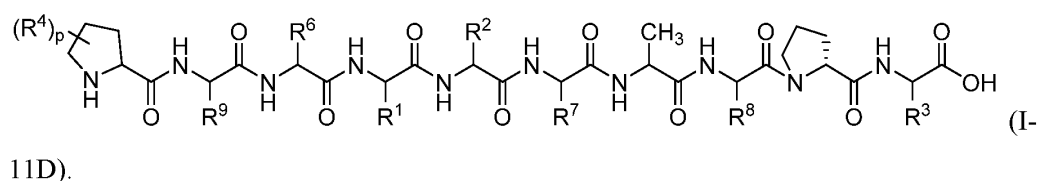
55. The salt of any one of claims 1-53, wherein the compound has the structure of formula (I-7D):



56. The salt of any one of claims 1-55, wherein the compound has the structure of formula (I-11L):



57. The salt of any one of claims 1-55, wherein the compound has the structure of formula (I-11D):



58. The salt of any one of claims 1-57, wherein R^8 is $-\text{CH}_3$ or $-\text{H}$.

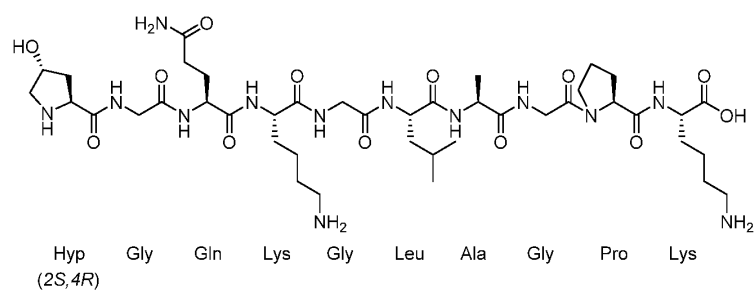
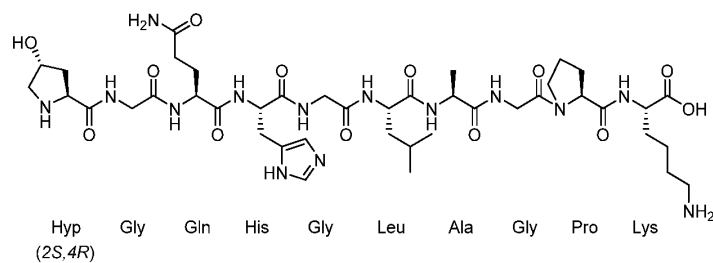
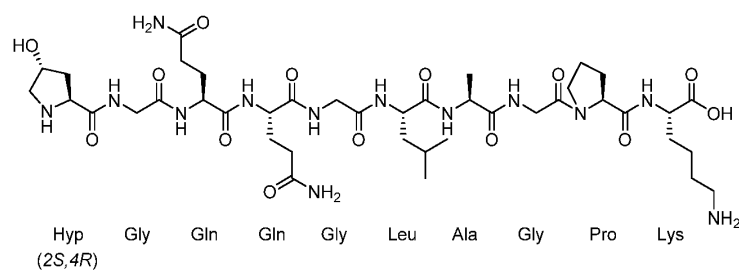
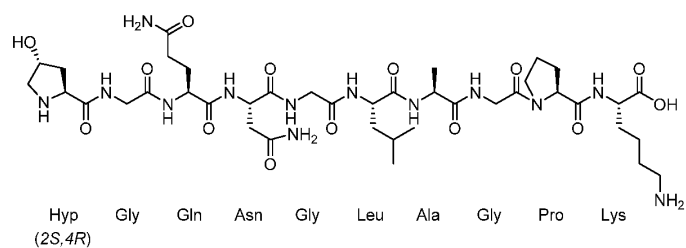
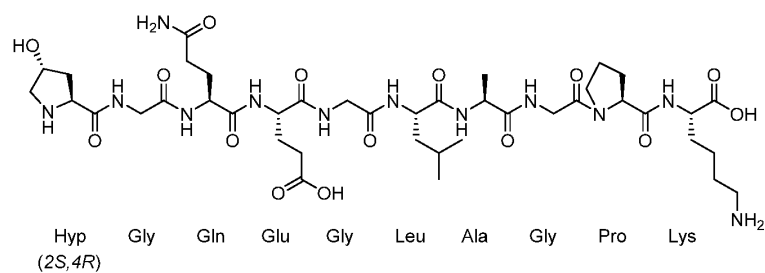
59. The salt of any one of claims 1-58, wherein R^8 is $-\text{H}$.

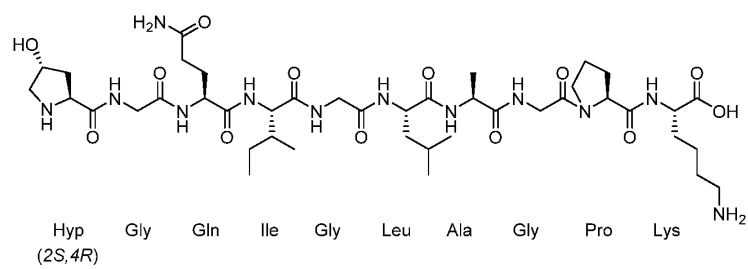
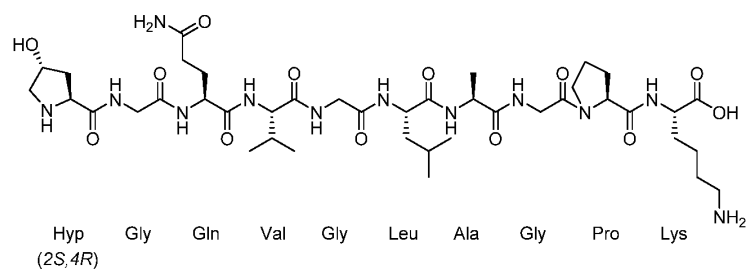
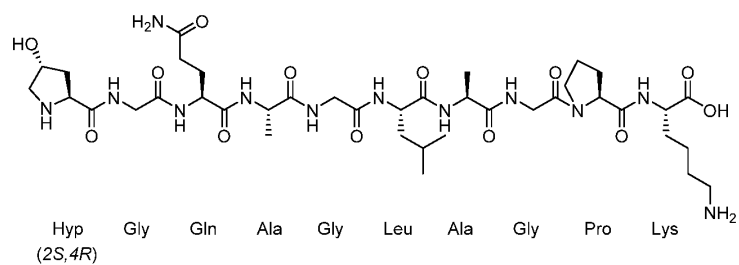
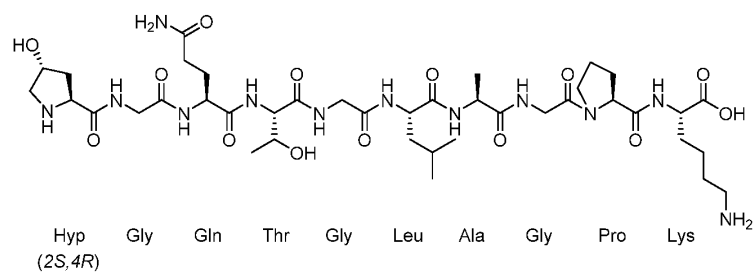
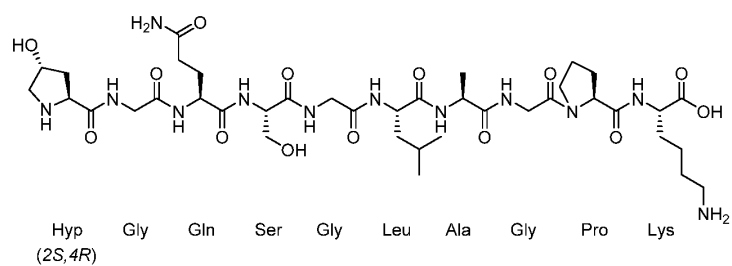
60. The salt of any one of claims 1-59, wherein R^9 is $-\text{CH}_3$ or $-\text{H}$.

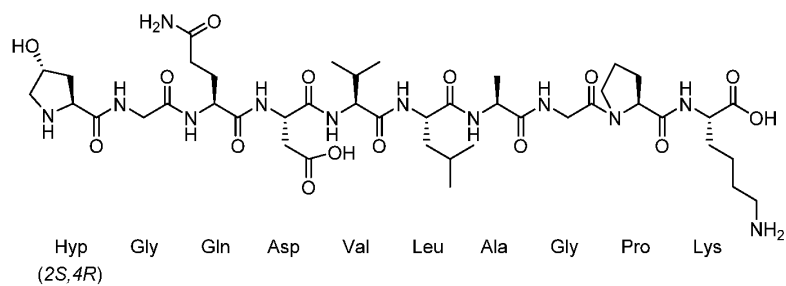
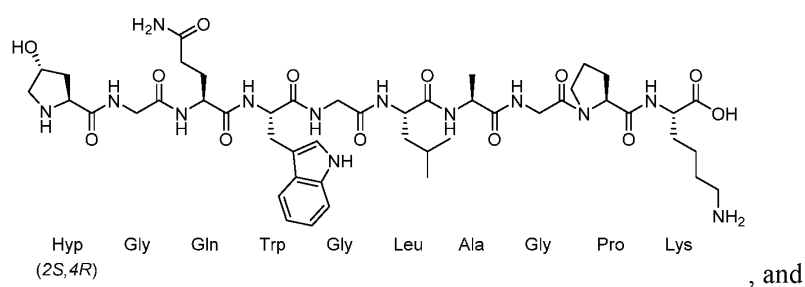
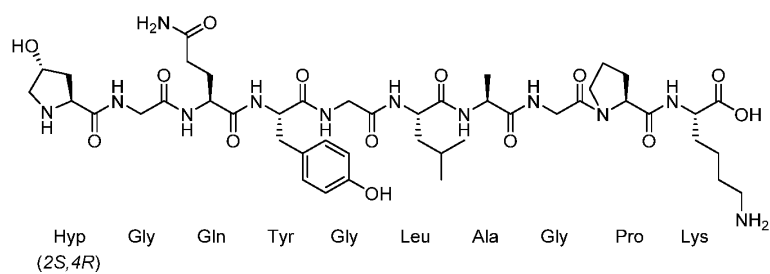
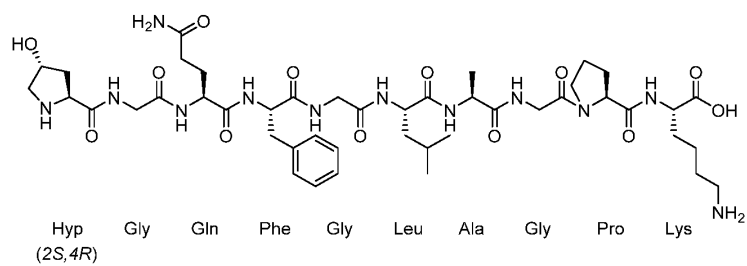
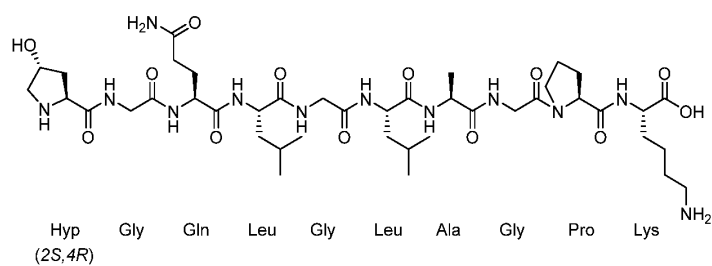
61. The salt of any one of claims 1-60, wherein R^9 is $-\text{H}$.

62. The salt of any one of claims 1-61, wherein the compound comprises at least two, at least three, at least four, at least five, at least six, at least seven, or at least eight D-amino acid residues.

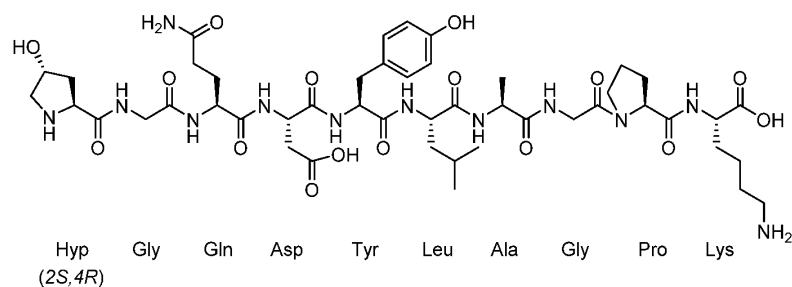
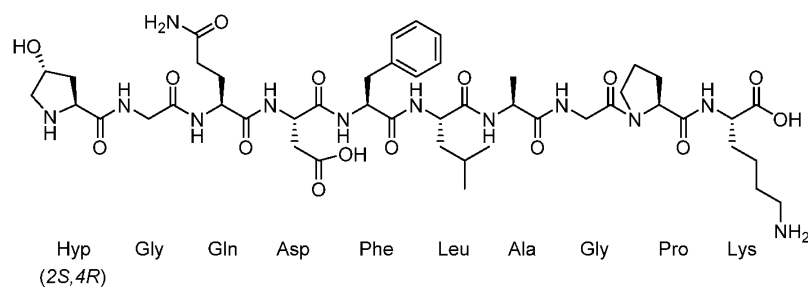
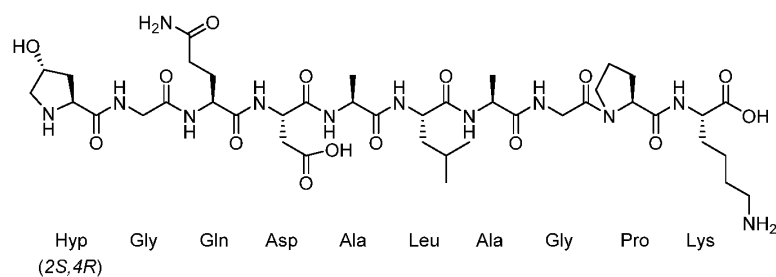
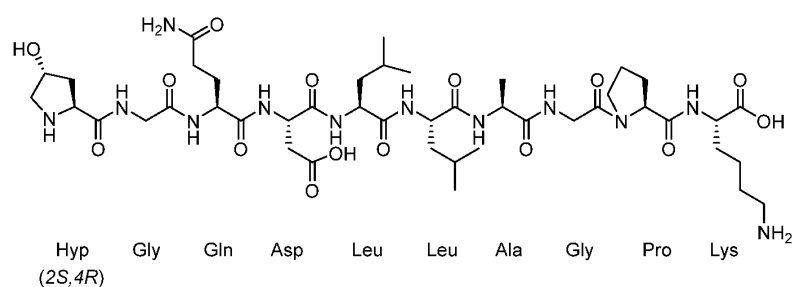
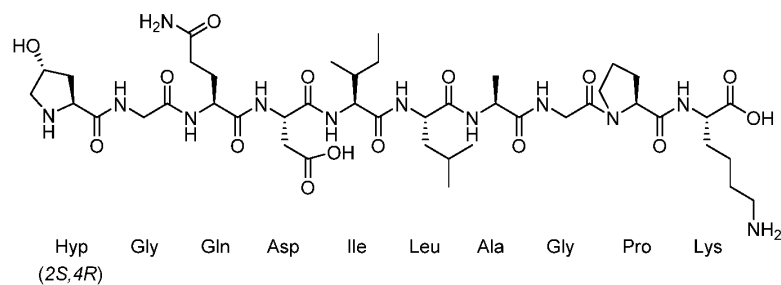
63. The salt of claim 1, wherein the compound is selected from the following:

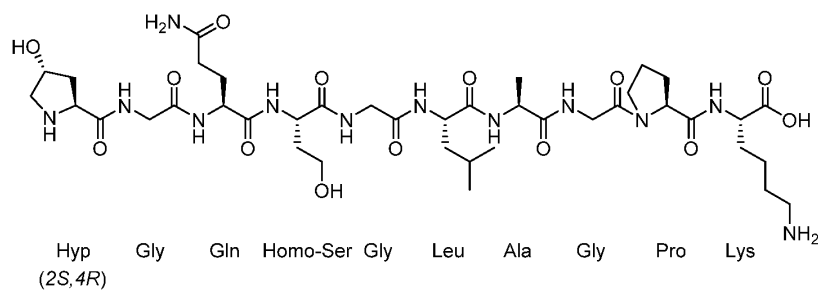
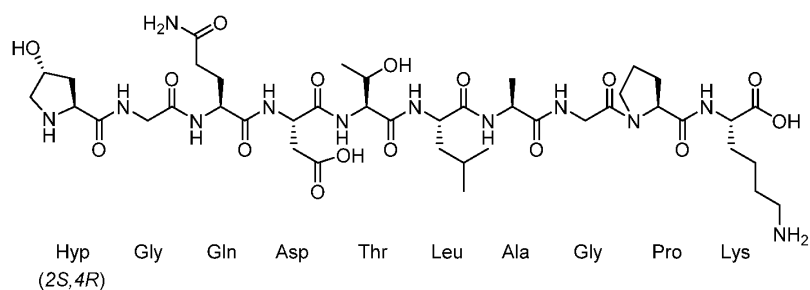
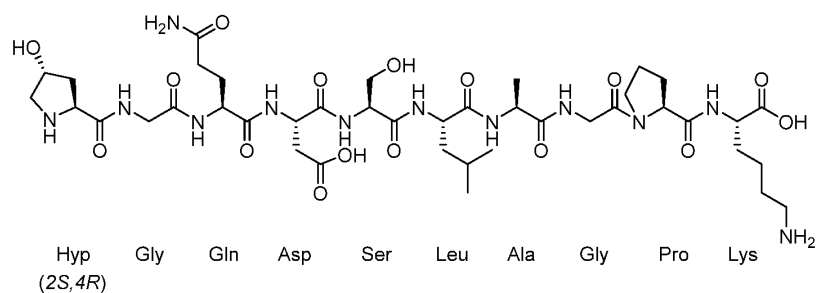
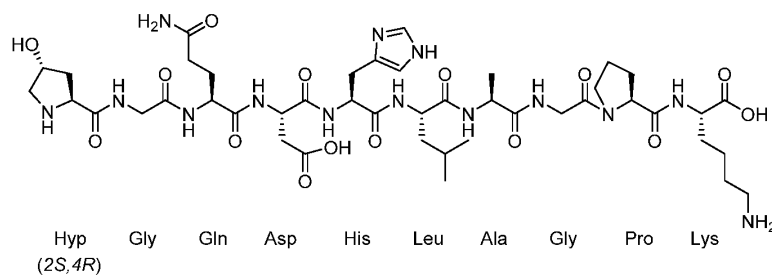
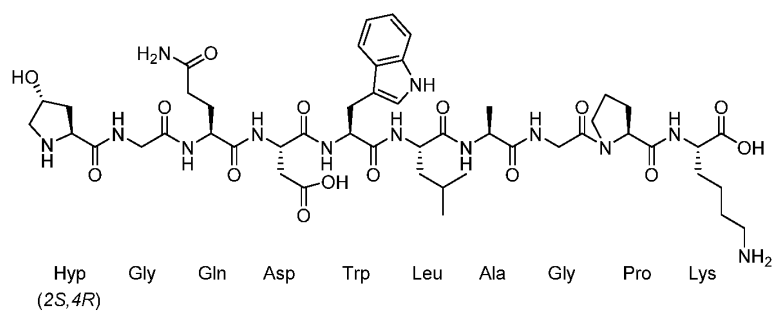


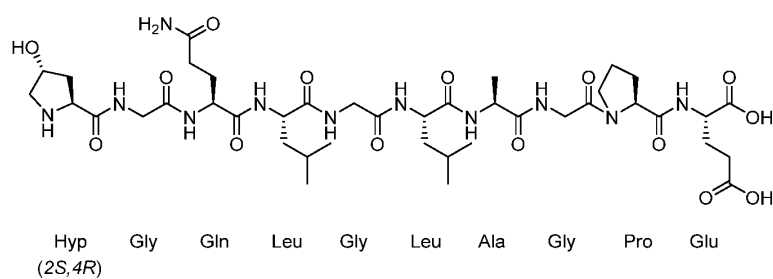
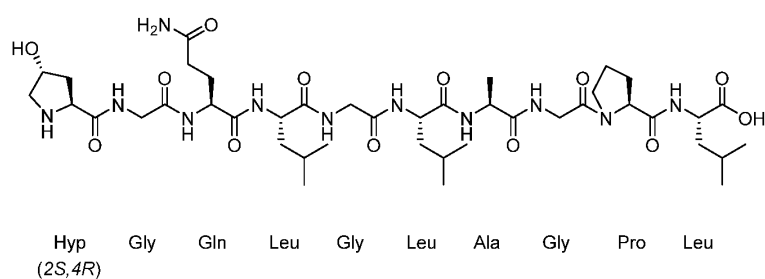
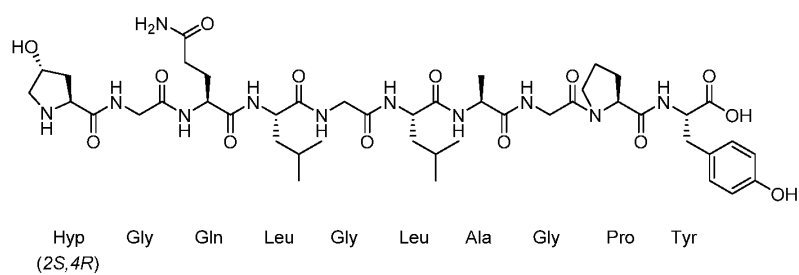
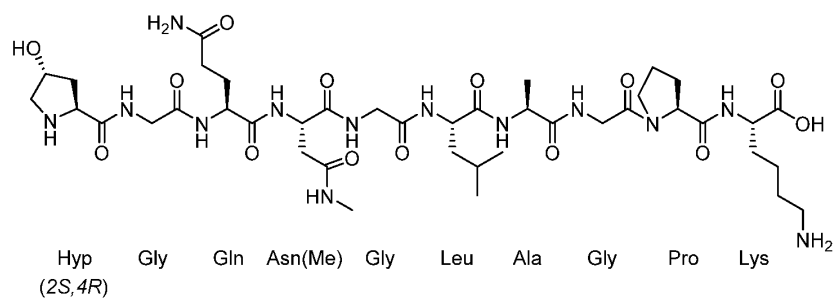
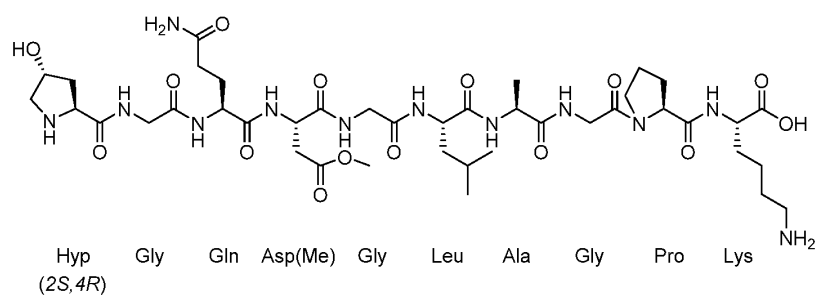




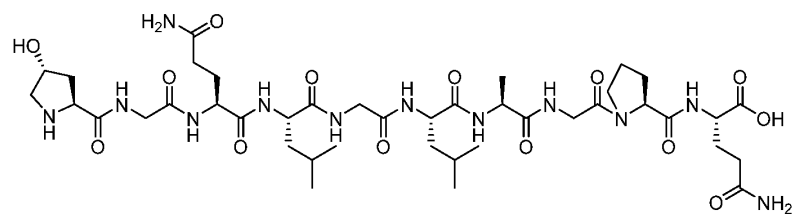
64. The salt of claim 1, wherein the compound is selected from the following:



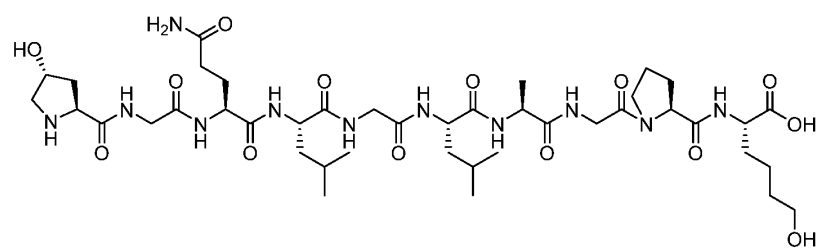




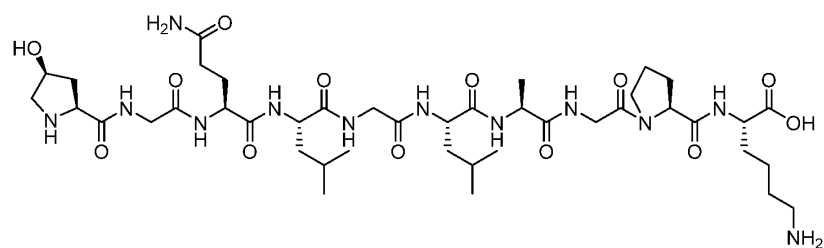
65. The salt of claim 1, wherein the compound is selected from the following:



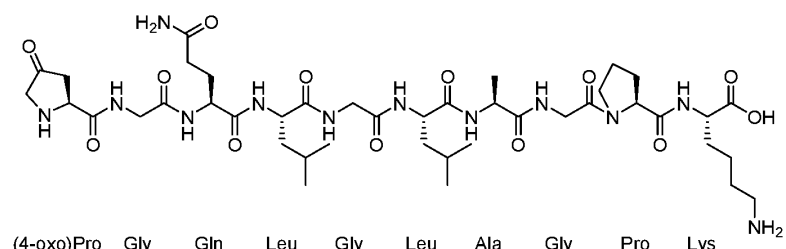
Hyp Gly Gln Leu Gly Leu Ala Gly Pro Gln
(2S,4R)



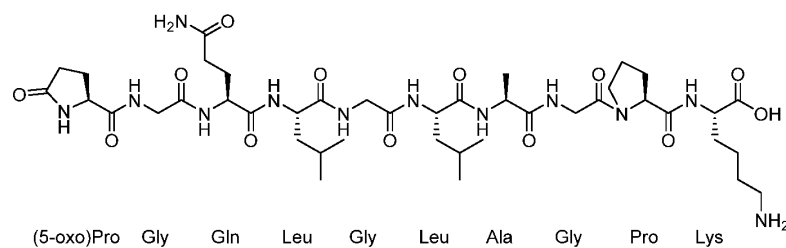
Hyp Gly Gln Leu Gly Leu Ala Gly Pro Nle(6-OH)
(2S,4R)



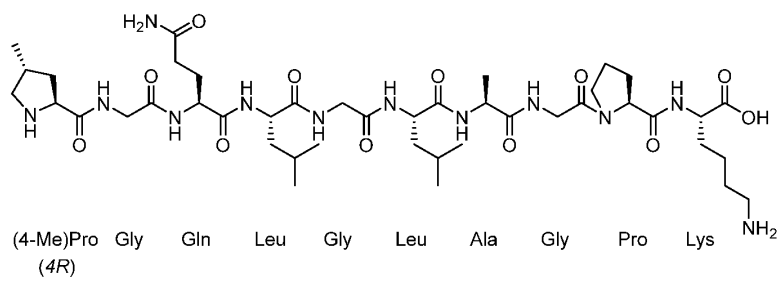
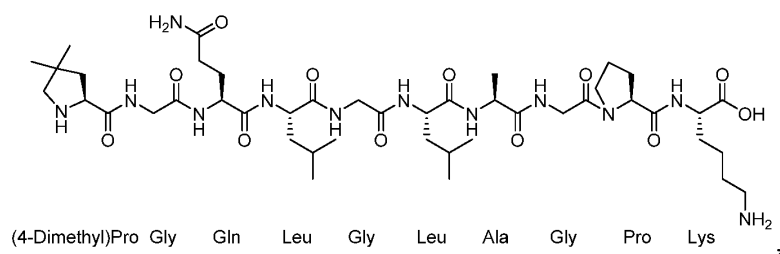
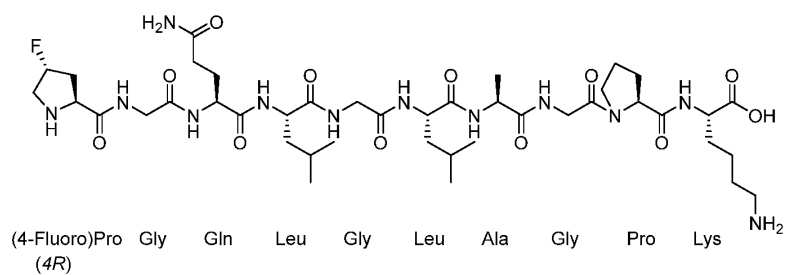
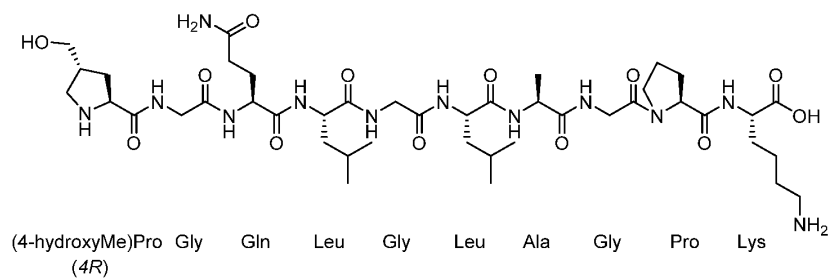
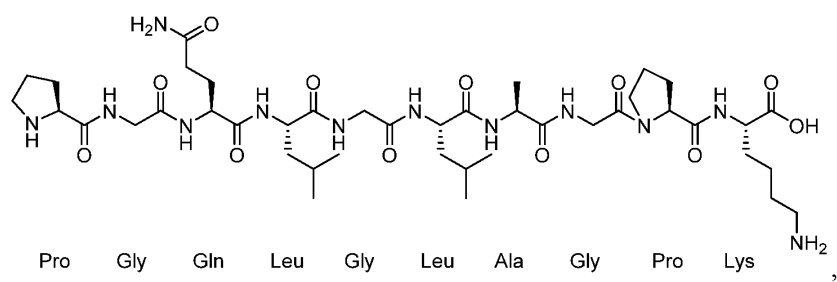
Hyp Gly Gln Leu Gly Leu Ala Gly Pro Lys
(2S,4S)

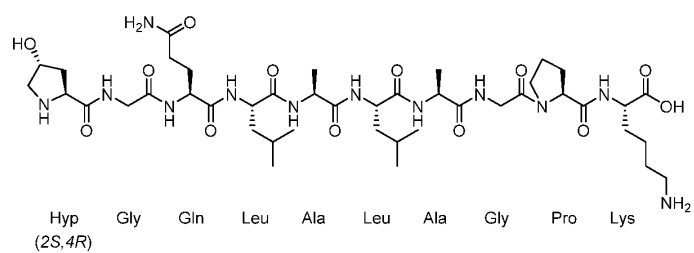
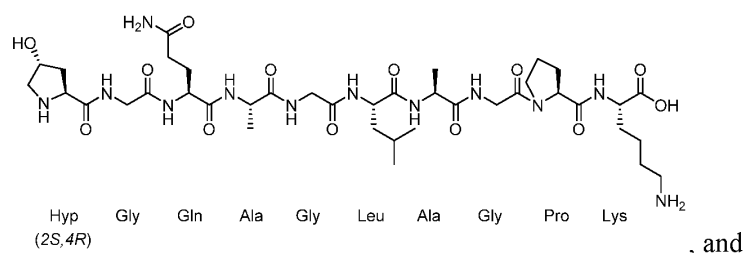
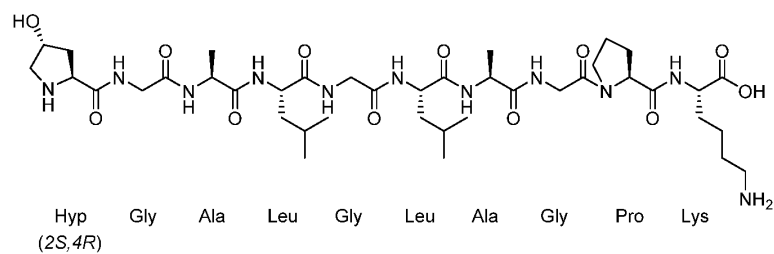
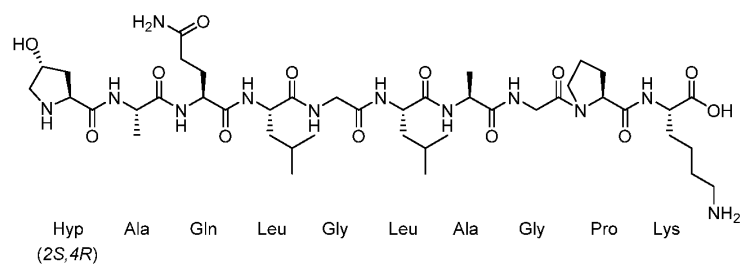
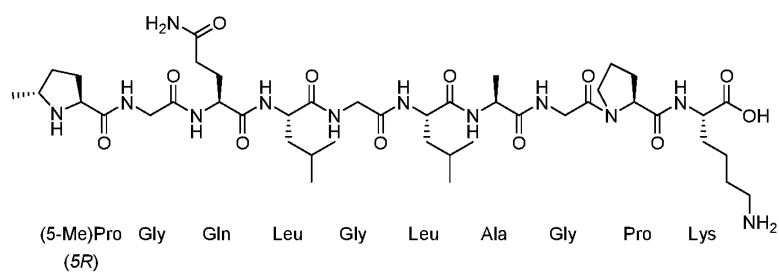


(4-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys

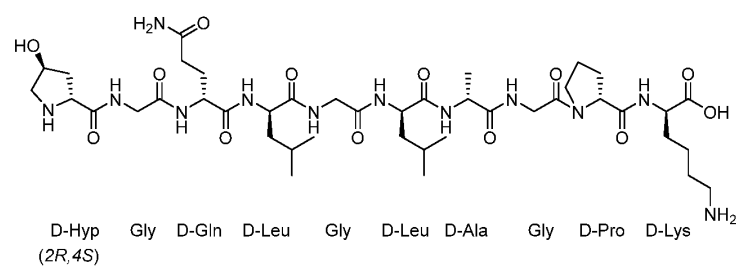
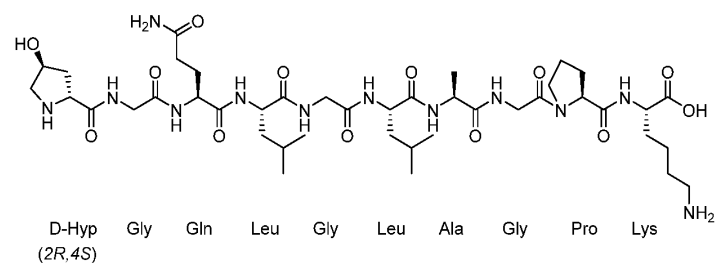
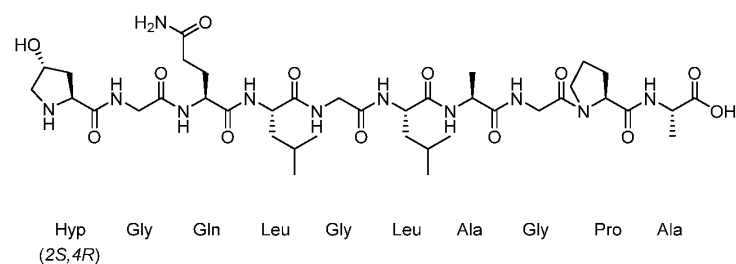
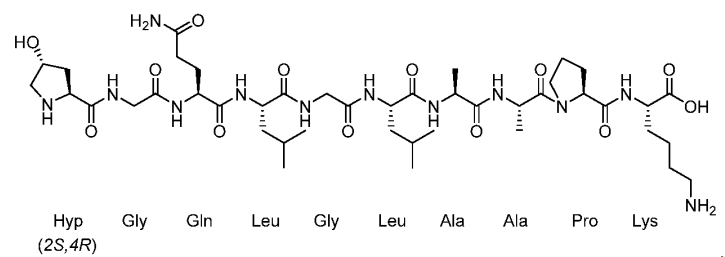
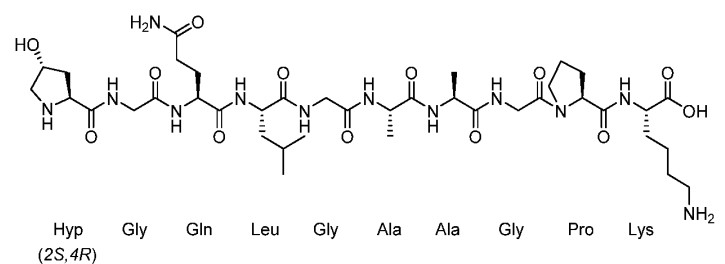


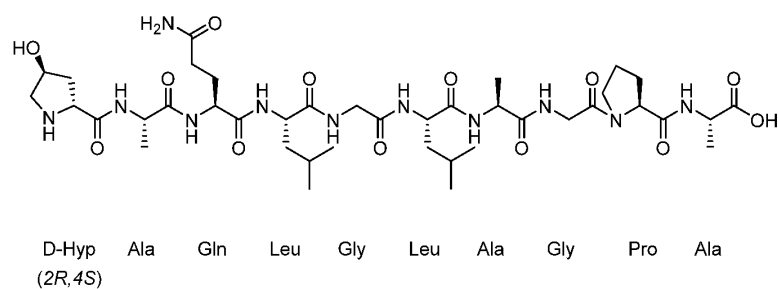
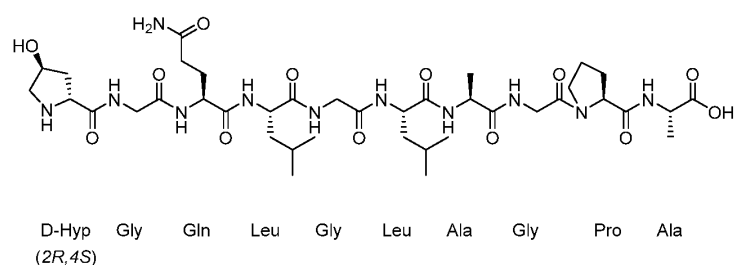
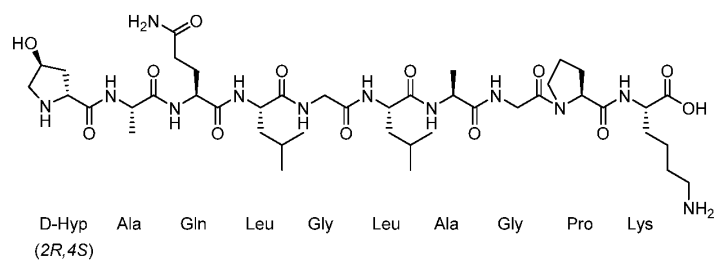
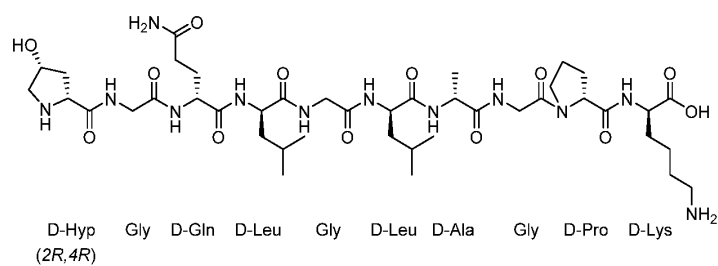
(5-oxo)Pro Gly Gln Leu Gly Leu Ala Gly Pro Lys



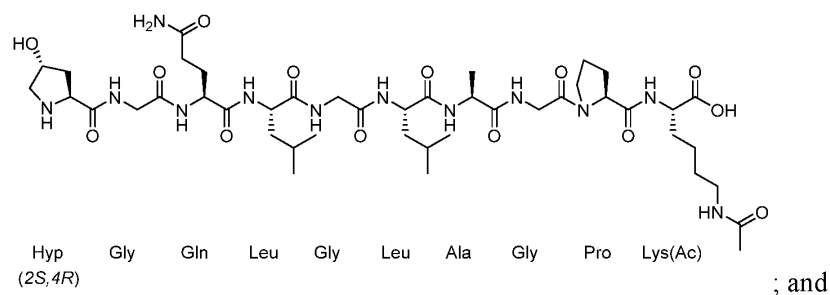


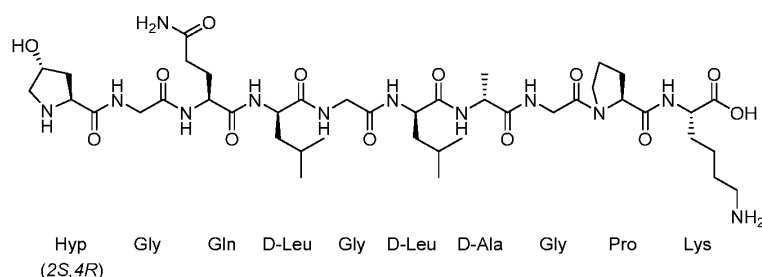
66. The salt of claim 1, wherein the compound is selected from the following:



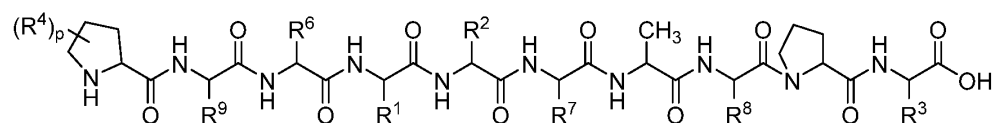


67. The salt of claim 1, wherein the compound is selected from the following:





68. A compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

wherein at least one of:

(a) at least one of R^1 , R^2 , and R^3 is substituted or unsubstituted (C_2 - C_{10})haloalkyl;

(b) at least one of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl is substituted with one or more substituents selected from $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, -

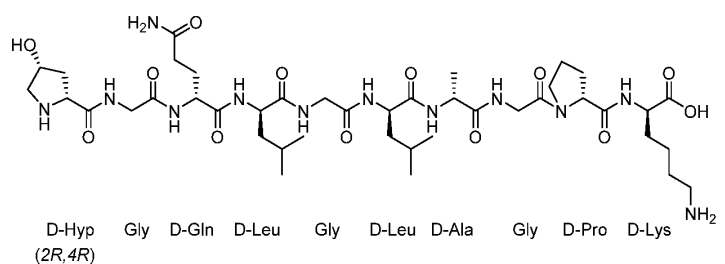
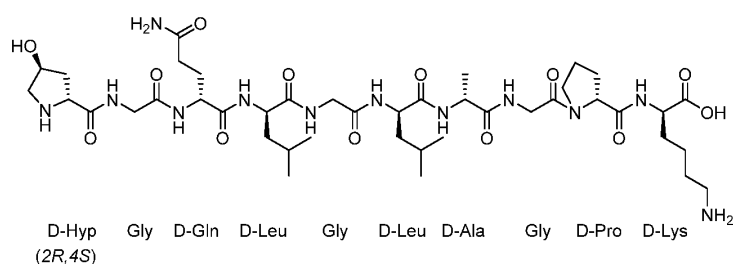
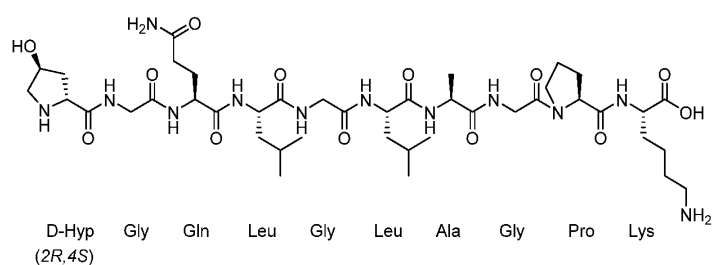
(alkylene)-C(=O)OR^a, -C(=S)OR^a, -C(=O)SR^a, -C(=S)SR^a, -(alkylene)-C(=O)N(R^a)₂, -C(=S)N(R^a)₂, and -C(-NR^a)N(R^a)₂; and

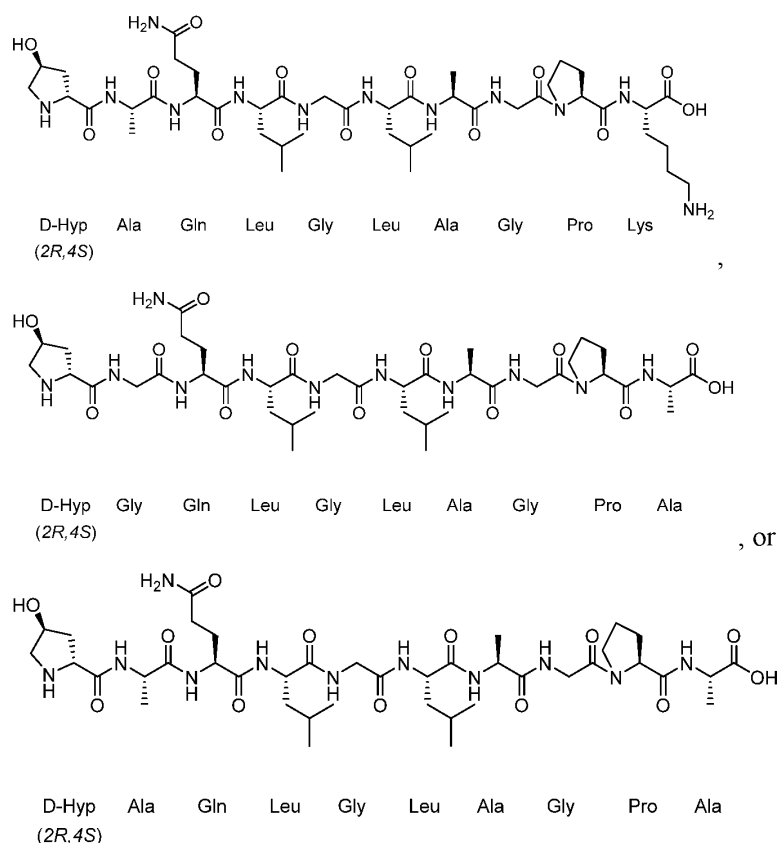
at least one occurrence of R^a or R^c is heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl;

- (c) the compound comprises at least one D-amino acid residue; or
- (d) at least two occurrences of R^a;
at least two occurrences of R^c; or
at least one occurrence of R^a and at least one occurrence of R^c; and
at least one occurrence of R^a and/or R^c differs from the other occurrences;

and

wherein the compound is not:





69. The compound of claim 68, wherein at least one of R^1 , R^2 , and R^3 is substituted or unsubstituted (C_2-C_{10}) haloalkyl.

70. The compound of claim 68 or 69, wherein at least one of alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl is substituted with one or more substituents selected from $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$; and at least one occurrence of R^a or R^c is heterocyclylalkyl, cycloalkyl, or (cycloalkyl)alkyl.

71. The compound of any one of claims 68-70, wherein the compound comprises at least one D-amino acid residue.

72. The compound of any one of claims 68-71, wherein the compound has:
 at least two occurrences of R^a ;
 at least two occurrences of R^c ; or
 at least one occurrence of R^a and at least one occurrence of R^c ; and
 at least one occurrence of R^a and/or R^c differs from the other occurrences.

73. The compound of any one of claims 68-72, wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, $-OR^b$, hydroxyalkyl, $-CH_2OR^b$, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclalkyl;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl.

74. The compound of any one of claims 68-73, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclalkyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, $-CN$, $-NO_2$, $=N-OH$, $-N_3$, $-R^a$, $-OR^a$, $-SR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $=NR^a$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-S(=O)_2R^c$, $-OS(=O)_2OR^a$, $-S(=O)_2OR^a$, $-S(=O)_2N(R^a)_2$, $-S(=O)R^c$, $-OP(=O)(OR^a)_2$, $-(alkylene)-C(=O)R^c$, $-C(=S)R^c$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, $-C(=S)OR^a$, $-C(=O)SR^a$, $-C(=S)SR^a$, $-(alkylene)-C(=O)N(R^a)_2$, $-C(=S)N(R^a)_2$, and $-C(-NR^a)N(R^a)_2$; and

R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

75. The compound of any one of claims 68-74, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclalkyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, $-R^a$, $-OR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $-NHC(=O)R^c$,

-C(=O)R^c, -C(=O)N(R^a)₂, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, and -(alkylene)-C(=O)N(R^a)₂; and

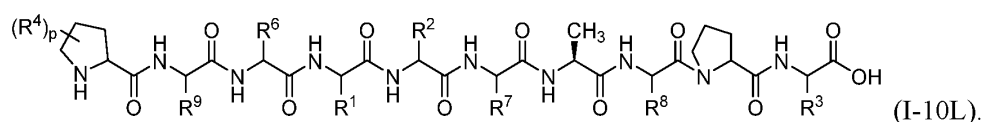
R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

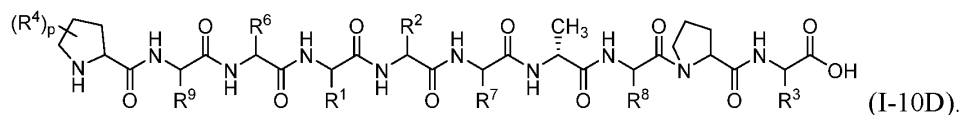
76. The compound of claim 75, wherein R^a, independently for each occurrence, is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl; and

R^c, independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl.

77. The compound of any one of claims 68-76, having the structure of formula (I-10L):



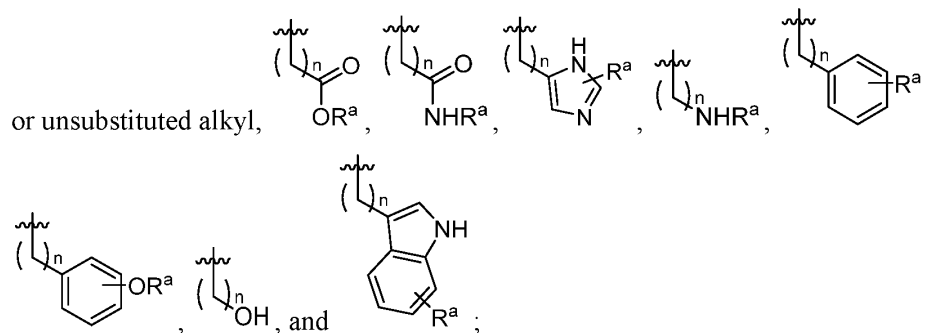
78. The compound of any one of claims 68-76, having the structure of formula (I-10D):



79. The compound of any one of claims 68-78, wherein R¹ is substituted or unsubstituted (C₂-C₁₀)haloalkyl.

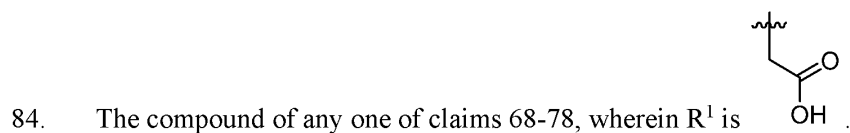
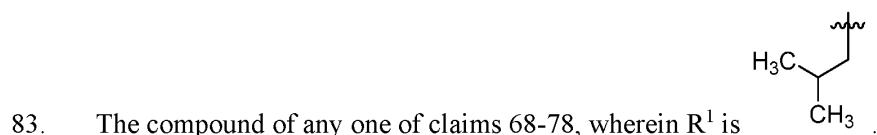
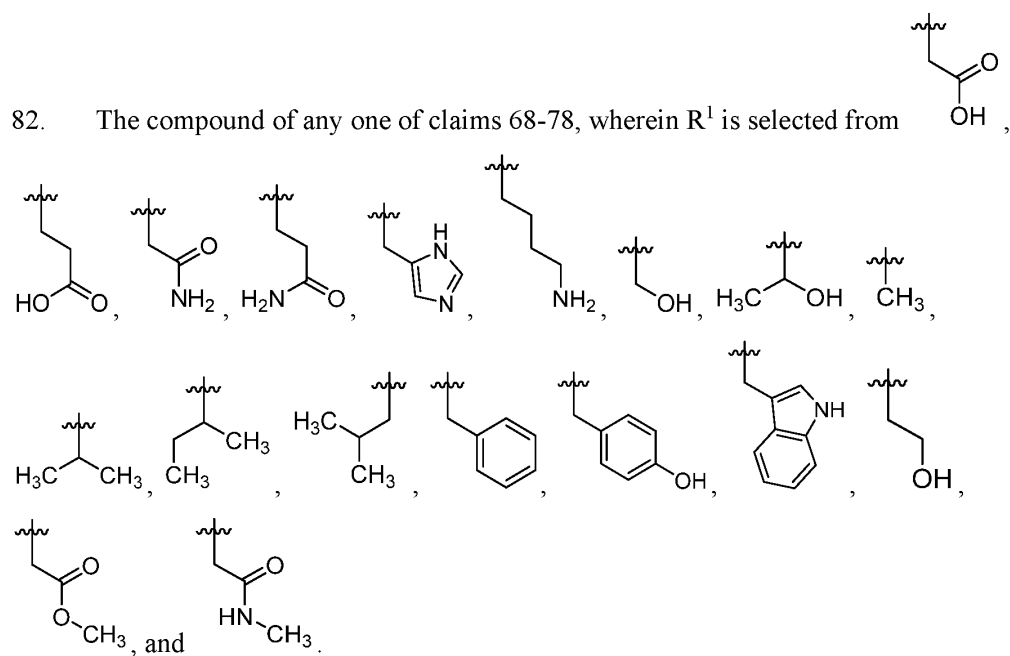
80. The compound of any one of claims 68-78, wherein R¹ is substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

81. The compound of any one of claims 68-78, wherein R^1 is selected from substituted

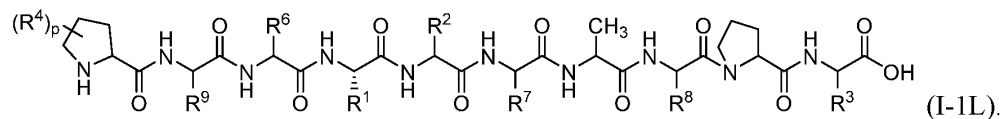


R^a is hydrogen or alkyl; and

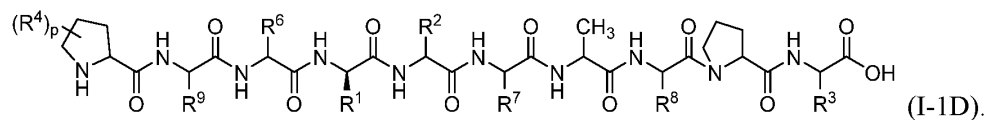
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.



85. The compound of any one of claims 68-84, having the structure of formula (I-1L)



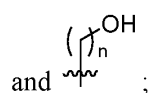
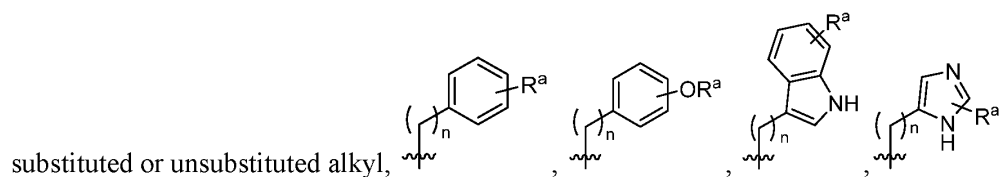
86. The compound of any one of claims 68-84, having the structure of formula (I-1D)



87. The compound of any one of claims 68-86, wherein R^2 is substituted or unsubstituted (C_2-C_{10}) haloalkyl.

88. The compound of any one of claims 68-86, wherein R^2 is H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

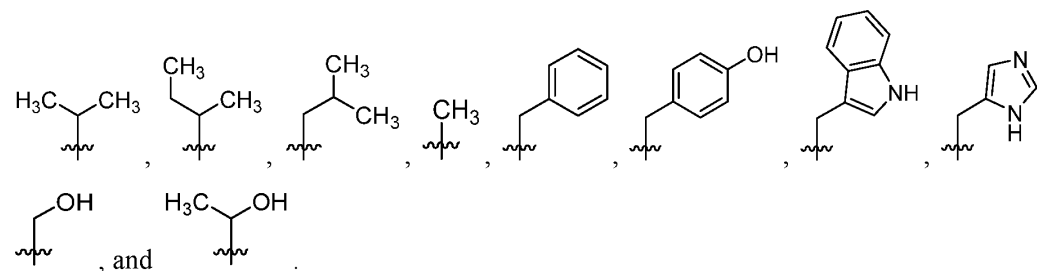
89. The compound of any one of claims 68-86, wherein R^2 is selected from hydrogen,



R^a is hydrogen or alkyl; and

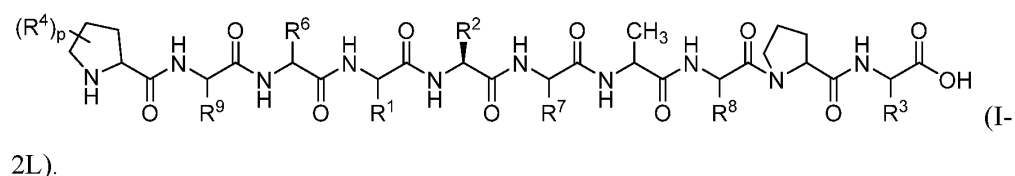
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

90. The compound of any one of claims 68-86, wherein R^2 is selected from ,

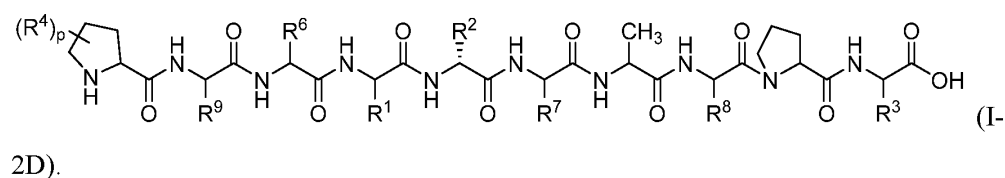


91. The compound of any one of claims 68-86, wherein R^2 is hydrogen.

92. The compound of any one of claims 68-90, having the structure of formula (I-2L):



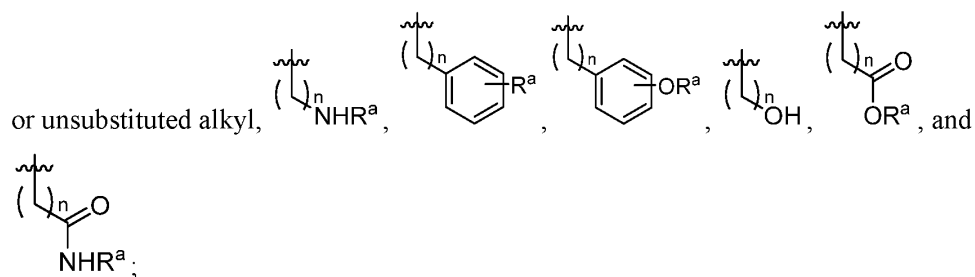
93. The compound of any one of claims 68-90, having the structure of formula (I-2D):



94. The compound of any one of claims 68-93, wherein R^3 is substituted or unsubstituted (C_2 - C_{10})haloalkyl.

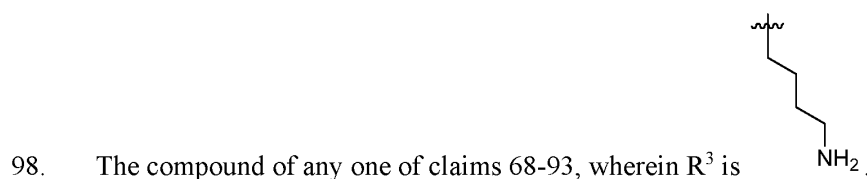
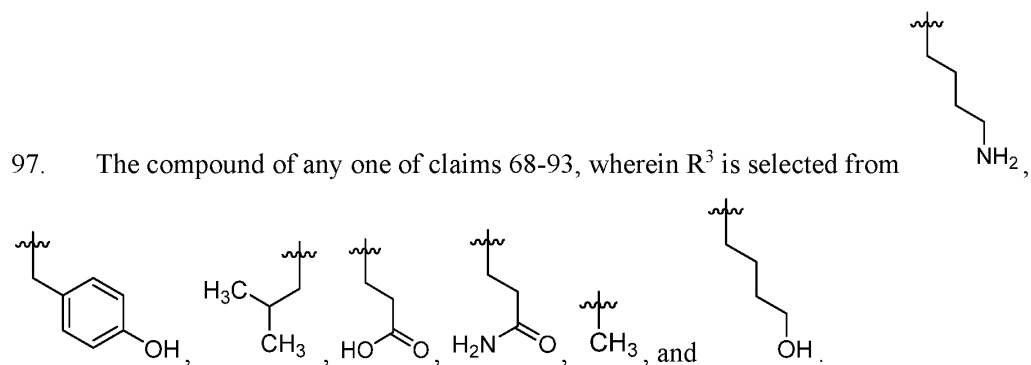
95. The compound of any one of claims 68-93, wherein R^3 is substituted or unsubstituted alkyl or arylalkyl.

96. The compound of any one of claims 68-93, wherein R^3 is selected from substituted

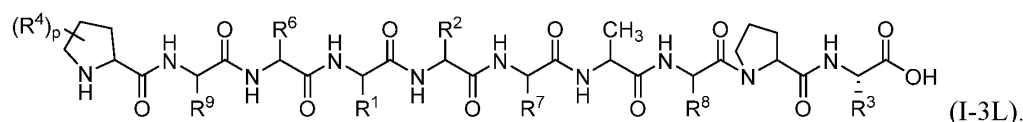


R^a is hydrogen or alkyl; and

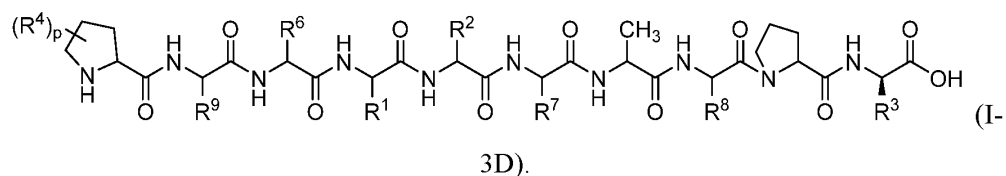
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.



99. The compound of any one of claims 68-98, having the structure of formula (I-3L):



100. The compound of any one of claims 68-98, having the structure of formula (I-3D):



101. The compound of any one of claims 68-100, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, $-OR^b$, $-\text{CH}_2OR^b$, halo, hydroxyl, and hydroxyalkyl.

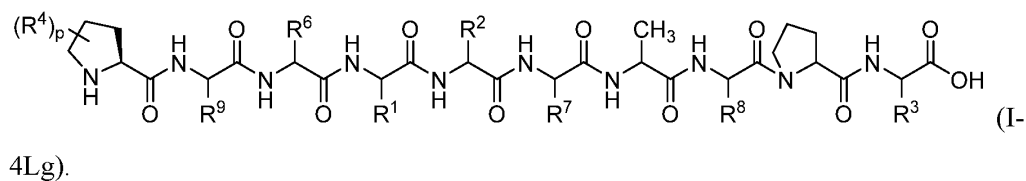
102. The compound of any one of claims 68-100, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from $-\text{CH}_3$, halo, hydroxyl, and hydroxyalkyl.

103. The compound of claim 102, wherein R^4 is hydroxyl.

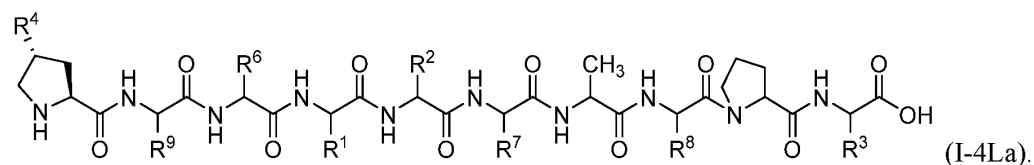
104. The compound of claim 102, wherein R⁴ is -CH₃.

105. The compound of any one of claims 101-104, wherein p is 1.

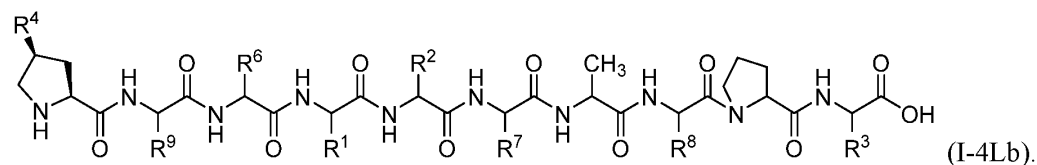
106. The compound of any one of claims 68-105, having the structure of formula (I-4Lg):



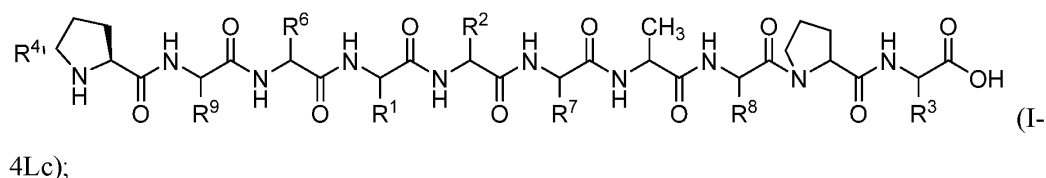
107. The compound of any one of claims 68-106, having the structure of formula (I-4La):



108. The compound of any one of claims 68-106, having the structure of formula (I-4Lb):

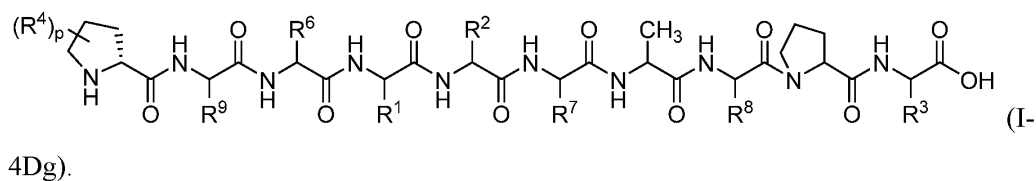


109. The compound of any one of claims 68-102 and 104-106, having the structure of formula (I-4Lc):

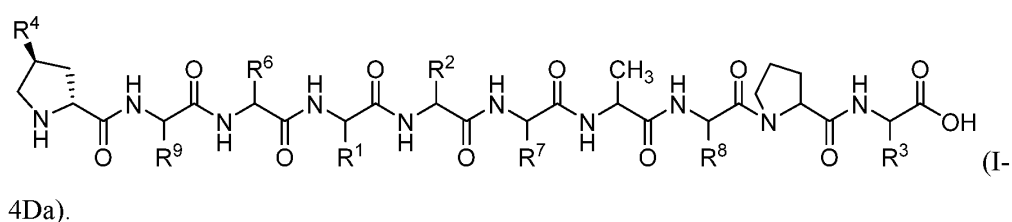


provided that R⁴ is not hydroxyl.

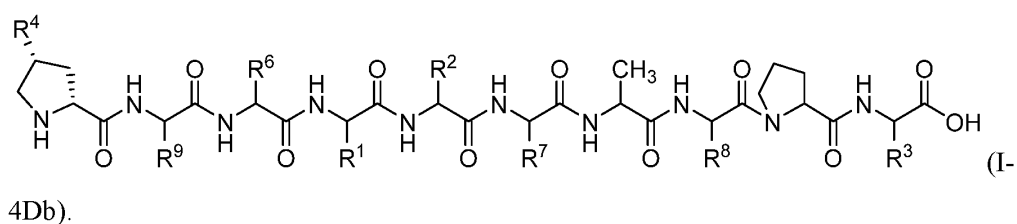
110. The compound of any one of claims 68-105, having the structure of formula (I-4Dg):



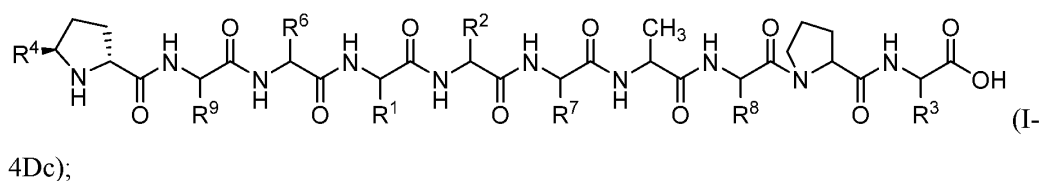
111. The compound of any one of claims 68-105 and 110, having the structure of formula (I-4Da):



112. The compound of any one of claims 68-105 and 110, having the structure of formula (I-4Db):



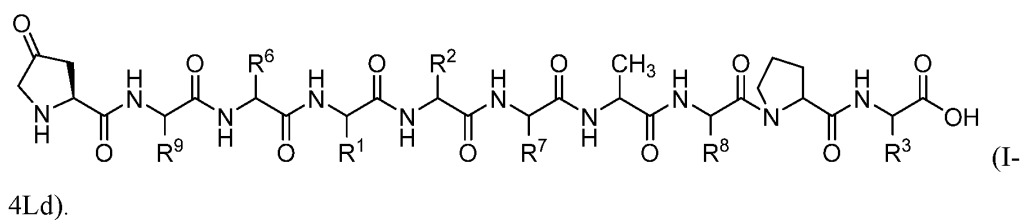
113. The compound of any one of claims 68-102, 104-106, and 110, having the structure of formula (I-4Dc):



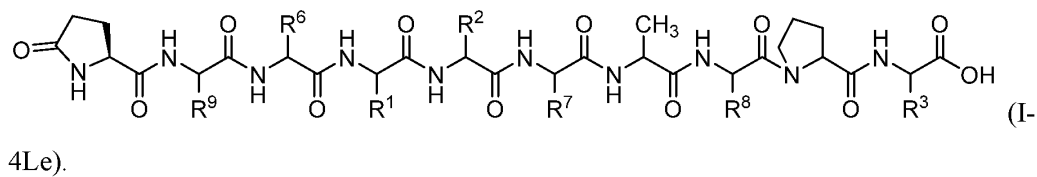
provided that R⁴ is not hydroxyl.

114. The compound of any one of claims 68-98, wherein R⁴ is oxo.

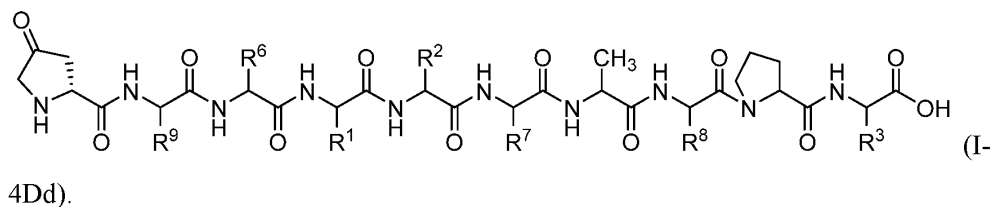
115. The compound of claim 114, having the structure of formula (I-4Ld):



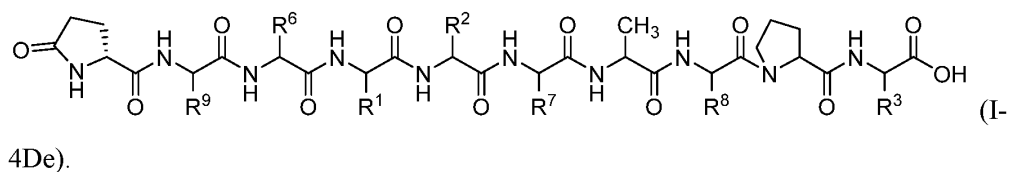
116. The compound of claim 114, having the structure of formula (I-4Le):



117. The compound of claim 114, having the structure of formula (I-4Dd):



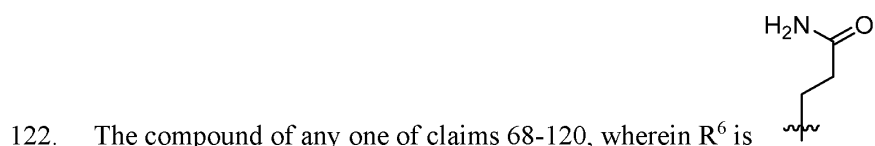
118. The compound of claim 114, having the structure of formula (I-4De):



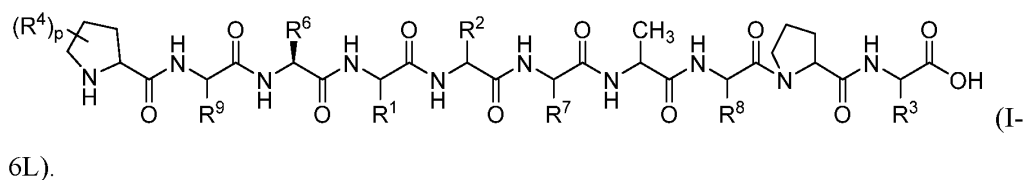
119. The compound of any one of claims 68-118, wherein R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$.

120. The compound of any one of claims 68-119, wherein R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$.

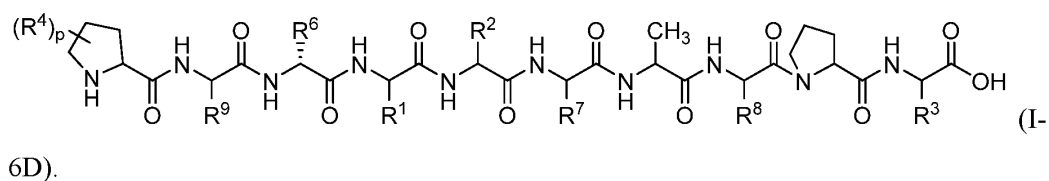
121. The compound of any one of claims 68-120, wherein R^6 is $-CH_3$.



123. The compound of any one of claims 68-122, having the structure of formula (I-6L):

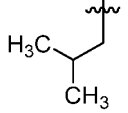


124. The compound of any one of claims 68-122, having the structure of formula (I-6D):

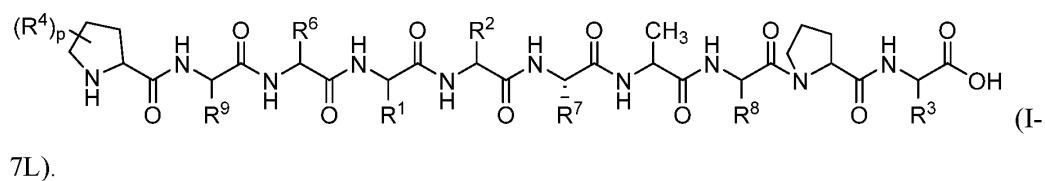


125. The compound of any one of claims 68-124, wherein R^7 is (C_1-C_{10}) alkyl.

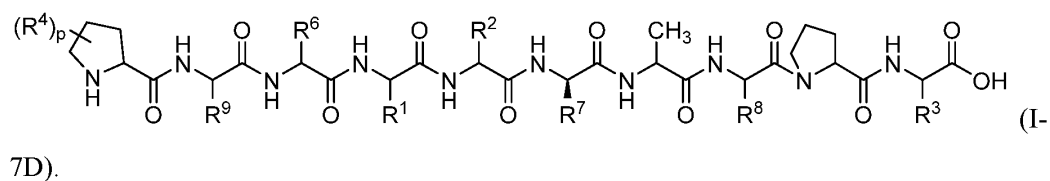
126. The compound of any one of claims 68-125, wherein R^7 is .

127. The compound of any one of claims 68-125, wherein R^7 is .

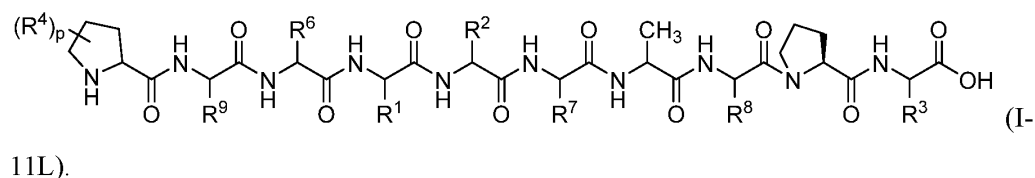
128. The compound of any one of claims 68-127, having the structure of formula (I-7L):



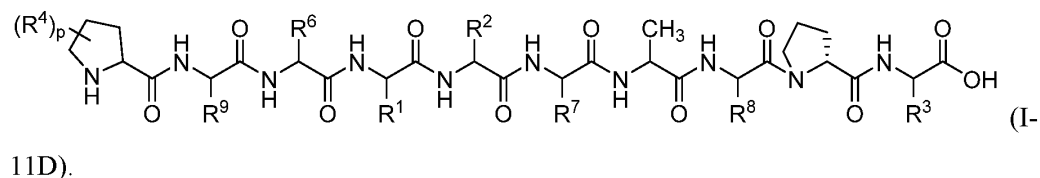
129. The compound of any one of claims 68-127, having the structure of formula (I-7D):



130. The compound of any one of claims 68-129, having the structure of formula (I-11L):



131. The compound of any one of claims 68-129, having the structure of formula (I-11D):



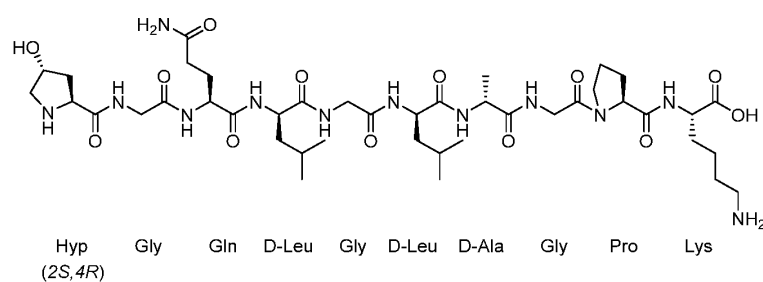
132. The compound of any one of claims 68-131, wherein R⁸ is –CH₃ or –H.

133. The compound of any one of claims 68-131, wherein R⁸ is –H.

134. The compound of any one of claims 68-133, wherein R⁹ is –CH₃ or –H.

135. The compound of any one of claims 68-133, wherein R⁹ is –H.

136. The compound of claim 68, wherein the compound is:



, or a pharmaceutically

acceptable salt thereof.

137. The compound of claim 68, wherein the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Xaa-Gly-Leu-Ala-Gly-Pro-Lys;

or a pharmaceutically acceptable salt and/or stereoisomer thereof;

wherein Xaa is selected from Glu, Asn, Gln, His, Lys, Ser, Thr, Ala, Val, Ile, Leu, Phe, Tyr,

Trp, homo-Ser, Asp(Me), and Asn(Me); and

at least one amino acid residue in the peptide is a D-amino acid residue.

138. The compound of claim 137, wherein at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

139. The compound of claim 68, wherein the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Asp-Xaa-Leu-Ala-Gly-Pro-Lys;

or a pharmaceutically acceptable salt and/or stereoisomer thereof;

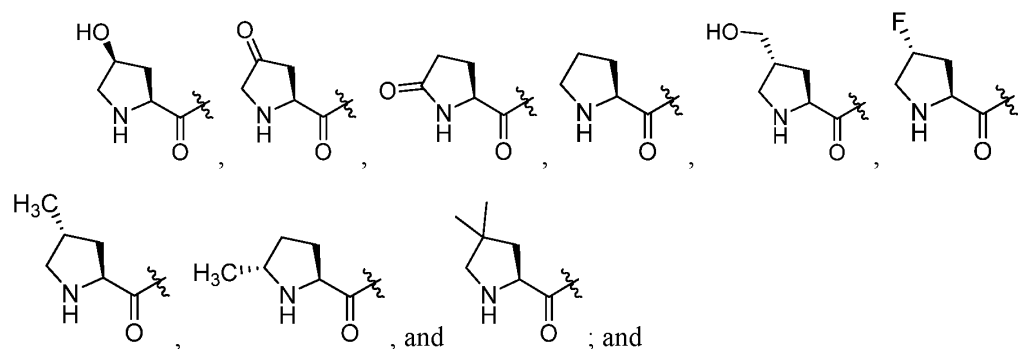
wherein Xaa is selected from Val, Ile, Leu, Ala, Phe, Tyr, Trp, Ser, Thr, and (N-Me)Gly;
and
at least one amino acid residue in the peptide is a D-amino acid residue.

140. The compound of claim 139, wherein at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

141. The compound of claim 68, wherein the compound is a peptide having an amino acid sequence represented by HyP-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Xaa;
or a pharmaceutically acceptable salt and/or stereoisomer thereof;
wherein Xaa is selected from Tyr, Leu, Glu, Gln, Ala, and Nle(6-OH); and
at least one amino acid residue in the peptide is a D-amino acid residue.

142. The compound of claim 141, wherein at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

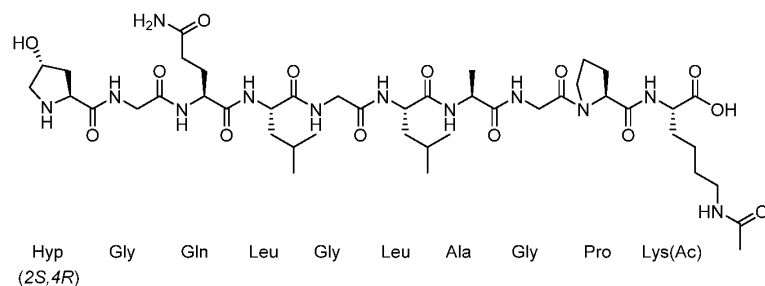
143. The compound of claim 68, wherein the compound is a peptide having an amino acid sequence represented by Xaa-Gly-Gln-Leu-Gly-Leu-Ala-Gly-Pro-Lys;
or a pharmaceutically acceptable salt and/or stereoisomer thereof;
wherein Xaa is selected from:



at least one amino acid residue in the peptide is a D-amino acid residue.

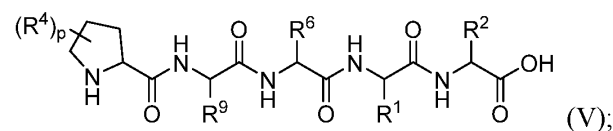
144. The compound of claim 143, wherein at least two, at least three, at least four, at least five, at least six, or at least seven amino acid residues in the peptide are D-amino acid residues.

145. A compound having the following structure:



; or a pharmaceutically acceptable salt thereof.

146. A compound represented by Formula (V):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

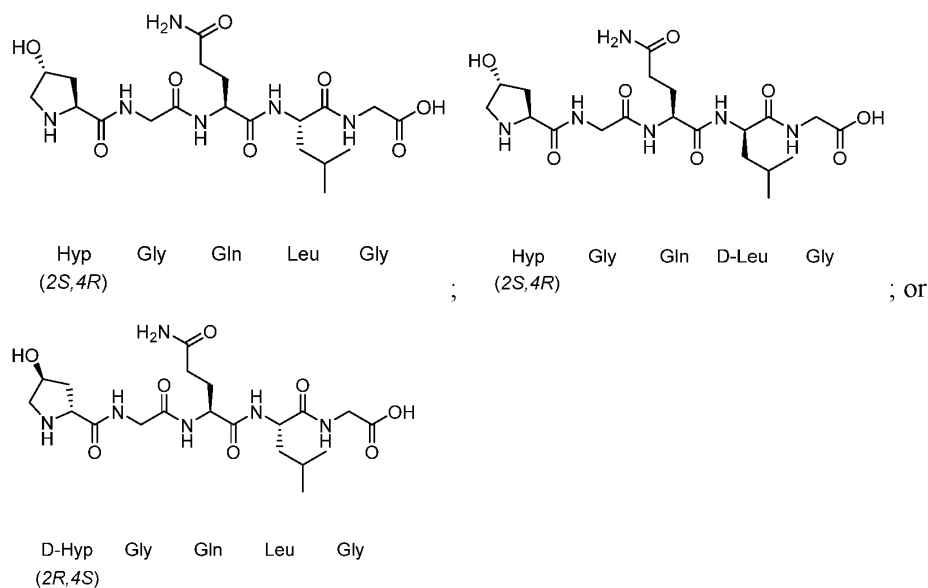
R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



147. The compound of claim 146, wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

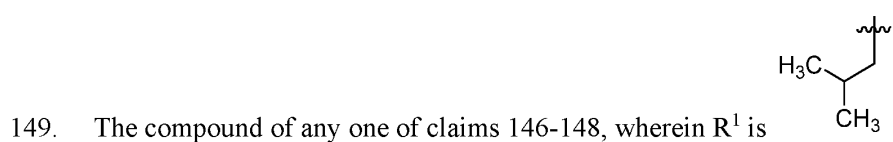
R^4 for each occurrence is hydroxyl;

p is 1;

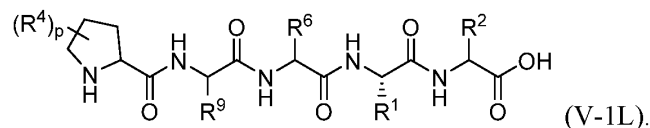
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

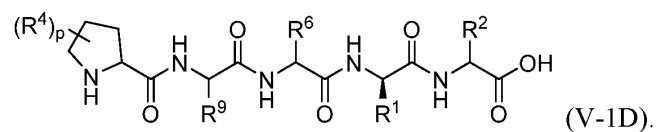
148. The compound of claim 146 or 147, wherein R^1 is substituted or unsubstituted alkyl.



150. The compound of any one of claims 146-149, having the structure of formula (V-1L)



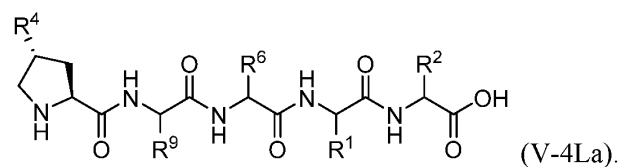
151. The compound of any one of claims 146-149, having the structure of formula (V-1D)



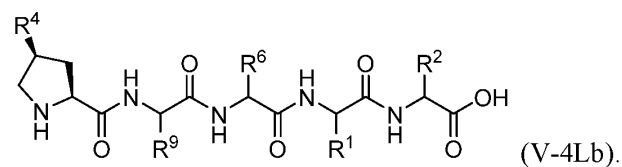
152. The compound of any one of claims 146-151, wherein R^2 is H.

153. The compound of any one of claims 146-152, wherein p is 1 and R^4 is hydroxyl.

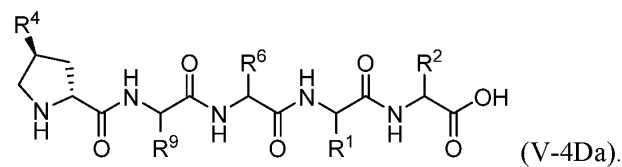
154. The compound of any one of claims 146-153, having the structure of formula (V-4La):



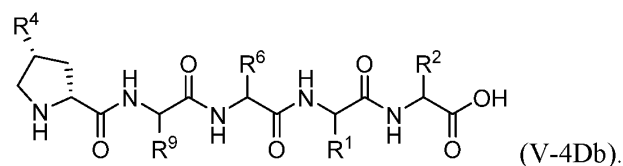
155. The compound of any one of claims 146-153, having the structure of formula (V-4Lb):



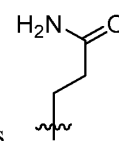
156. The compound of any one of claims 146-153, having the structure of formula (V-4Da):



157. The compound of any one of claims 146-153, having the structure of formula (V-4Db):

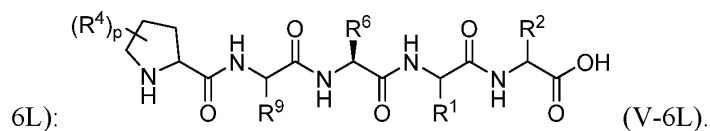


158. The compound of any one of claims 146-157, wherein R^6 is alkyl substituted with one occurrence of $-C(=O)NH_2$.

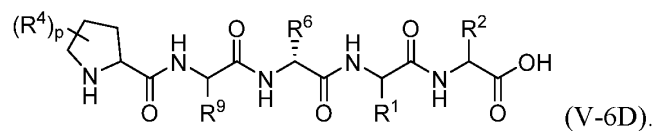


159. The compound of any one of claims 146-158, wherein R^6 is

160. The compound of any one of claims 146-159, having the structure of formula (V-

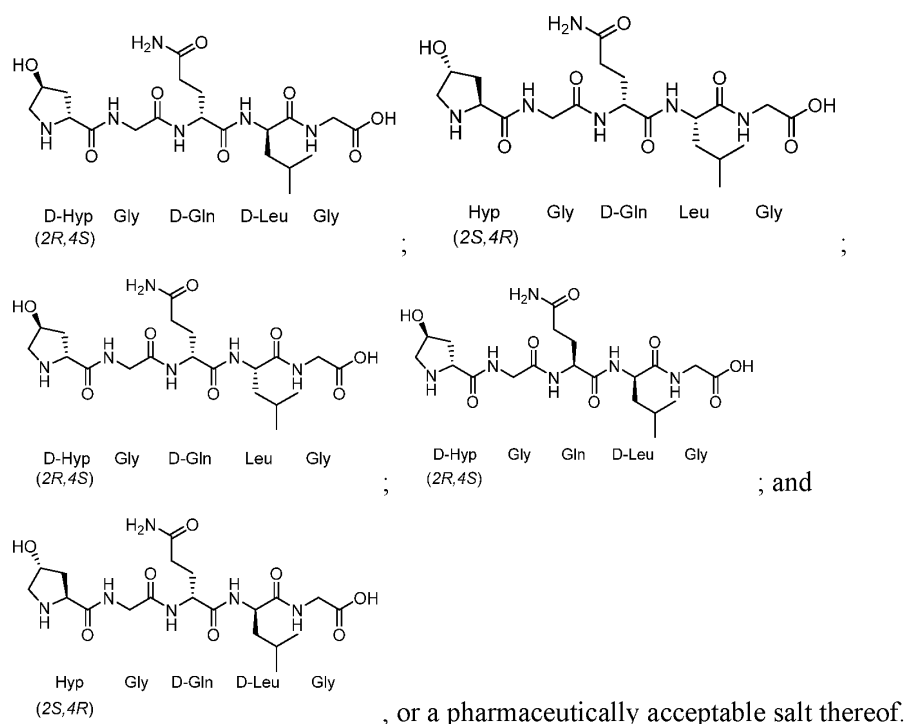


161. The compound of any one of claims 146-159, having the structure of formula (V-6D):

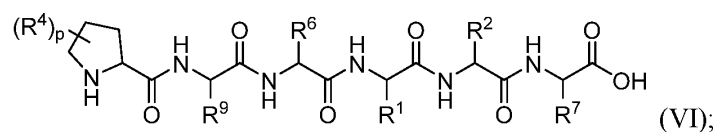


162. The compound of any one of claims 146-161, wherein R^9 is $-H$.

163. The compound of claim 146, selected from the following:



164. A compound represented by Formula (VI):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclylalkyl

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

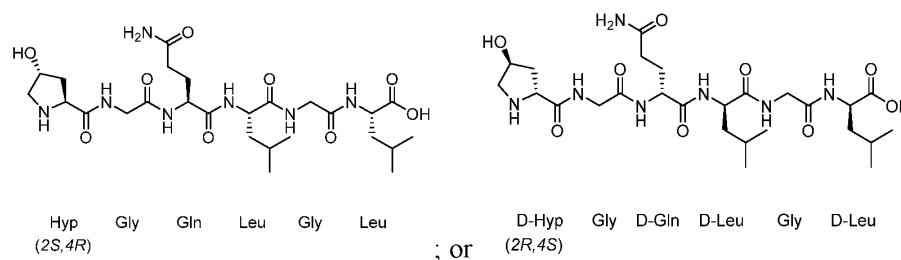
p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 is hydrogen or alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



165. The compound of claim 164, wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

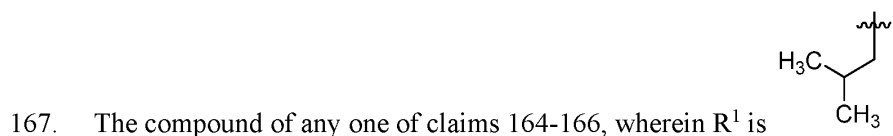
R^4 for each occurrence is hydroxyl;

p is 1;

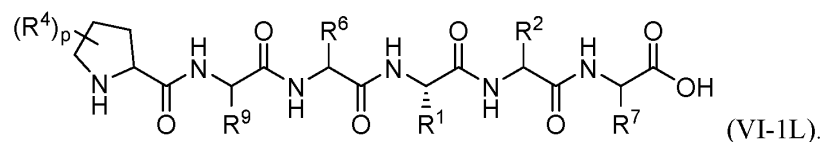
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

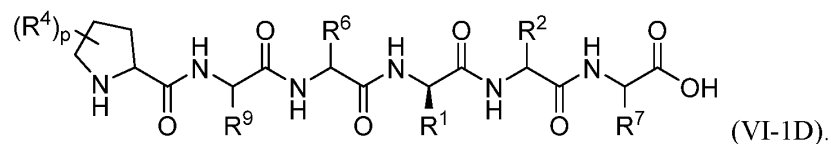
166. The compound of claim 164 or 165, wherein R^1 is substituted or unsubstituted alkyl.



168. The compound of any one of claims 164-167, having the structure of formula (VI-1L)



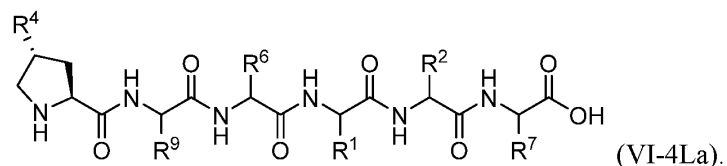
169. The compound of any one of claims 164-167, having the structure of formula (VI-1D)



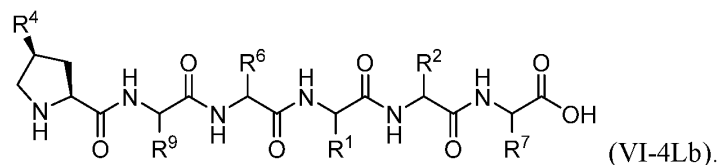
170. The compound of any one of claims 164-169, wherein R^2 is H.

171. The compound of any one of claims 164-170, wherein p is 1 and R⁴ is hydroxyl.

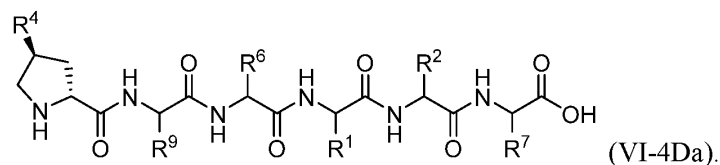
172. The compound of any one of claims 164-171, having the structure of formula (VI-4La):



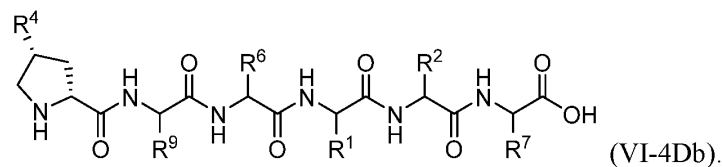
173. The compound of any one of claims 164-171, having the structure of formula (VI-4Lb):



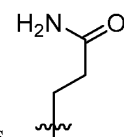
174. The compound of any one of claims 164-171, having the structure of formula (VI-4Da):



175. The compound of any one of claims 164-171, having the structure of formula (VI-4Db):

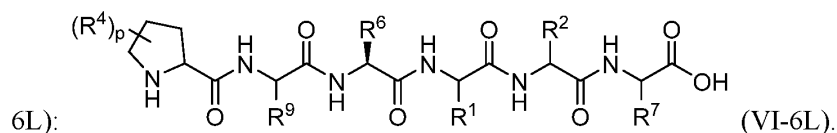


176. The compound of any one of claims 164-175, wherein R⁶ is alkyl substituted with one occurrence of -C(=O)NH₂.

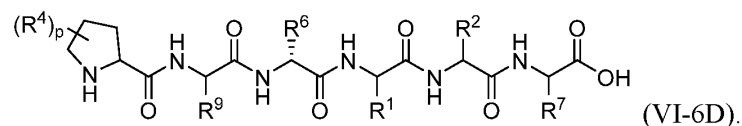


177. The compound of any one of claims 164-176, wherein R^6 is

178. The compound of any one of claims 164-177, having the structure of formula (VI-



179. The compound of any one of claims 164-177, having the structure of formula (VI-6D):



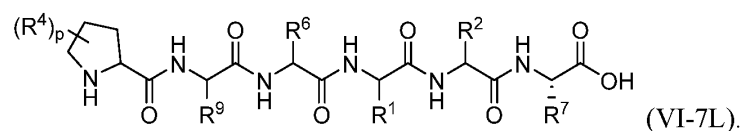
180. The compound of any one of claims 164-179, wherein R^9 is $-H$.

181. The compound of any one of claims 164-180, wherein R^7 is (C_1-C_{10}) alkyl.

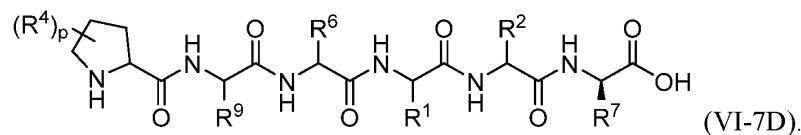
182. The compound of any one of claims 164-180, wherein R^7 is .

183. The compound of any one of claims 164-180, wherein R^7 is .

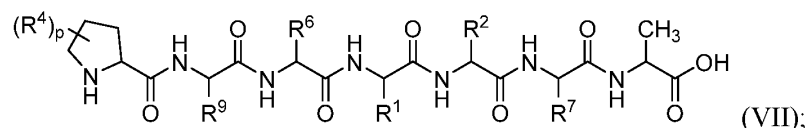
184. The compound of any one of claims 164-183, having the structure of formula (VI-7L):



185. The compound of any one of claims 164-183, having the structure of formula (VI-7D):



186. A compound represented by Formula (VII):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

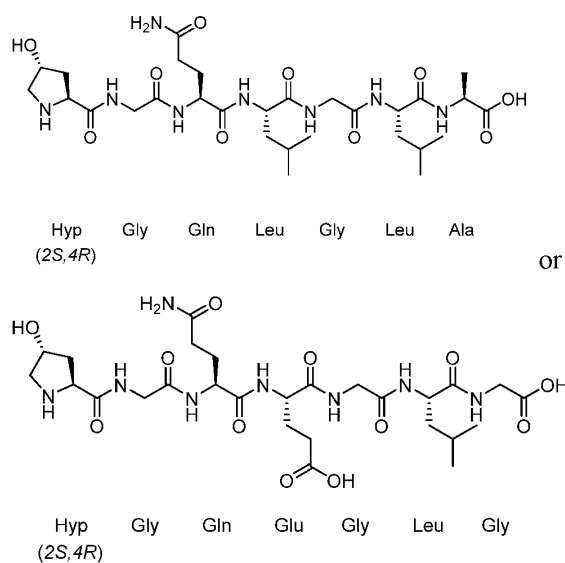
p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 is hydrogen or alkyl; and

R^9 is hydrogen or alkyl;

wherein the compound is not:



187. The compound of claim 186, wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

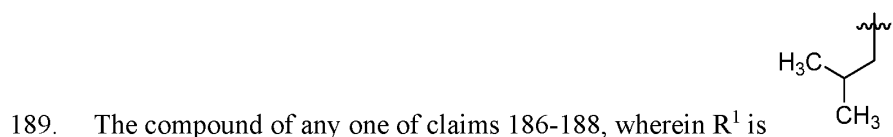
R^4 for each occurrence is hydroxyl;

p is 1;

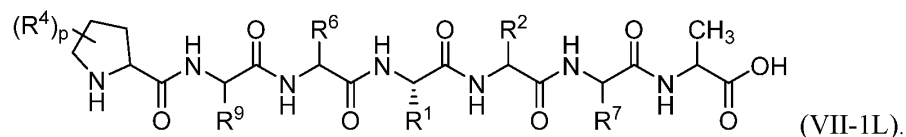
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

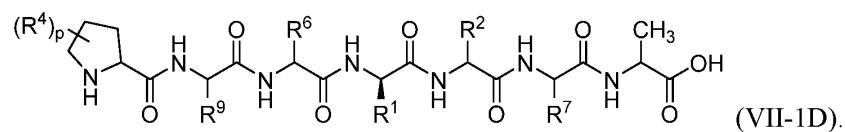
188. The compound of claim 186 or 187, wherein R^1 is substituted or unsubstituted alkyl.



190. The compound of any one of claims 186-189, having the structure of formula (VII-1L)



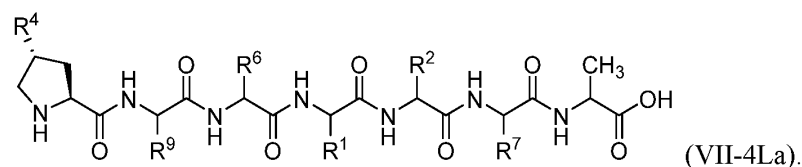
191. The compound of any one of claims 186-189, having the structure of formula (VII-1D)



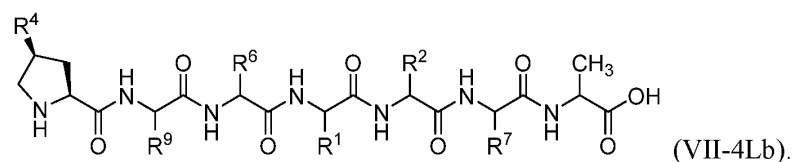
192. The compound of any one of claims 186-191, wherein R^2 is H.

193. The compound of any one of claims 186-192, wherein p is 1 and R^4 is hydroxyl.

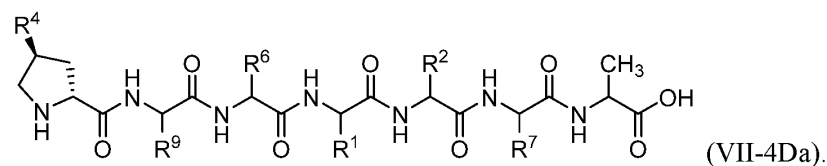
194. The compound of any one of claims 186-193, having the structure of formula (VII-4La):



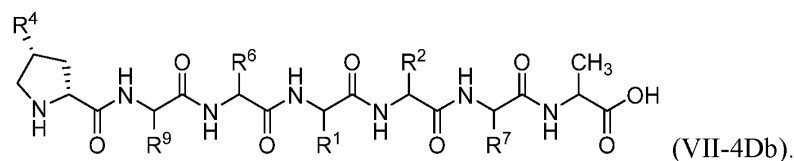
195. The compound of any one of claims 186-193, having the structure of formula (VII-4Lb):



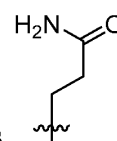
196. The compound of any one of claims 186-193, having the structure of formula (VII-4Da):



197. The compound of any one of claims 186-193, having the structure of formula (VII-4Db):

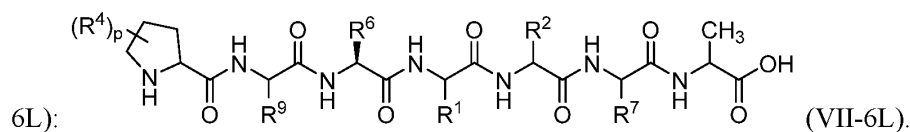


198. The compound of any one of claims 186-197, wherein R⁶ is alkyl substituted with one occurrence of -C(=O)NH₂.

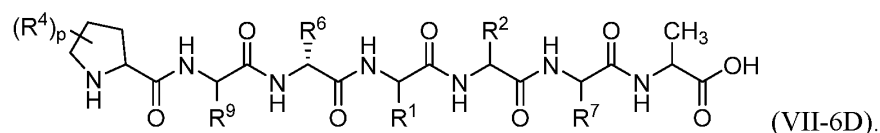


199. The compound of any one of claims 186-198, wherein R⁶ is

200. The compound of any one of claims 186-199, having the structure of formula (VII-



201. The compound of any one of claims 186-199, having the structure of formula (VII-6D):

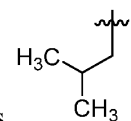


202. The compound of any one of claims 186-201, wherein R⁹ is -H.

203. The compound of any one of claims 186-202, wherein R⁷ is (C₁-C₁₀)alkyl.

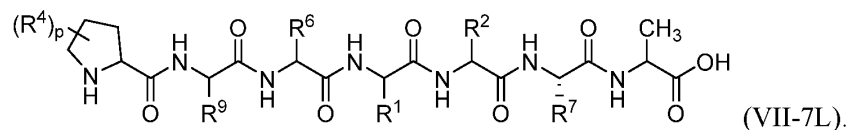
204. The compound of any one of claims 186-203, wherein R⁷ is



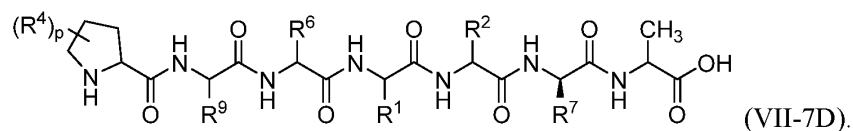


205. The compound of any one of claims 186-203, wherein R^7 is

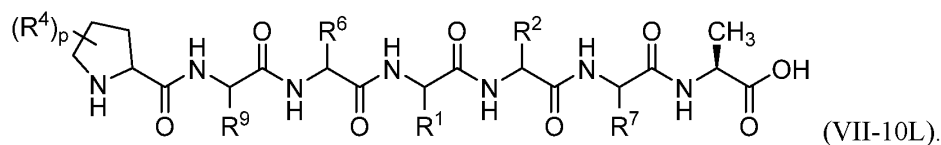
206. The compound of any one of claims 186-205, having the structure of formula (VII-7L):



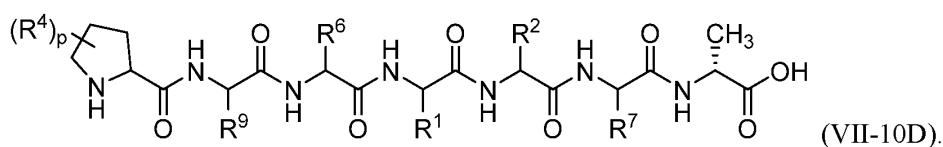
207. The compound of any one of claims 186-205, having the structure of formula (VII-7D):



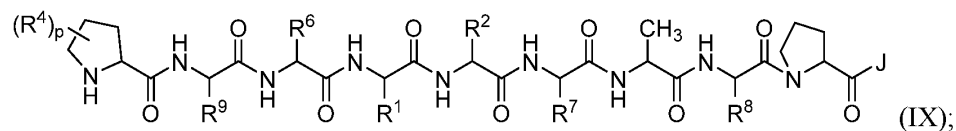
208. The compound of any one of claims 186-207, having the structure of formula (VII-10L):



209. The compound of any one of claims 186-207, having the structure of formula (VII-10D):



210. A compound represented by Formula (IX):



or a pharmaceutically acceptable salt thereof;

wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R^6 is hydrogen or substituted or unsubstituted alkyl;

R^7 , R^8 , and R^9 are each independently hydrogen or alkyl;

J is OH or $-NR^xR^y$; and

R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

211. The compound of claim 210, wherein:

R^1 and R^2 are each independently H or substituted or unsubstituted alkyl;

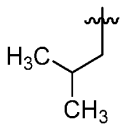
R^4 for each occurrence is hydroxyl;

p is 1;

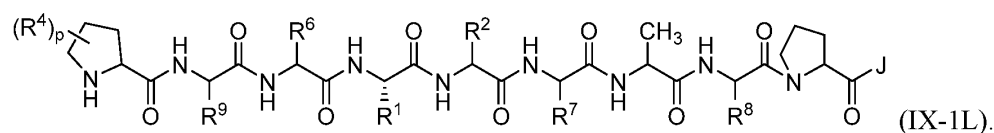
R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$; and

R^9 is hydrogen.

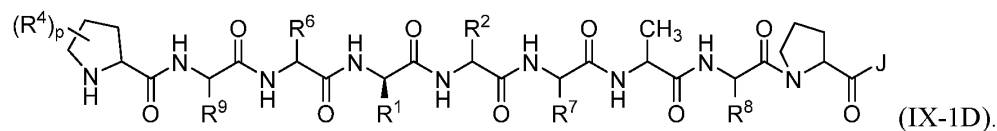
212. The compound of claim 210 or 211, wherein R^1 is substituted or unsubstituted alkyl.

213. The compound of any one of claims 210-212, wherein R^1 is .

214. The compound of any one of claims 210-213, having the structure of formula (IX-1L)



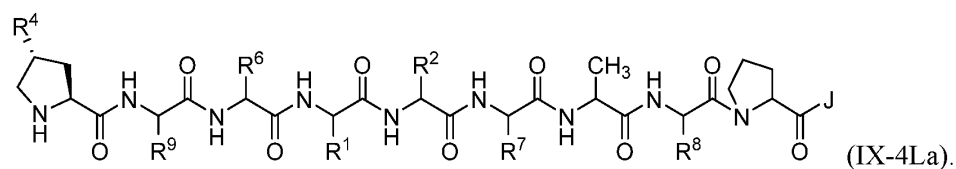
215. The compound of any one of claims 210-213, having the structure of formula (IX-1D)



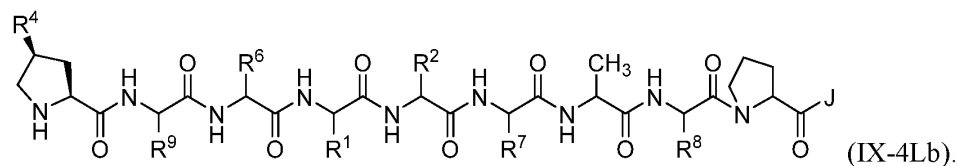
216. The compound of any one of claims 210-215, wherein R^2 is H.

217. The compound of any one of claims 210-216, wherein p is 1 and R^4 is hydroxyl.

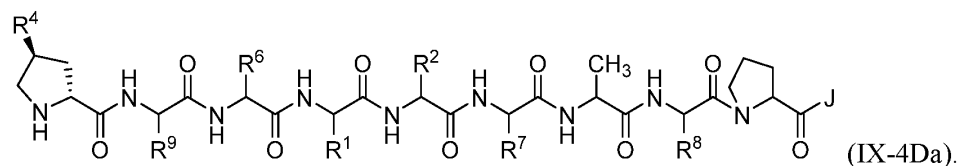
218. The compound of any one of claims 210-217, having the structure of formula (IX-4La):



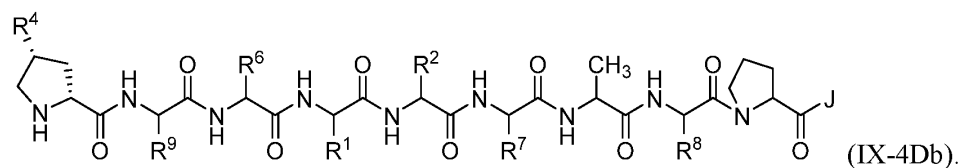
219. The compound of any one of claims 210-217, having the structure of formula (IX-4Lb):



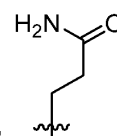
220. The compound of any one of claims 210-217, having the structure of formula (IX-4Da):



221. The compound of any one of claims 210-217, having the structure of formula (IX-4Db):

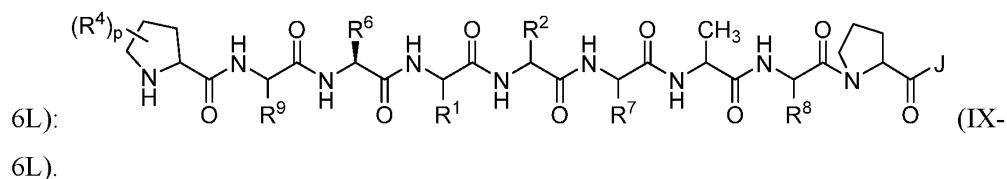


222. The compound of any one of claims 210-221, wherein R^6 is alkyl substituted with one occurrence of $-C(=O)NH_2$.

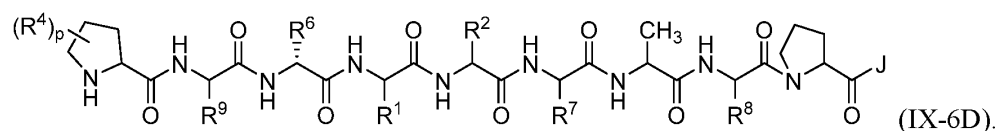


223. The compound of any one of claims 210-222, wherein R^6 is

224. The compound of any one of claims 210-223, having the structure of formula (IX-



225. The compound of any one of claims 210-223, having the structure of formula (IX-6D):

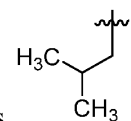


226. The compound of any one of claims 210-225, wherein R^9 is $-H$.

227. The compound of any one of claims 210-226, wherein R^7 is (C_1-C_{10}) alkyl.

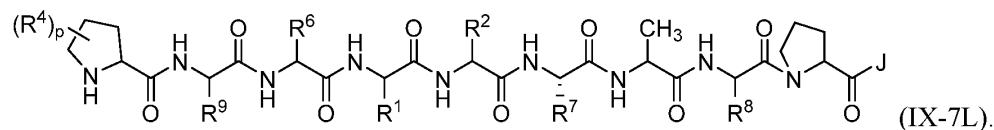


228. The compound of any one of claims 210-227, wherein R^7 is

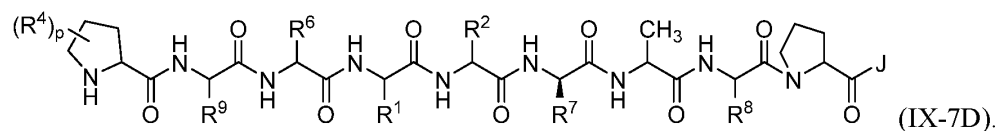


229. The compound of any one of claims 210-227, wherein R^7 is

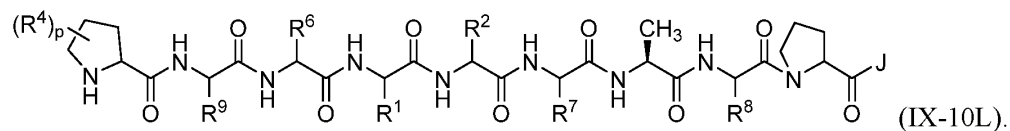
230. The compound of any one of claims 210-229, having the structure of formula (IX-7L):



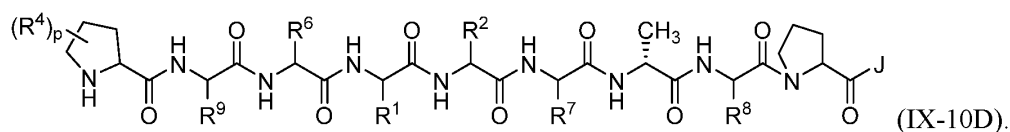
231. The compound of any one of claims 210-229, having the structure of formula (IX-7D):



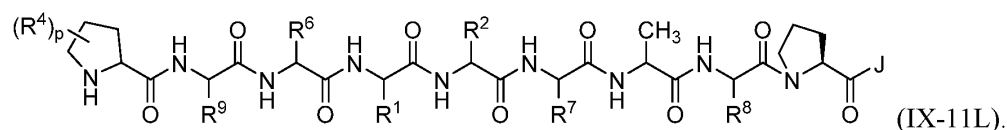
232. The compound of any one of claims 210-231, having the structure of formula (IX-10L):



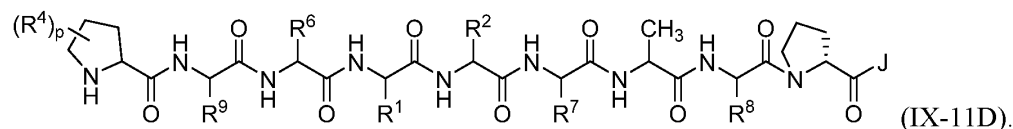
233. The compound of any one of claims 210-231, having the structure of formula (IX-10D):



234. The compound of any one of claims 210-233, wherein the compound has the structure of formula (IX-11L):



235. The compound of any one of claims 210-233, wherein the compound has the structure of formula (IX-11D):



236. The compound of any one of claims 210-235, wherein R^8 is $-\text{CH}_3$ or $-\text{H}$.

237. The compound of any one of claims 210-236, wherein R^8 is $-\text{H}$.

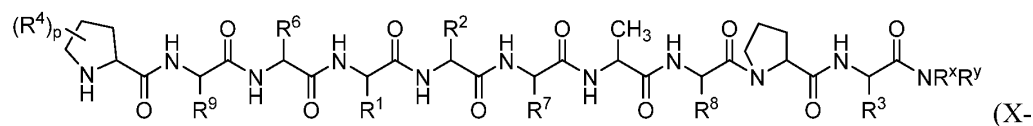
238. The compound of any one of claims 210-237, wherein J is OH.

239. The compound of any one of claims 210-237, wherein J is $-\text{NR}^x\text{R}^y$.

240. The compound of claim 239, wherein R^x and R^y are each independently alkyl.

241. The compound of claim 239, wherein R^x and R^y taken together with the intervening nitrogen atom form a ring.

242. A compound represented by Formula (X-am):



am);

or a pharmaceutically acceptable salt thereof;

wherein:

R^1 , R^2 , and R^3 are each independently H or substituted or unsubstituted alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl;

R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, oxo, $-\text{OR}^b$, $-\text{CH}_2\text{OR}^b$, halo, hydroxyl, and hydroxyalkyl;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclyl;

p is 0, 1, or 2;

R⁶ is hydrogen or substituted or unsubstituted alkyl;

R⁷, R⁸, and R⁹ are each independently hydrogen or alkyl;

J is OH or -NR^xR^y; and

R^x and R^y are each independently selected from H, optionally substituted alkyl, optionally substituted alkoxyalkyl, or R^x and R^y taken together with the intervening nitrogen atom form a ring.

243. The compound of claim 242, wherein:

R¹, R², and R³ are each independently H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl;

R⁴, independently for each occurrence, is selected from substituted or unsubstituted alkyl, oxo, hydroxyl, -OR^b, hydroxyalkyl, -CH₂OR^b, and halo;

R^b is substituted or unsubstituted alkyl, aryl, arylalkyl, or heterocyclalkyl;

R⁶ is hydrogen or substituted or unsubstituted alkyl; and

R⁷, R⁸, and R⁹ are each independently hydrogen or alkyl.

244. The compound of claim 242 or 243, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclalkyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, -CN, -NO₂, =N-OH, -N₃, -R^a, -OR^a, -SR^a, -N(R^a)₂, -N(R^a)₃⁺, =NR^a, -NHC(=O)R^c, -C(=O)R^c, -C(=O)N(R^a)₂, -S(=O)₂R^c, -OS(=O)₂OR^a, -S(=O)₂OR^a, -S(=O)₂N(R^a)₂, -S(=O)R^c, -OP(=O)(OR^a)₂, -(alkylene)-C(=O)R^c, -C(=S)R^c, -C(=O)OR^a, -(alkylene)-C(=O)OR^a, -C(=S)OR^a, -C(=O)SR^a, -C(=S)SR^a, -(alkylene)-C(=O)N(R^a)₂, -C(=S)N(R^a)₂, and -C(-NR^a)N(R^a)₂; and

R^a, independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkylalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c, independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclalkyl, heterocyclalkylalkyl, cycloalkyl, or (cycloalkyl)alkyl.

245. The compound of any one of claims 242-244, wherein, where indicated, alkyl, alkoxy, haloalkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroalkyl, cycloalkyl, heterocyclyl, or heterocyclalkyl is unsubstituted or is substituted with one or more substituents selected from halo, haloalkyl, oxo, $-R^a$, $-OR^a$, $-N(R^a)_2$, $-N(R^a)_3^+$, $-NHC(=O)R^c$, $-C(=O)R^c$, $-C(=O)N(R^a)_2$, $-C(=O)OR^a$, $-(alkylene)-C(=O)OR^a$, and $-(alkylene)-C(=O)N(R^a)_2$; and

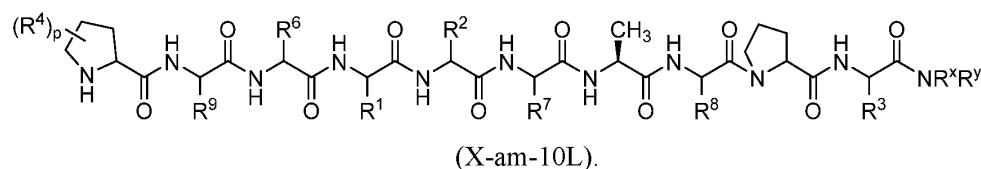
R^a , independently for each occurrence, is hydrogen, or substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl; and

R^c , independently for each occurrence, is substituted or unsubstituted alkyl, aryl, arylalkyl, heterocyclyl, heterocyclalkyl, cycloalkyl, or (cycloalkyl)alkyl.

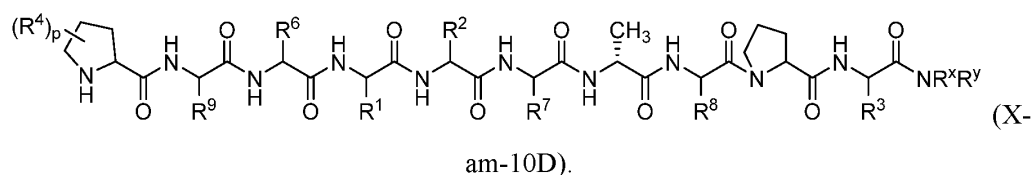
246. The compound of claim 245, wherein R^a , independently for each occurrence, is hydrogen, alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl; and

R^c , independently for each occurrence, is alkyl, aryl, arylalkyl, heterocyclyl, or heterocyclalkyl.

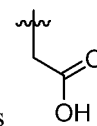
247. The compound of any one of claims 242-246, having the structure of formula (X-am-10L):



248. The compound of any one of claims 242-246, having the structure of formula (X-am-10D):

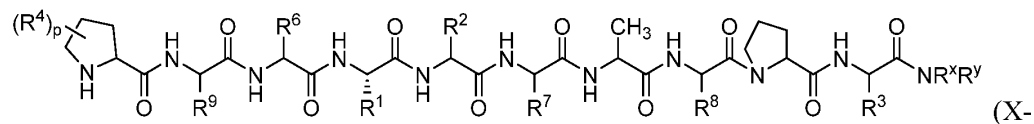


249. The compound of any one of claims 242-248, wherein R^1 is substituted or unsubstituted (C_2-C_{10}) haloalkyl.



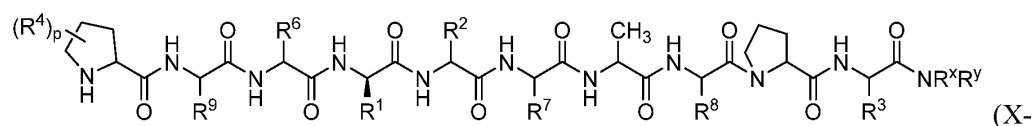
254. The compound of any one of claims 242-248, wherein R¹ is

255. The compound of any one of claims 242-254, having the structure of formula (X-am-1L)



(X-am-1L).

256. The compound of any one of claims 242-254, having the structure of formula (X-am-1D)

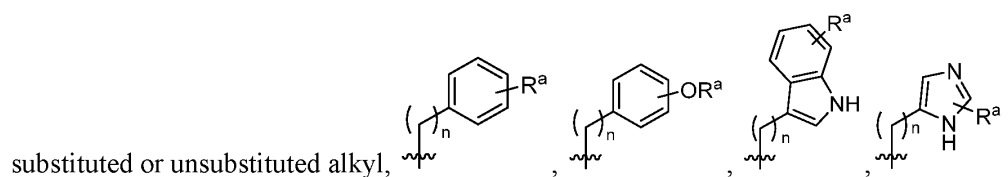


(X-am-1D).

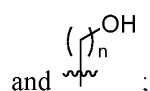
257. The compound of any one of claims 242-256, wherein R² is substituted or unsubstituted (C₂-C₁₀)haloalkyl.

258. The compound of any one of claims 242-256, wherein R² is H or substituted or unsubstituted alkyl, arylalkyl, or heterocyclalkyl.

259. The compound of any one of claims 242-256, wherein R² is selected from hydrogen,



substituted or unsubstituted alkyl,

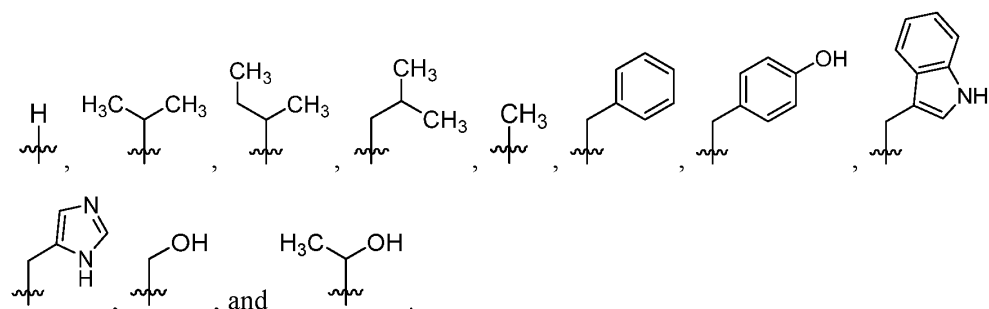


and

R^a is hydrogen or alkyl; and

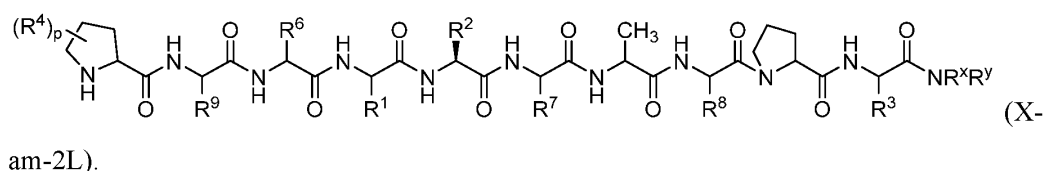
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

260. The compound of any one of claims 242-256, wherein R^2 is selected from

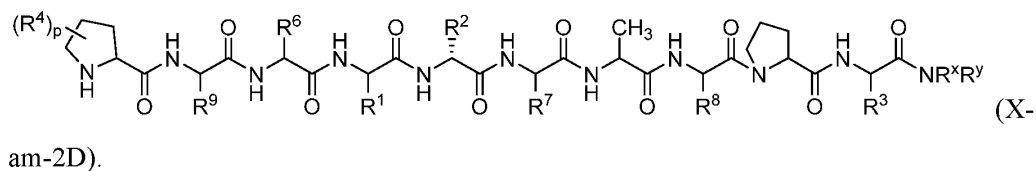


261. The compound of any one of claims 242-256, wherein R^2 is hydrogen.

262. The compound of any one of claims 242-260, having the structure of formula (X-am-2L):



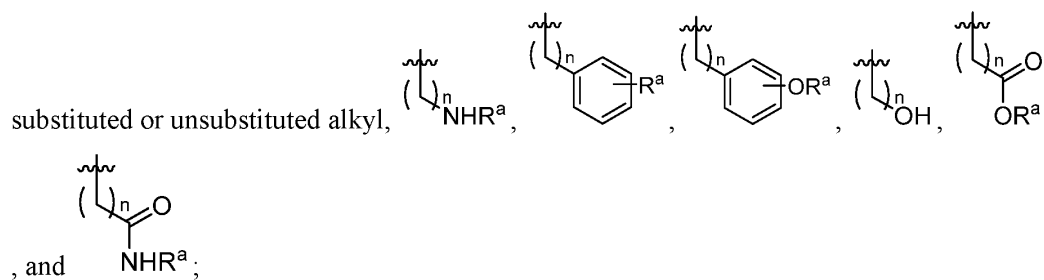
263. The compound of any one of claims 242-260, having the structure of formula (X-am-2D):



264. The compound of any one of claims 242-263, wherein R^3 is substituted or unsubstituted (C_2-C_{10}) haloalkyl.

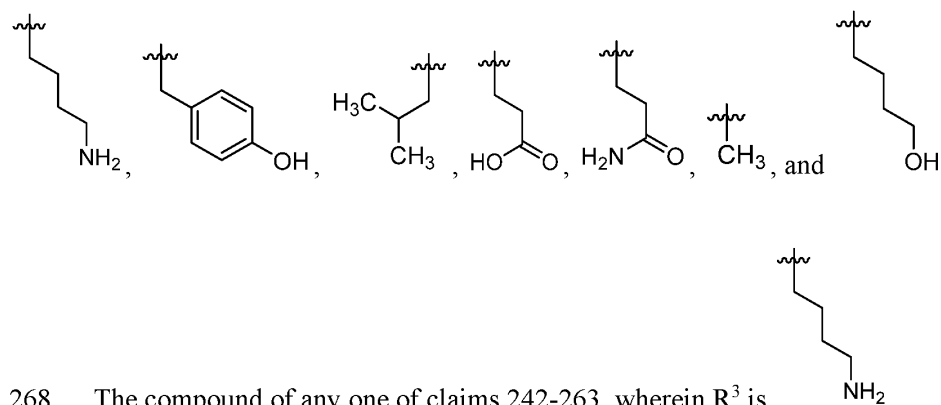
265. The compound of any one of claims 242-263, wherein R^3 is substituted or unsubstituted alkyl or arylalkyl.

266. The compound of any one of claims 242-263, wherein R^3 is selected from



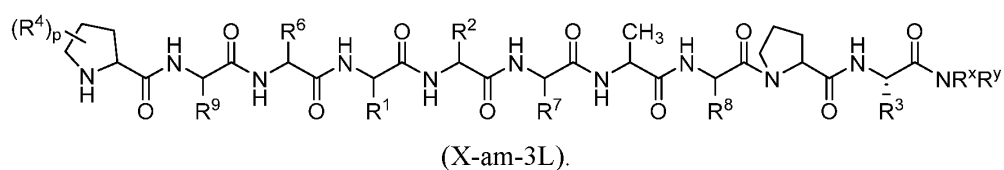
n is an integer from 1 to 10, preferably 1-5, more preferably 1-3.

267. The compound of any one of claims 242-263, wherein R^3 is selected from

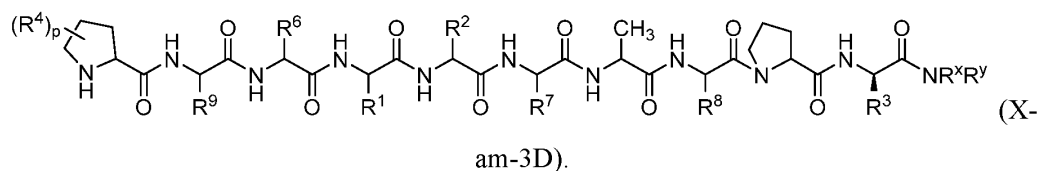


268. The compound of any one of claims 242-263, wherein R^3 is

269. The compound of any one of claims 242-268, having the structure of formula (X-am-3L):



270. The compound of any one of claims 242-268, having the structure of formula (X-am-3D):



271. The compound of any one of claims 242-270, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from substituted or unsubstituted alkyl, $-OR^b$, $-CH_2OR^b$, halo, hydroxyl, and hydroxyalkyl.

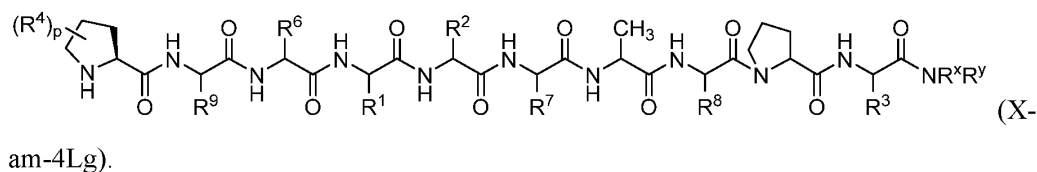
272. The compound of any one of claims 242-270, wherein p is 1 or 2; and R^4 , independently for each occurrence, is selected from $-CH_3$, halo, hydroxyl, and hydroxyalkyl.

273. The compound of claim 272, wherein R^4 is hydroxyl.

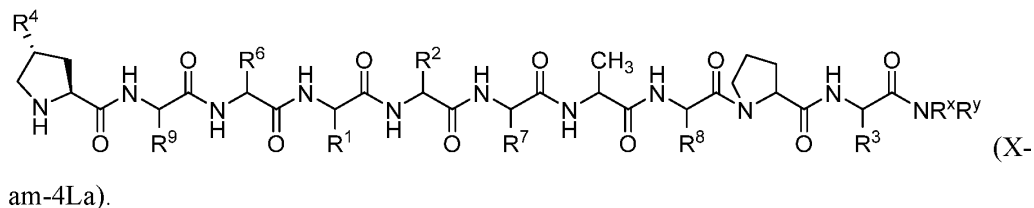
274. The compound of claim 272, wherein R^4 is $-CH_3$.

275. The compound of any one of claims 271-274, wherein p is 1.

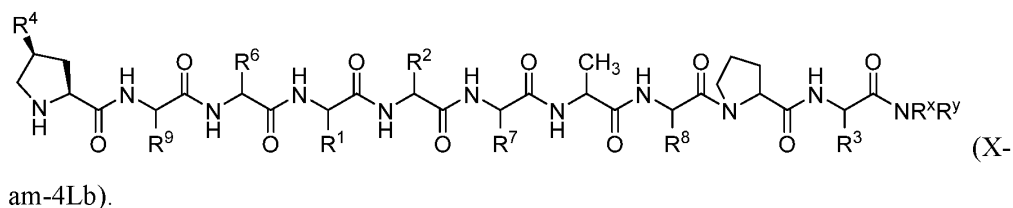
276. The compound of any one of claims 242-275, having the structure of formula (X-am-4Lg):



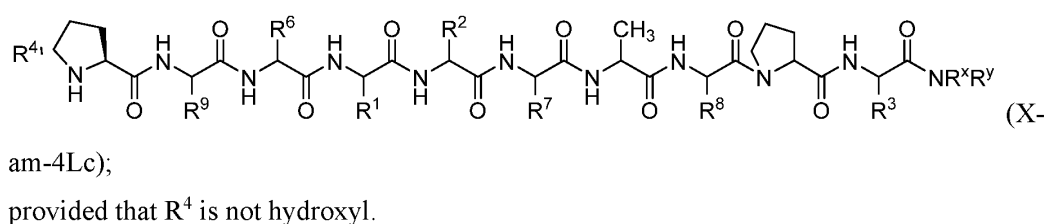
277. The compound of any one of claims 242-276, having the structure of formula (X-am-4La):



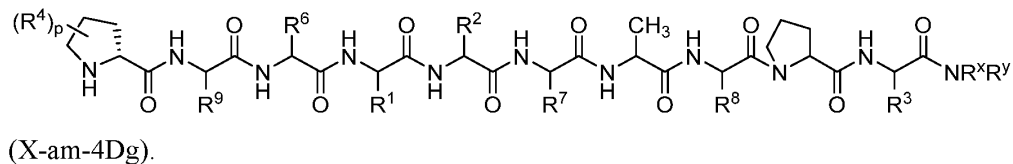
278. The compound of any one of claims 242-276, having the structure of formula (X-am-4Lb):



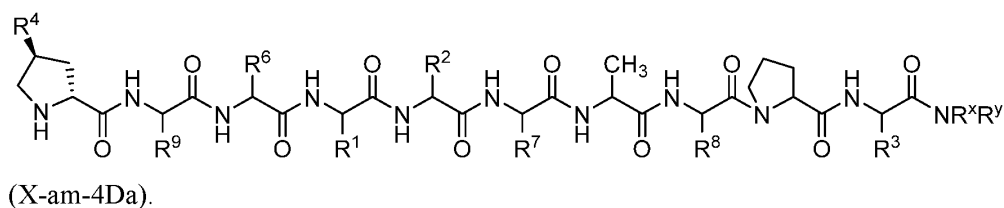
279. The compound of any one of claims 242-272 and 274-276, having the structure of formula (X-am-4Lc):



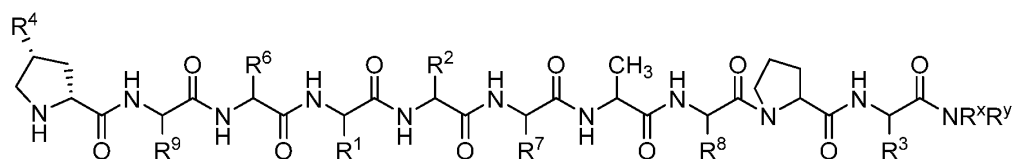
280. The compound of any one of claims 242-275, having the structure of formula (X-am-4Dg):



281. The compound of any one of claims 242-275 and 280, having the structure of formula (X-am-4Da):

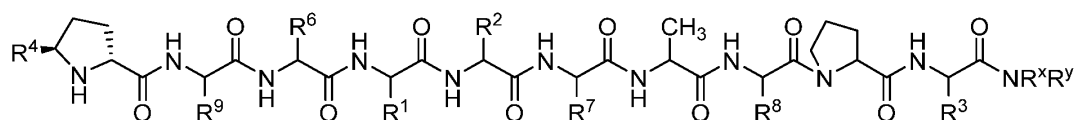


282. The compound of any one of claims 242-275 and 280, having the structure of formula (X-am-4Db):



(X-am-4Db).

283. The compound of any one of claims 242-272, 274-276, and 280, having the structure of formula (X-am-4Dc):

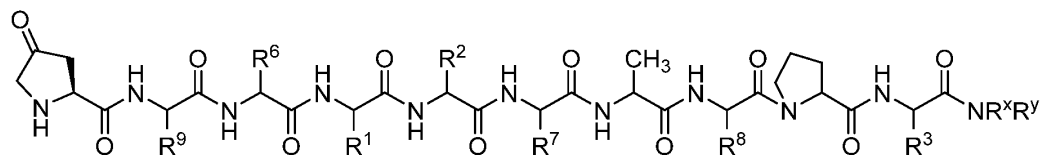


(X-am-4Dc);

provided that R⁴ is not hydroxyl.

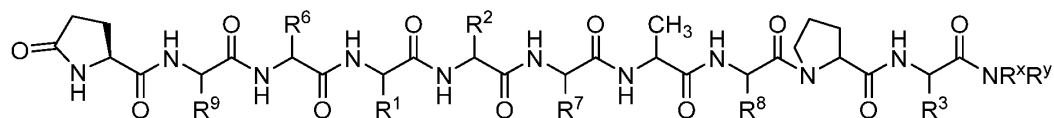
284. The compound of any one of claims 242-268, wherein R⁴ is oxo.

285. The compound of claim 284, having the structure of formula (X-am-4Ld):



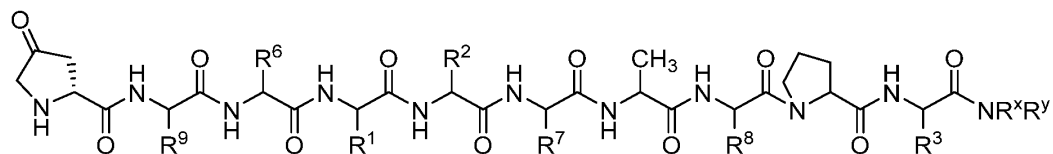
(X-am-4Ld).

286. The compound of claim 284, having the structure of formula (X-am-4Le):



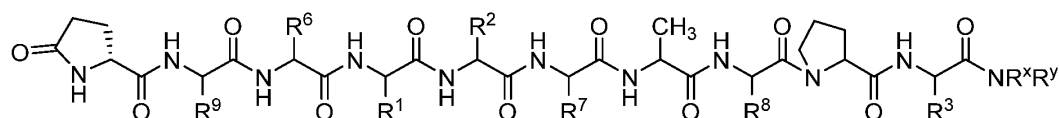
(X-am-4Le).

287. The compound of claim 284, having the structure of formula (X-am-4Dd):



(X-am-4Dd).

288. The compound of claim 284, having the structure of formula (X-am-4De):

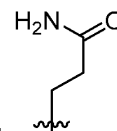


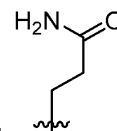
(X-am-4De).

289. The compound of any one of claims 242-288, wherein R^6 is hydrogen or alkyl, wherein the alkyl is optionally substituted with one occurrence of $-C(=O)NH_2$.

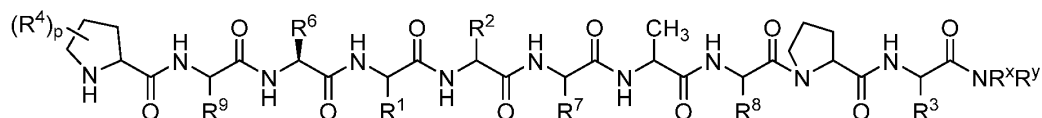
290. The compound of any one of claims 242-289, wherein R^6 is alkyl optionally substituted with one occurrence of $-C(=O)NH_2$.

291. The compound of any one of claims 242-290, wherein R^6 is $-CH_3$.



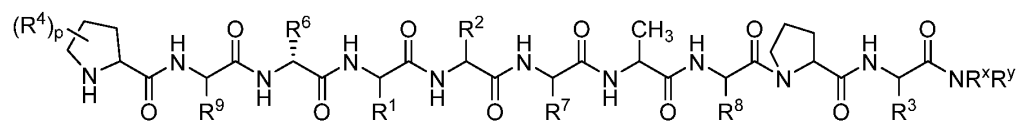
292. The compound of any one of claims 242-290, wherein R^6 is .

293. The compound of any one of claims 242-292, having the structure of formula (X-am-6L):



(X-am-6L).

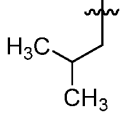
294. The compound of any one of claims 242-292, having the structure of formula (X-am-6D):



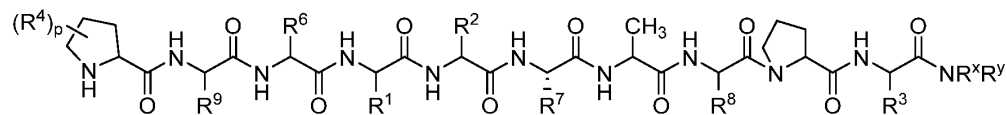
(X-am-6D).

295. The compound of any one of claims 242-294, wherein R^7 is (C_1-C_{10}) alkyl.

296. The compound of any one of claims 242-295, wherein R^7 is .

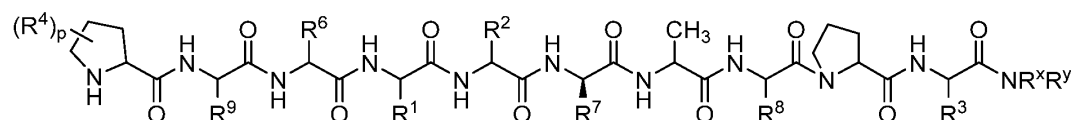
297. The compound of any one of claims 242-295, wherein R^7 is .

298. The compound of any one of claims 242-297, having the structure of formula (X-am-7L):



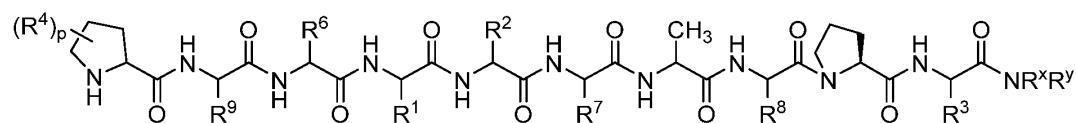
(X-am-7L).

299. The compound of any one of claims 242-297, having the structure of formula (X-am-7D):



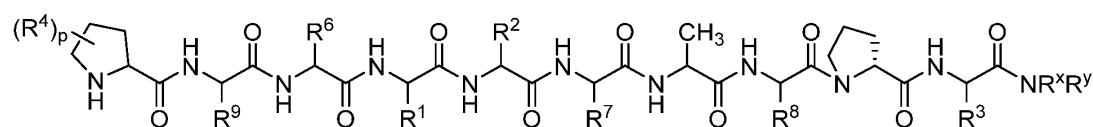
(X-am-7D).

300. The compound of any one of claims 242-299, having the structure of formula (X-am-11L):



(X-am-11L).

301. The compound of any one of claims 242-299, having the structure of formula (X-am-11D):



(X-am-11D).

302. The compound of any one of claims 242-301, wherein R^8 is $-\text{CH}_3$ or $-\text{H}$.

303. The compound of any one of claims 242-301, wherein R^8 is $-\text{H}$.

304. The compound of any one of claims 242-303, wherein R^9 is $-\text{CH}_3$ or $-\text{H}$.

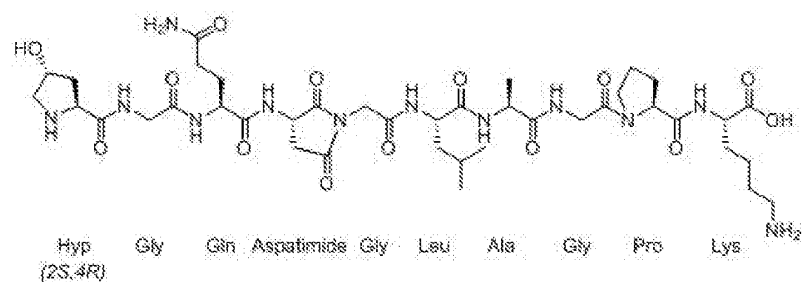
305. The compound of any one of claims 242-303, wherein R^9 is $-\text{H}$.

306. The compound of any one of claims 242-305, wherein R^x and R^y are each independently optionally substituted alkyl.

307. The compound of any one of claims 242-305, wherein R^x and R^y are each independently optionally substituted alkoxyalkyl.

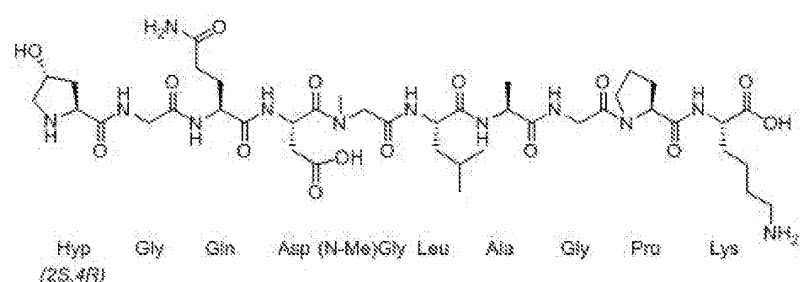
308. The compound of any one of claims 242-305, wherein R^x and R^y taken together with the intervening nitrogen atom form a ring.

309. A salt of a compound represented by Formula 8:



[Formula 8].

310. A salt of a compound represented by Formula 10:



[Formula 10].

311. A pharmaceutical composition comprising a salt of any one of claims 1-67, 309, and 310 or a compound of any one of claims 68-308 and a pharmaceutically acceptable carrier.

312. The pharmaceutical composition of claim 311, wherein the pharmaceutical composition is formulated for topical administration to the eye, e.g., as eye drops.

313. The pharmaceutical composition of claim 311 or 312, comprising a compound of any one of claims 68-308, wherein at least 50%, 60%, 70%, 80%, or 90% of the compound is present as a salt.

314. The pharmaceutical composition of claim 313, wherein at least 95% of the compound is present as a salt.

315. The pharmaceutical composition of claim 314, wherein at least 99% of the compound is present as a salt.

316. A method of treating eye disease, comprising administering to a subject in need thereof salt of any one of claims 1-67, 309, and 310 or a compound of any one of claims 68-308, or the pharmaceutical composition of any one of claims 311-315.

317. The method of claim 316, wherein the eye disease is selected from retinopathy, keratitis, dry-macular degeneration, wet-macular degeneration, dry eye syndrome, heratoconjunctivitis sicca and keratoconjunctival epithelium disorder.

318. The method of claim 316 or 317, wherein administering the compound or composition comprises topical administration to the eye of the subject.